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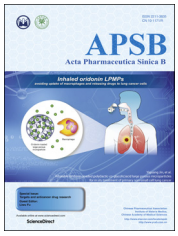

REVIEW

Targeting calcium signaling in cancer therapy

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Abstract The intracellular calcium ions (Ca^{2+}) act as second messenger to regulate gene transcription, cell proliferation, migration and death. Accumulating evidences have demonstrated that intracellular Ca^{2+} homeostasis is altered in cancer cells and the alteration is involved in tumor initiation, angiogenesis, progression and metastasis. Targeting derailed Ca^{2+} signaling for cancer therapy has become an emerging research area. This review summarizes some important Ca^{2+} channels, transporters and Ca^{2+}-ATPases, which have been reported to be altered in human cancer patients. It discusses the current research effort toward evaluation of the blockers, inhibitors or regulators for Ca^{2+} channels/transporters or Ca^{2+}-ATPase pumps as anti-cancer drugs. This review is also aimed to stimulate interest in, and support for research

Abbreviations: 20-GPPD, 20-*O*-*β*-D-glucopyranosyl-20(*S*)-protopanaxadiol; CaM, calmodulin; CaMKII, calmodulin-dependent protein kinase II; CBD, cannabidiol; CBG, cannabigerol; CPZ, capsazepine; CRAC, Ca^{2+} release-activated Ca^{2+} channel; CTL, cytotoxic T cells; CYP3A4, cytochrome P450 3A4; ER/SR, endoplasmic/sarcoplasmic reticulum; HCX, H^+/Ca^{2+} exchangers; IP_3, inositol 1,4,5-trisphosphate; IP_3R (1, 2, 3), IP_3 receptor (type 1, type 2, type 3); mAb, monoclonal antibody; MCU, mitochondrial Ca^{2+} uniporter; MCUR1, MCU uniporter regulator 1; MICU (1, 2, 3), mitochondrial calcium uptake (type 1, type 2, type 3); MLCK, myosin light-chain kinase; NCX, Na^+/Ca^{2+} exchanger; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma cells; PKC, protein kinase C; PM, plasma membrane; PMCA, plasma membrane Ca^{2+}-ATPase; PTP, permeability transition pore; ROS, reactive oxygen species; RyR, ryanodine receptor; SERCA, SR/ER Ca^{2+}-ATPase; SOCE, store-operated Ca^{2+} entry; SPCA, secretory pathway Ca^{2+}-ATPase; TEA, tetraethylammonium; TG, thapsigargin; TPC2, two-pore channel 2; TRIM, 1-(2-(trifluoromethyl) phenyl) imidazole; TRP (A, C, M, ML, N, P, V), transient receptor potential (ankyrin, canonical, melastatin, mucolipin, no mechanoreceptor potential C, polycystic, vanilloid); VGCC, voltage-gated Ca^{2+} channel

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into the understanding of cellular mechanisms underlying the regulation of Ca^{2+} signaling in different cancer cells, and to search for novel therapies to cure these malignancies by targeting Ca^{2+} channels or transporters.

1. Introduction

Intracellular calcium ions (Ca^{2+}), the most abundant second messenger in human body, have a substantial diversity of roles in fundamental cellular physiology, including gene expression, cell cycle control, cell motility, autophagy and apoptosis[1]. Since the cytosol Ca^{2+} is maintained very low ($\sim 10^{-7}$ mol/L), a small fraction of Ca^{2+} either through release from intracellular organelles ($\sim 10^{-5}$ mol/L) or through influx from extracellular reservoir ($\sim 10^{-3}$ mol/L) can generate marked signals to activate downstream signaling cascade. Increase in Ca^{2+} levels are highly localized, such as the microdomains in the vicinity of inositol 1,4,5-trisphosphate receptor (IP_3R) or store-operated Ca^{2+} entry (SOCE) channel[2]. Alternatively, local changes in intracellular Ca^{2+} can diffuse across the cell as a wave and elicit an effect at a distant site[3]. The prolonged intracellular elevation of Ca^{2+} can be toxic and triggers cell death[4]. Therefore, the Ca^{2+} signals in the form of waves, spikes or oscillations must be spatially-temporally tightly regulated[5].

Among the three Ca^{2+} signal forms, intracellular Ca^{2+} oscillations provide efficient means to transmit intracellular biological information. For example, our previous study showed that intracellular Ca^{2+} oscillations provided essential proliferation signals for esophageal cancer cells[6]. In particular, the frequency, amplitude, and duration of these intracellular Ca^{2+} oscillations compose the specific Ca^{2+} codes for selective activation of transcription factors for gene transcription, cell proliferation and migration[7,8]. The decoding of the oscillatory form is achieved by intracellular downstream effectors, including calmodulin (CaM), nuclear factor of activated T-cells (NFAT), nuclear factor-κB (NF-κB), calmodulin-dependent protein kinase II (CaMKII) and calpain, which differ in their on- and off-rates for Ca^{2+} and subsequently activate different cellular processes[9–11]. Furthermore, different Ca^{2+} regulated kinases and enzymes often occupy distinct locations within the cell. Therefore, the size, kinetics and spatial profile of a cytoplasmic Ca^{2+} signal are all important in determining which Ca^{2+}-dependent response will be activated, when and for how long. Intracellular Ca^{2+} oscillations can reduce the effective Ca^{2+} threshold for signaling transduction, thereby increasing signal detection at low levels of stimulation[12].

Disruption of normal Ca^{2+} signaling contributes to the development of malignant phenotypes[13]. In order to proliferate at high rates, to increase cell motility and invasion, to escape death, to fool immune-attack, or to have neovascularization, tumors remodel their Ca^{2+} signaling network. There has been an increasing awareness that tumorigenic pathways are associated with altered expression level or abnormal activation of Ca^{2+} channels, transporters or Ca^{2+}-ATPases[6,14–20]. Correction of these derailed Ca^{2+} signals could provide potential cancer therapies. In this review, we will summarize the Ca^{2+} channels, transporters and Ca^{2+}-ATPases, which are altered and play important roles in cancer biology. We will also discuss the current effort in this emerging research area toward evaluation of a certain numbers of Ca^{2+} channel blockers or regulators and Ca^{2+}-ATPase pump inhibitors as anti-cancer drugs.

2. Altered Ca^{2+} channels/transporters in cancer

The intracellular Ca^{2+} homeostasis is governed by a network composed of various Ca^{2+} channels and transporters: (1) IP_3R or ryanodine receptor (RyR) mediating Ca^{2+} release from endoplasmic/sarcoplasmic reticulum (ER/SR); (2) Ca^{2+}-ATPase pumping Ca^{2+} from cytosol back to ER/SR or extracellular space; (3) Ca^{2+} channels or transporters allowing Ca^{2+} influx across plasma membrane (PM) from extracellular Ca^{2+} reservoir, such as voltage-gated Ca^{2+} channel (VGCC), transient receptor potential channel (TRP), Ca^{2+} release-activated Ca^{2+} channel (CRAC), Na^+/Ca^{2+} exchanger (NCX) and purinergic receptor; (4) mitochondrial Ca^{2+} uniporter (MCU) regulating mitochondrial Ca^{2+} uptakes (Fig. 1). It is beyond the scope of this brief review to cover all the Ca^{2+} channels, transporters or Ca^{2+}-ATPases for intracellular Ca^{2+} homeostasis; instead, we will focus on a few important ones, which have been reported to be dysregulated in cancer cells (Table 1).

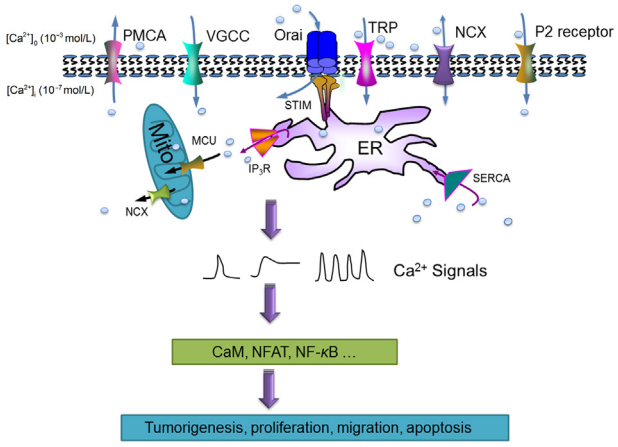

Figure 1 Important Ca^{2+} channels/transporters/pumps in cancer cells. The dynamic of intracellular Ca^{2+} is governed by a series of proteins: (1) IP_3Rs mediating Ca^{2+} release from endoplasmic reticulum (ER); (2) Ca^{2+}-ATPases pumping Ca^{2+} from cytosol to the ER or to extracellular space; (3) plasma membrane Ca^{2+} channels or transporters, such as VGCCs, TRPs, CRACs, NCXs and P2 receptors; (4) mitochondrial Ca^{2+} uniporter. The tightly regulated Ca^{2+} signals in the form of waves, spikes or oscillations can regulate a wide range of cellular events, including gene transcription, proliferation, migration and apoptosis. Targeting the dysregulated Ca^{2+} channels/transporters/pumps may provide a promising chemotherapy for cancer patients.

2.1. IP_3Rs — ER Ca^{2+} release channels

ER and SR are the major intracellular Ca^{2+} storage organelles in non-excitable and excitable cells, respectively. While RyRs are predominantly expressed in excitable cells, IP_3Rs are the main intracellular Ca^{2+} release channels in non-excitable cells, including many cancer cells. So far, three isoforms of IP_3R, *i.e.* IP_3R1, IP_3R2 and IP_3R3 have been identified, which display different affinity to IP_3 with similar but not identical functional properties[21]. The general domain structure of IP_3Rs includes the IP_3 binding site at the N-terminal region, the six transmembrane spanning domains at the C-terminal, a large number of cytoplasmic regulatory sites and protein-binding domains. Among these protein-binding domains, a significant one between amino acid 1390–1409 mediates the interaction with the BH4 domain of anti-apoptotic protein Bcl-2. IP_3R-mediated ER Ca^{2+} release participates in the overall intracellular Ca^{2+} signaling network and regulates fundamental cellular functions, such as cell proliferation and differentiation[22]. Moreover, recent studies have demonstrated that mitochondria and ER can form structural link. Together with other interacting proteins, such as BCL-2 and BAX/BAM, the Ca^{2+} channels residing in the two organelles are assembled in a macromolecular complex in which the IP_3R directly stimulates the mitochondrial Ca^{2+} uptake[23]. Through this ER/mitochondrial crosstalk, IP_3Rs can further determine the cell fate by controlling the mitochondrial Ca^{2+}elevation and metabolism.

Altered IP_3R activity and/or the remodeling of IP_3R-expression profile have been found in a number of cancers (Table 1). Compared with normal brain tissues, human glioblastoma samples present decreased IP_3R1 and increased IP_3R3. Kang et al.[24] demonstrated that caffeine could inhibit IP_3R3-mediated Ca^{2+} release, thus reduced migration of cultured glioblastoma cells and greatly increased mean survival in a mouse xenograft model of glioblastoma. The upregulation of IP_3R3 has been observed in gastric cancer cell lines established from malignant ascites, but not in a cell line established from primary tumor or normal gastric epithelial cells[25]. In a clinical association study, Shibao et al.[26] examined whether gain of expression of IP_3R isoforms is associated with development of colorectal cancer using colorectal carcinomas tissues surgically resected from over a hundred patients. They found that IP_3R1 and IP_3R2 were expressed in both normal colorectal mucosa and colorectal cancer, while IP_3R3 was only observed in colorectal cancer, especially in the advancing margins of tumors correlated with depth of invasion, lymph node metastasis, liver metastasis, and TNM stage. High expression of IP_3R3 is associated with aggressiveness of colorectal carcinoma since it is related with decreased 5-year survival. A mutation in IP_3R3 encoding gene *ITPR3* was identified in genetic landscape of metastatic and recurrent head and neck squamous cell carcinoma[27]. Similarly like IP_3R1 and IP_3R3, the dysregulation of IP_3R2 was observed in chronic lymphocytic leukemia cells[28]. The expression of IP_3R2 is significantly upregulated, which in turn may enhance mitochondrial function and energy production to accommodate for the higher metabolic activity and the induced proliferation of leukemia cells. It is notable that the role of IP_3R2 may be complicated. Ouyang et al., recently reported that IP_3R2 mediated Ca^{2+} signaling is required to reinforce the developmentally important transcription factor TCF-1 for normal development and thymocyte neoplasia prevention. Mice without IP_3Rs in thymocyte developed aggressive T-cell malignancies that resemble human T-cell acute lymphoblastic leukemia[29].

2.2. Ca^{2+}-ATPases

The low cytosolic Ca^{2+} concentration is maintained by the Ca^{2+} transport system, *i.e.* Ca^{2+}-ATPases. They rapidly pump cytosolic Ca^{2+} ions back into intracellular organelles, *e.g.* ER, or to extrude Ca^{2+} ions to extracellular space. These Ca^{2+}-ATPases belong to the superfamily of P-type ATPase (E1E2-type) and can be further divided into three subtypes according to their subcellular localizations: plasma membrane Ca^{2+}-ATPase (PMCA), ER/SR Ca^{2+}-ATPase (SERCA), golgi/golgi-derived vesicles secretory pathway Ca^{2+}-ATPase (SPCA). Each subtype contains multiple isoforms and splice variants, which present tissue-specific expression, regulation, and kinetic characteristics. As such, the Ca^{2+}-ATPases contribute to a highly complex and fine-tuned intracellular Ca^{2+} signaling network[30].

Among the Ca^{2+}-ATPases family members, SERCA is the best characterized one. SERCA is responsible for replenishing ER Ca^{2+} stores, maintaining protein proper folding/maturation whereas dysregulated SERCA results in depleted or overloaded ER lumen Ca^{2+} stores, increased ER stress, dysregulated chaperones and synthesis of lipids. Mutations and altered expression levels of SERCA isoforms have been identified in various cancers, such as cancers of colon, gastric, lung, myeloid leukemia and choroid plexus tumors[31] (Table 1). Overexpression of SERCA2 was found in colorectal cancer cells, which may drive proliferation and migration[32]. On the other hand, SERCA3 was reported to have progressively lost during multistage process of colon tumorigenesis after initial increased expression during cell differentiation[33]. In B lymphocytes, SERCA3 was also found to be downregulated after the infection of Epstein Barr virus, a human gammaherpesvirus involved in various malignancies including Burkitt's and other lymphomas[34].

Altered expression of SPCA isoforms occurs in various types of cancer including breast, colon and prostate[20]. Clinical data showed that SPCA1 is highly expressed in basal-like breast cancers and has a low expression in the luminal subtypes[35]. Feng et al.[36] identified up-regulation of SPCA2 in breast cancer-derived cells and human breast tumors. Knockdown of SPCA2 resulted in attenuated growth as well as decreased colony formation of MCF7 cells in soft agar and reduced tumor formation in xenografted mice. Furthermore, overexpression of SPCA2 is able to confer increased proliferation and colony formation capability in soft agar assay in MCF10A cells, a nonmalignant mammary epithelial cell line. On the other hand, knockdown of SPCA2 and low Ca^{2+} conditions are able to decrease activity of ERK1/2 pathway, which may result in decreased proliferation in breast cancer cells. SPCA2 appears to have the unique ability to elicit store-independent Ca^{2+} entry, *i.e.* a constitutive Ca^{2+} entry pathway, which in turn promotes proliferative potential of cancer cells[36].

The association between altered PMCAs and cancer has been reported in a few studies as well (Table 1). PMCA2, the isoform predominantly expressed in mammary epithelia for the apical efflux of Ca^{2+} during lactation, is highly expressed in certain numbers of breast cancer cell lines[37]. In these breast cancer cell lines, PMCA2 is constitutively expressed at levels as over 100-fold high as in non-tumorigenic lines. As such, PMCA2 can keep low cytosolic Ca^{2+} levels and bypass apoptosis by preventing increased uptake of Ca^{2+} into mitochondria. On the contrary, PMCA4 and PMCA1 are down-regulated in colon or oral squamous cell carcinoma, respectively, which increase cytosolic Ca^{2+} to enhance cell proliferation[38,39]. These observations suggest

that different cancer cells may develop different means to fulfill special needs for intracellular Ca^{2+} signaling, and either up or down regulation of Ca^{2+}-ATPases is used to facilitate a particular type of cancer cells to escape from normal cellular control and to promote tumorigenesis.

2.3. *Plasma membrane Ca^{2+} channels*

2.3.1. *Voltage-gated Ca^{2+} channels*

VGCCs (also known as Ca_v family) mediate a fast Ca^{2+} influx in response to membrane depolarization. There are 6 subfamilies of VGCCs, *i.e.* L-, N-, P-, Q-, R- and T-type. The Ca_v1 conducts L-type Ca^{2+} currents, initiating muscle contraction and endocrine secretion; the Ca_v2 conducts N-, P/Q- and R-type Ca^{2+} currents, initiating rapid synaptic transmission; the Ca_v3 conducts T-type Ca^{2+} currents, which are characterized by more rapid activation and inactivation by membrane depolarization[40].

A recent meta-analysis of microarray datasets revealed VGCCs mRNA gene profile of different types of cancers[41]. L-type Ca^{2+} channels are implicated in the development and progression of several tumors, such as significantly up-regulated in colon and esophageal cancers. Novel splice variants of T-type Ca^{2+} channel are commonly found in human glioma, breast, ovarian, prostate colon and esophageal cancer cells. For example, $Ca_v3.1a$ transcripts predominate in the normal adult brain and $Ca_v3.1b$ is mostly fetal-specific; but human glioma and glioma cell lines contains $Ca_v3.1bc$ as predominant splice and $Ca_v3.1ac$ as a novel splice variant, which is absent in normal brain or fetal astrocytes[42–46].

2.3.2. *TRP channels*

The super family of TRP channels include more than 30 members, which can be further divided into 7 subgroups, *i.e.* TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystic), TRPN (no mechanoreceptor potential C), and TRPV (vanilloid)[47]. Mammalian TRP proteins form homo- or hetero tetrameric as non-selective Ca^{2+}-permeable cation channels, which can be activated and regulated by a wide variety of stimuli, such as Ca^{2+}, temperature, pH, ROS, chemical and mechanical stress. As such, they are perfect candidates for cellular sensors and are believed to actively participate in the tumor–microenvironment cross-talk[48].

As summarized in Table 1, a large number of TRP members present altered expression and/or channel activity in a variety of cancers. For example, the presence of the TRPC, TRPM, and TRPV subfamilies correlates with malignant growth and cancer progression[49–53]. TRPM7, 8 and TRPV2, 6 are associated with the prostate cancer progression and TRPC6 as a novel therapeutic target for esophageal carcinoma[18,54–58]. In breast cancer, TRPC1, TRPC6, TRPM7, TRPM8, and TRPV6 are overexpressed, and their expression profiles are associated with pathologic parameters, suggesting their use as prognostic markers[53,59]. The expression profile of TRPM7/8 depends on both invasive and hormonal status: in non-invasive estrogen-positive cells, TRPM7 is highly expressed and mediates Ca^{2+} influx, which results in proliferation and poor differentiation[60]; on the other hand, TRPM8 is highly expressed in non-invasive well-differentiated estrogen-positive breast cancer, and may serve as a good prognostic marker for this type cancer[61]; in aggressive estrogen-negative cancers, they regulate cell migration through an interaction with cytoskeleton proteins[62]. Besides mentioned above, there are still some of other TRP family proteins involved and contributed to cancer development, which were summarized in Table 1. Therefore the expression of TRP channels has been proposed as a tool for diagnosis or predicting prognosis in several cancers, and targeting TRP channels has been suggested as a novel therapeutic strategy[48].

2.3.3. *Orai and STIM*

Another type of Ca^{2+} influx channels, including CRAC, arachidonate-regulated Ca^{2+} entry channel and SOCE channel has been demonstrated to heavily involve in cancer biology (Table 1). The activation of canonic SOCE pathway contains several steps, i.e. reduction or depletion of ER Ca^{2+} stores, translocation of ER-localized Ca^{2+} sensor STIM1 to ER-plasma membrane junctions, aggregation and conformational changes of cell surface Orai channels, and final Ca^{2+} influx. To date, three isoforms of Orai (Orai1, Orai2 and Orai3) and two isoforms of STIM (STIM1 and STIM2) have been identified in mammals[63].

Among these SOCE machinery proteins, Orai1 and STIM1 are the two well characterized. Yang et al.[64] first reported that STIM1 and Orai1 played a crucial role in breast cancer migration and metastasis. We also showed that Orai1 expression was elevated in tumor tissues compared with normal adjacent tissues removed from patients suffering from esophageal squamous cell carcinoma; more importantly, the elevated Orai1 expression was associated with poor prognosis. Inhibition of Orai1 channel either by pharmacological compounds or knocking-down of Orai1 expression could block cancer cell proliferation and migration *in vitro* and tumor growth *in vivo*[6]. Later, Orai1 and STIM1 were also found to promote cell proliferation, migration, invasion and apoptotic resistance in glioblastoma[65], pancreatic adenocarcinoma[66], prostate cancer[67,68], hepatocellular carcinoma[69], and clear cell renal cell carcinoma[70]. Interestingly, STIM1 and STIM2 are involved in the anti-tumor activity of cytotoxic T cells, *i.e.* secretion of cytokines, such as TNFα, IL-2 and IFNγ, which induce apoptosis of cancer cells[71,72]. Studies about roles of STIM2 in cancer still unconsolidated. A few reports demonstrated STIM2, as a proliferation suppressor, contributed to apoptotic resistance in colorectal cancer cells; while others revealed STIM2-mediated SOCE promote melanoma cells proliferation[73,74]. This may indicate that multifaceted STIM2 exert specific functions in different types of cancer.

Compared with Orai1, much less is known about Orai2 and Orai3 in malignant diseases. Except up-regulated in non-small cell lung cancer (NSCLC) and contributed to cell proliferation and tumor grades, Orai3 is also overexpressed in breast cancer tissues, cell lines MCF-7 and T47D as respectively compared to adjacent normal tissues and non-cancerous cell line MCF-10A[75,76]. Motiani et al.[77,78] showed that abnormal SOCE was mediated by Orai3 in estrogen-receptor-positive breast cancer lines and this increased the proto-oncogenes NFAT transcriptional activity through MAP kinase pathway. Orai3 and Orai1 form arachidonate-regulated Ca^{2+} entry channel and their ratio represents an oncogenic switch, which facilitates proliferation and apoptotic resistance in prostate cancer[68]. More detailed discussion on recent advances in SOCE and its contribution to cancer can be found in our review article published elsewhere[79].

2.3.4. *Purinergic receptors*

Purinergic signaling receptors for extracellular nucleotides (P1 and P2 receptors) are widely expressed by mammalian cells. The P2 receptors are divided into P2X and P2Y groups and each group contains several members with distinct ion selectivity and regulatory properties. Numerous studies have demonstrated that P2 receptors involve in cancer cells and are expressed to a very high level in some cases, such as P2X3, P2X5, P2X7 and P2Y2 and

P2Y4[42,80–83] (Table 1). In terms of clinical evaluation, P2X3 receptor overexpression was reported to be associated with poor recurrence-free survival in hepatocellular carcinoma patients[84].

2.4. *Mitochondrial Ca^{2+} uniporter*

Mitochondria are capable for rapid Ca^{2+} uptake and thus actively shape the overall intracellular Ca^{2+} signaling. Their Ca^{2+} uptakes are mediated largely by mitochondrial Ca^{2+} uniporter (MCU) and regulated by a gate keeper protein mitochondrial Ca^{2+} uptake 1 (MICU1)[85]. The accumulated mitochondrial Ca^{2+} ions are quickly pumped back to cytosol by mitochondrial NCX and mitochondrial H^+/Ca^{2+} exchangers (HCX)[86]. A wide variety of studies reported the involvement of these mitochondrial Ca^{2+} handling proteins in cancer cell metabolism, apoptosis and proliferation. Overexpression of MCU is reported in the clinical estrogen receptor negative and basal-like breast cancer samples[87]. However, down-regulation of MCU in colon and prostate-derived cancers has been shown to promote increased proliferation and bestows resistance to cell death stimuli through diminished mitochondrial Ca^{2+} levels[88]. Down-regulation of MICU1, which results in mitochondrial Ca^{2+} overload, did not alter proliferation in HeLa cells; however, it triggers excessive mROS generation and significantly enhances sensitivity to apoptotic stress[85,89].

Table 1 Altered Ca^{2+} channels/transporters/pumps in cancers.

Channel/transporter		Cancer type	Changes	Ref.
IP_3R	IP_3R1	Glioma	Decreased	24
	IP_3R2	Lymphocytic leukemia	Increased	28
	IP_3R3	Glioma, gastric, colon, head and neck cancer	Increased/Mutation	24–27
Ca2+-ATPase	SERCA2	Colon cancer	Increased	32
	SERCA3	Gastric, lung, choroid plexus tumors, and in myeloid leukemia	Decreased	31
	SPCA1	Breast cancer	Increased	35
	SPCA2	Breast cancer	Increased	36
	PMCA1	Oral cancer	Decreased	39
	PMCA2	Breast cancer	mRNA elevated	37
	PMCA4	Colon cancer	Decreased	38
VGCC	$Ca_v1.2$	Colon and esophageal cancer	Increased	42
	$Ca_v2.3$	Glioma	Increased	42
	$Ca_v3.1$	Glioma	Increased	46
	$Ca_v3.2$	Prostate, ovarian, glioma, breast, esophageal, hepatoma, melanoma, and colon cancer	Increased	42–45
TRP	TRPC1	Breast cancer	Increased	49
	TRPC3	Ovarian and breast cancer	Increased	50, 51
	TRPC6	Esophageal, glioma and breast cancer	Increased	51, 57, 90
	TRPM1	Melanoma	Decreased	91
	TRPM7	Pancreatic and breast cancer	Increased	60, 92
	TRPM8	Pancreatic, prostate, bladder, breast, melanoma, colon and lung cancer	Increased	58,92, 93
	TRPV1	Bladder and prostate cancer	Decreased/Increased	94, 95
	TRPV2	Bladder, prostate cancer and hepatocarcinoma	Decreased/Increased	96
	TRPV4	Non-melanoma skin cancer, tumor endothelial cell derived prostate and breast cancer	Decreased	97–99
	TRPV6	Breast, prostate, lung, thyroid, colon and ovarian cancer	Increased	100–103
Orai & STIM	Orai1	Pancreatic adenocarcinoma, glioma, melanoma, breast, esophageal, renal, and NSCLC	Increased/Constitutive activated	6, 36, 65, 66, 74, 104–106
	Orai3	Breast, prostate and lung cancer	Increased	68, 76, 78
	STIM1	Hepatoma, melanoma, cervical, colorectal cancer, breast and pancreatic adenocarcinoma	Increased	66, 69, 104, 107–109
	STIM2	Breast, colorectal cancer and melanoma	Increased/Decreased	73,74,109, 110
Purinergic receptor	P2X3	Hepatoma	Increased	84
	P2X5	Melanoma, colorectal, brain, breast and renal cancer	Increased	42
	P2X7	Neuroblastoma, melanoma, leukemia, breast, prostate, papillary thyroid, pancreatic, colon, renal, cervical and B chronic cancer	Increased	42,80
	P2Y2	Highly metastatic breast cancer, hepatoma and colon cancer	Increased	81–83
	P2Y4	Colon cancer	Increased	83
MCU		Breast, colon and prostate cancer	Decreased/Increased	87,88

3. Drugs targeting Ca^{2+} channels/transporters/pumps for cancer treatment

The complexity of widespread Ca^{2+} channels/transporters/pumps with the diverse activation process, offers an abundance of potential targets for pharmacological regulation and cancer chemotherapy. Progress in understanding of the intracellular Ca^{2+} signaling network, especially the channels/transporters/pumps structure, has significantly advanced the field of drug design and development with particular focus on potentials and specific selectivity inhibitor or regulator. In this section, we attempt to summarize the known compounds or antibodies targeting these above mentioned cancer-involved Ca^{2+} channels/transporters/pumps, which have been studied in pre-clinical research or even in clinical trials (Table 2). A certain number of these compounds have been demonstrated with promising ability to be used in cancer therapy.

3.1. Ca^{2+}-ATPase inhibitors

The sustained high cytoplasm Ca^{2+} is toxic for cells by activating cell death signaling[4]. Ca^{2+}-ATPases can be easily targeted by shutting-down of these pumps to generate such toxic cytosolic Ca^{2+} concentrations for either apoptosis or necrosis. A PMCA selective inhibitor [Pt(O,O'-acac)(γ-acac)(DMS)] is used to rapidly induce apoptosis in MCF-7 cells, which may induce ROS in addition to cytosol Ca^{2+} elevation[117]. Our earlier work showed that the depletion of ER Ca^{2+} stores itself is sufficient to cause ER stress and to induce programmed cell death pathways[188]. A selective inhibitor of SERCA pump, thapsigargin (TG), is used to inhibit Ca^{2+} uptake into ER and deplete ER Ca^{2+} stores. The application of TG as chemotherapeutic agent has been extensively studied in prostate cancer and other cancers[14,112]. However, a barrier preventing the direct usage of TG as clinical effective drug is its non-selectivity since TG will destroy intracellular Ca^{2+} homeostasis not only in cancer cells but also in normal cells. Thus the research effort on development of TG as chemotherapy drug has been focused on tumor targeting. One successful example is G202, in which an analogue to TG is conjugated to prostate-specific membrane antigen (PSMA) targeting peptide. PSMA is a type II membrane carboxypeptidase and is overexpressed in prostate cancer cells and most tumor endothelial cells, but not in normal vasculature or normal tissue epithelium. As a prodrug, G202 itself is non-toxic since it cannot enter the cell due to its size. Once it reaches tumor, it binds with PSMA and subsequently PSMA can cleave the peptide and release active cytotoxic analog of TG. G202, later termed as mipsagargin, significantly inhibits tumor progression including prostate, breast and bladder cancers, while presenting minimally toxicity to the host animals[112]. G202 has showed promising results in several pre-clinical studies and is currently in phase II clinical trial for prostate cancer and progressive glioblastoma.

3.2. Voltage-gated Ca^{2+} channel inhibitors

The first well-studied family of compounds targeting Ca^{2+} signaling are the inhibitors for VGCCs, which are widely used in the cardiovascular or nervous system diseases[189]. As accumulating evidences reveal the important roles of VGCCs in a number of cancers, many investigators have launched the studies to repurpose the FDA approved drugs targeting VGCCs for cancer treatment[42]. In fact, as early as in 1990s, some structurally unrelated L-type VGCCs antagonists were tested for their potent inhibitory effects on breast tumor progression[190]. The dihydropyridine Ca^{2+} channel blocker, amlodipine, was found to inhibit the growth of human epidermoid carcinoma A431 cells both *in vitro* and *in vivo*, *via* arresting cell cycle at G1 phase and reducing phosphorylation of retinoblastoma protein, expression levels of cyclin D1 and cyclin dependent kinase 4[120]. Another interesting case is mibefradil, a T- and L-type Ca^{2+} channel blocker used for anti-hypertensive. It was later voluntarily withdrawn from market due to its side effect of inhibiting cytochrome P450 enzymes 2D6, 3A4 and p-glycoprotein. However, mibefradil was shown to be able efficiently to reduce tumor size, to improve the survival rate in glioma animal model as well as in a patient derived pancreas xenograft animal model[42,121]. Therefore, mibefradil was repurposed for pancreatic cancer and high-grade glioma therapy. FDA swiftly approved mibefradil as an orphan drug for pancreatic cancer treatment in 2008 and its use for glioma treatment has also been moved into clinical trial[191]. Moreover, a mibefradil derived novel compound, NNC-55-0396, was developed to selectively target Ca^{2+} channel and exhibits less inhibitory effect on cytochrome P450 3A4. This new derived mibefradil compound appears to be a promising chemotherapy drug for that it is able to effectively inhibit angiogenesis in cancer cell lines but with minimal off-target effect[42,119].

3.3. TRP channel regulators

The imidazole compound SKF-96365 and related antimycotic compounds including econazole, miconazole, and clotrimazole can inhibit CRACs and some TRP channels[192]. While SKF-96365 was firstly described to block receptor-mediated Ca^{2+} entry in human platelets, neutrophils and endothelial cells[193], it later was used to inhibit ovarian cancerous cell growth and tumorigenesis *via* reducing activities of different subtypes of TRPCs[194]. Treatment of SKF-96365 was reported to enhance radio-sensitization in glioblastoma, which contain high expressing levels of TRPC6 channels[90]. In addition, SKF-96365 can also cause cell cycle arrest at S and G2 phases in glioblastoma cells via enhancing reverse mode of the NCX1, independent of TRPCs[181].

Using a structure-based design, a synthetic compound TH-1177 mimicking dihydropyridines was developed as a TRPV channel blocker. It inhibits prostate cancer cell proliferation *in vitro* and *in vivo*[154]. However, there is one issue preventing TH-1177 from further clinical application. It preferentially inhibits TRPV5 but less effective for TRPV6 channel; whereas TRPV6 is the most abundant Ca^{2+} entry channel in prostate cancer cells with its expression level as high as 45-fold more than TRPV5. Thus, TH-1177 was further modified to possess high selectivity for TRPV6 and this new agent has been demonstrated significantly improved inhibitory effects on cell proliferation in prostate and breast cancer[152].

GSK1016790A is a selective TRPV4 channel agonist developed recently. It is at least 300-fold more potent than the commonly used TRPV4 activator 4α-PDD[142]. TRPV4 is able to regulate tumor angiogenesis and vessel maturation, thus GSK1016790A has been proposed to be used together with other anticancer drugs, such as cisplatin, to improve tumor penetration for more effective cancer therapy[98]. By mimicking the C-terminus of soricidin, two TRPV6 inhibitors, the SOR-C13 and SOR-C27 bind TRPV6 with high affinity in ovarian cancer cells. SOR-C13 is currently in phase I clinical trial for advanced cancers, in which

Table 2 Summary of compounds targeting Ca^{2+} channels/transporters/pumps.

Channel/Transporter		Compound	Mechanism	Cancer	Ref.
Ca^{2+}-ATPase	SERCA	Cyclopiazonic acid, thapsigargin, G202, KP1019 Saikosaponin-d, Alisol B	Inhibitor	Prostate, hepatoma, colon, cervical, breast cancer and nasopharyngeal	111–115
	SERCA2	RL71	Inhibitor	Colon cancer	116
	PMCA	[Pt(*O,O′*-acac)(γ-acac)(DMS)]	Inhibitor	Breast cancer	117
VGCC	T-type	KYS05047, mibefradil, NNC-55-0396, amlodipine	Blocker	Hepatoma, lung pancreatic cancer, epidermoid carcinoma and glioma	118–121
	T-type	Ghrelin	Increase protein expression	Prostate cancer	122
TRP	TRPA1	HC-030031	Inhibitor	–	123
		Polygodial and analog	Activator	Glioma, melanoma, uterine, lung and breast cancer	124
	TRPC	20-GPPD	Activator	Colon cancer	125
	TRPC	SKF96365, M804	Blocker	Glioma	126,127
	TRPC1	EVP4593	Inhibitor	Neuroblastoma	128
	TRPC4/5	(−)-Englerin A	Activator	Renal and colon cancer	129,130
	TRPC4/5	M804 analog, ML204	Inhibitor	–	126,131
	TRPC3/6	GSK2332255B, GSK2833503A	Inhibitor	–	132
	TRPC6	GaQ_3	Induce protein expression	Breast, lung, osteosarcoma and hepatoma	133
	TRPV	CPZ	Inhibitor	OSCC	134
	TRPV1	CBD, Capsaicin	Agonist	Colon cancer, renal carcinoma.	135–138
	TRPV2	2-APB, cannabinoid, lysophospholipid and probenecid	Agonist	Glioblastoma, bladder cancer	96,139,140
		Ruthenium red, TEA, TRIM, 4-aminopyridine, SKF96365 and tranilast	Antagonist	Breast cancer	96,139,141
	TRPV4	GSK1016790A	Agonist	Prostate cancer	98,142
		GSK2193874, RN-9893, BTP2	Inhibitor	–	143–145
	TRPM8	CBG, M8-B	Inhibitor	Lymphoma, lung, breast, prostate and skin pancreatic,	146–148
		D-3263	Agonist	Various advanced cancer	93,149
	TRPML	ML-SA1	Agonist	–	150
	TRPML1	MK6-83	Agonist	–	151
	TRPV6	TH-1177, Soricidin, SOR-C13 and SOR-C27	Inhibitor	Ovarian, prostate and brain cancer	152–154
Orai	CRAC	Carboxyamidotriazole, dihydropyridine, MRS-1844, MRS-1845, BTP2	Inhibitor	Hepatoma, lung, bladder, kidney, NSCLC, glioma and leukemia	155–159
	STIM1	ML-9	Translocation inhibitor	Prostate Cancer	160,161
	Orai1-STIM1	SKF96365	Inhibitor	Esophageal, breast and colon cancer	6,64,108
	Orai1	La^{3+}, Gd^{3+}, AnCoA4, SB01990, SPB06836, KM06293, RH01882, GSK-5503A, GSK-7975A, mAbs	Inhibitor	Lung cancer and glioma	65,162–166
	–	2-APB and its analogues, DPB-162AE and DPB-163AE	Inhibitor/Activator	Colon cancer and glioma	65,108,167,168
	–	RO2959	Inhibitor	–	169

Table 2 (*continued*)

Channel/Transporter		Compound	Mechanism	Cancer	Ref.
Purinergic receptor	–	Suramin	Inhibitor	Prostate cancer	170
	P2X7	AZ10606120, A-740003, A-438079, brilliant blue G, oxidized ATP	Inhibitor	Colon cancer and renal melanoma	171,172
	P2X2/3	A-317491, AF-353	Inhibitor	–	172
RyR	–	4-Chloro-*m*-cresol, caffeine and its analogs	Agonist	Breast and prostate	173,174
NCX	–	ORM-10103, KB-R7943, OSW-1, DMS, bepridil and benzothiazepine analogues, such as diltiazem, clonazepam and CGP-37157	Blocker	Leukemia, colon and brain cancer	175–180
		SKF96365	Enhancer	Glioma	181
		Ghrelin	Increase protein expression	Prostate cancer	122
IP_3R	–	Xestospongin B, xestospongin C	Inhibitor	Neuroblastoma, prostate and breast cancer	182–184
	IP_3R1	2-APB	Inhibitor	Gastric cancer	25,185,186
	IP_3R3	Heparin, caffeine	Inhibitor	Colon cancer and glioma	186,187

–Not Known

TRPV6 channels are normally overexpressed[153]. Another compound in phase I clinical trial with similar mechanism is D-3263. It is an activator for TRPM8 and induces cancer cell apoptosis, which is proposed to be used for patients with solid tumors[93].

Capsaicin, a well-known activator for TRPV1, was shown to induce apoptosis by its action on TRPV6 but independent on TRPV1, followed by activation of calpains in human small cell lung cancer cells (SCLC) *in vitro* and *in vivo*[101]. TRPV antagonist capsazepine (CPZ) was demonstrated to effectively inhibit oral squamous cell carcinoma cells (OSCC) growth *in vivo*. The anticancer mechanism of CPZ may also rely on ROS release, independent of TRPV1[134]. Subcutaneous injection of either capsaicin or CPZ significantly suppresses PC-3 tumor growth by inducing apoptosis of tumor cells *in vivo*, suggesting they are promising chemotherapy drugs[195]. Sesquiterpene (−)-englerin A is a selective and potent activator for TRPC4 and TRPC5, which results in massive Ca^{2+} influx followed by cell death and retarded tumor cell growth[129,130]. However, its severe lethal side effect must be resolved before it can be considered as a potential therapeutic agent. The natural compound, 20-GPPD, a metabolite of ginseng saponin, induces TRPC-mediated Ca^{2+} influx and apoptosis in CT-26 cells and reduces tumor mass by 75% *in vivo* although the exact molecular target remains unknown[125]. Some cannabinoid compounds, in particular cannabidiol (CBD), stimulate TRPV1 while the non-psychotropic cannabigerol (CBG) is an antagonist of TRPM8[146]. CBD displayed anti-invasive action in human lung carcinoma A549 cells, dependent on the effect of CBD cannabinoid receptor and TRPV1[196].

3.4. *Orai inhibitors*

Among many known compounds targeting CRAC or SOCE, the Orai channel blockers are particularly well studied. Because CRAC channels present highly selective Ca^{2+} conductance, they are subject to blockage by the trivalent ions La^{3+} and Gd^{3+}. Both La^{3+} and Gd^{3+} can directly block CRAC pore formed by the I–II loop region of Orai1. However, this effect is not specific for CRAC, as La^{3+} and Gd^{3+} also block other Ca^{2+} channels as well, such as Ca_v, TRP channel and PMCA[162,163,197].

The first Orai1 inhibitor used in cancer study is SKF-96365. Yang et al.[64], demonstrated that SKF-96365 can inhibit breast cancer cell migration *in vitro* and reduce tumor growth and metastasis *in vivo*. We also showed that SKF-96365 inhibited Orai1-mediated SOCE and intracellular Ca^{2+} oscillations in esophageal cancer cells and resulted in significant retarded tumor growth in nude mice[6].

Another commonly used SOCE inhibitor is 2-APB, which was initially identified as a noncompetitive antagonist of IP_3R (at rather high concentration ~100 μmol/L)[185]. The effects of 2-APB on SOCE are multifaceted. On one hand, 2-APB inhibits Orai1 current without interrupting STIM1 and Orai1 interaction[198]; on the other hand, it can directly activate Orai3 channel independent on store depletion or STIM1[199,200]. There is also a dose-dependent bimodal effect of 2-APB on SOCE, with strong enhancement at low doses (<5 μmol/L) and transient enhancement followed by inhibition at high concentrations (>20 μmol/L)[167,201]. Although several studies demonstrated that 2-APB effectively inhibit cancer cell proliferation and tumor progression, the non-selective and multiple-target nature renders 2-APB unsuitable for chemotherapy[25,108]. Much effort has been devoted to develop 2-APB derived compounds to overcome the obstacle. For example, DPB-162AE

and DPB-163AE are constructed as dimers of 2-APB. They are over 100-fold more potent than 2-APB on SOCE inhibition, without affecting IP_3R function at such concentrations[168]. Nevertheless, there will be a long journey before such compounds can be developed as effective chemotherapeutic drug.

Another line of research is screening of small-molecule compounds that bound to Orai1 and/or STIM1 in a microarray system containing minimal functional domains of STIM1 and Orai1. Some novel STIM–Orai inhibitors have been identified using this high-throughput screen approach, such as AnCoA4. AnCoA4 inhibits CRACs and attenuates T-cell activation both in *in vitro* and *in vivo*. It reduces the recruitment of Orai1 into puncta and also inhibits the activity of the constitutively active $Orai1^{V102C}$ channels, independent on STIM1[166].

ML-9 is an inhibitor for myosin light-chain kinase (MLCK) and appears to be able to disperse STIM1 puncta, thus to inhibit SOCE. Although its target and mechanism of action are unclear, ML-9 is the only known inhibitor so far to inhibit SOCE through interference with STIM1 translocation[160]. Later, ML-9 alone was proved to effectively induce prostate cancer cell death associated with autophagy in a concentration and Ca^{2+} dependent manner. Furthermore, combination of ML-9 and some existing anticancer drugs, such as docetaxel, significantly promotes cancer cell death, suggesting ML-9 as a promising adjuvant drug for chemotherapy[161].

RO2959 is a novel, potent and selective SOCE inhibitor (IC_{50}, ~40 nmol/L). It inhibits a wide range of Ca^{2+} dependent cellular functions including gene expression, cytokine production, and proliferation in T cells. To achieve the IC_{50} values at nmol/L level, it requires pre-incubation of cells for more than 30 min, which suggests that RO2959 may act on Orai1 channels indirectly[169]. The effect of RO2959 in cancer and molecular basis of drug action, including whether it affects the function and choreography of STIM1, are still unclear.

Another class of potent CRAC inhibitor is designed targeting the Ca^{2+} selectivity filter of Orai channel. In particular, E106 accounts for Ca^{2+} selectivity in Orai1 and can be blocked by extracellular protons[202]. This class of inhibitor includes SB01990, SPB06836, KM06293 and RH01882, which all present the capability to alter the pore geometry of Orai1 and diminishes SOCE[164].

Two pyrazole derivatives GSK-5503A and GSK-7975A slowly inhibit Orai1- and Orai3-mediated SOCE currents without affecting STIM1–Orai1 coupling. It takes a few minutes for the two compounds to have effects, suggesting that the mechanism is likely other than through the CRAC channel activation process[165]. The IC_{50} is increased 10-fold in the $Orai1^{E106D}$ and in 2-APB activated Orai3 channels, both of which are poorly selective for Ca^{2+} and exhibit wider pores than the $Orai1^{WT}$ channel[165,200,203]. Interestingly, these compounds also inhibit TRPV6 channels, possibly due to similarities between CRAC and TRPV6 channels in the target site[204]. The Pyr analogs, including Pyr2, 3, 6 and 10, show different selectivity on TRPC3 and Orai1/STIM1-mediated Ca^{2+} entry. Pyr10 is potent and selective for TRPC3-mediated responses (18-fold), and Pyr6 prefers Orai1/STIM1, while Pyr3 equally blocked the two channels[205]. The best-studied member of this group is Pyr2 (also known as BTP2 or YM-58483), a potent inhibitor for both CRAC and TRPC-mediated Ca^{2+} entry[127,157,206]. However, it also proposed that a key mechanism of BTP2 inhibition of Ca^{2+} influx and cytokine release might be related to its ability to depolarize the cell membrane *via* TRPM4 activation, thereby reducing the driving force for Ca^{2+} entry[145]. Synta 66 selectively inhibits I_{CRAC} in RBL-1 cells, which is structurally similar to BTP2 but contains a biphenyl group rather than the pyrazole ring in BTP2[207]. Compared with BTP2 and the GSK compounds, the speed of inhibition by Synta 66 is rather slow. It requires pre-incubation with cells for more than 1 h and its effect is poorly reversible. These data suggest that the pore blocking mechanism is unlikely the case for Synta66. Moreover, Synta66 has no effect on STIM1 puncta formation, suggesting that it does not inhibit the early steps of STIM1 activation and translocation to junctional ER-PM sites[208]. CM2489 and CM3457 are another two promising inhibitors for SOCE, demonstrated in lymphocytes and T cell-derived cytokine production[209]. CM2489 has completed phase I clinical trials for the treatment of moderate-to-severe plaque psoriasis. This is the first CRAC channel inhibitor to be tested on humans and represents a promising lead for the development of novel therapeutics for human diseases, including cancers.

Recombinant Orai1 monoclonal antibodies (mAbs) exhibit strong and specific binding against Orai1 at amino acid residues 210–217 in the second extracellular loop. These mAbs, especially 2C1.1, inhibit I_{CRAC} in Orai1 high expressed Jurkat T cells as well as HEK293[210]. Functional assays indicate that these mAbs strongly inhibited NFAT-dependent gene transcription in Jurkat cells or TG- and ionomycin-induced cytokine secretion from human T cells. Taking a similar approach, another specific anti-Orai1 mAb targeting the second extracellular loop, inhibits the proliferation of T cells and cytokine production both *in vitro* and *in vivo*. Further mechanistic studies suggested that mAb-targeted Orai1 proteins are internalized, which resulting in loss of functional SOCE activity[211]. Although the anti-Orai1 mAbs-based potential therapy is limited in immune diseases, it raises high hope of similar application for cancer treatment.

3.5. *Miscellaneous*

Many regulators targeting Ca^{2+} channels/transporters/pumps other than the above mentioned, have been used in various areas, such as immune suppression, anti-hypertension and anti-cancer. Xestospongin B as a specific IP_3R inhibitor has been demonstrated to reduce proliferation and colony formation ability, while induce necrotic death, specifically in tumorigenic breast cells, compared with non-tumorigenic cell lines[184]. Caffeine, a RyR agonist, can induce apoptosis in prostate cancer cells, while another agonist 4-chloro-*m*-cresol can inhibit the breast cancer cell growth[173]. Several compounds targeting NCX, such as OSW-1, showed apoptosis-induce function by causing mitochondrial Ca^{2+} overload in leukemia[174]. Brilliant blue G, a P2X7 antagonist, exhibits inhibitory effect on glioma growth. Emodin, a P2X non-specific inhibitor, reduces P2X7-mediated cancer cell migration. A number of P2X7 receptor regulators, such as antagonist A-438079 and A-740003 are mainly studied in pain relief. Since the P2 receptors play important roles in a certain number of cancers, it is reasonable to believe these antagonists may be potential effective anti-cancer drugs as well[172]. If that holds true, these compounds could exert dual functions as both chemotherapeutic agents and pain killer.

4. Conclusion and future directions

It is becoming evident that Ca^{2+} channels/transporters/pumps are involved in a wide range of cancers. Dysregulated Ca^{2+} homeostasis may play a role more like a “driver” than a “passenger” in carcinogenesis or tumorigenesis. As summarized in this review, this relatively new field has already importantly contributed to the

identification of possible chemotherapeutic agents for a certain number of cancers, with a few even moved to clinical trials. Since many of the Ca^{2+} channels/transporters/pumps may play a role in normal physiology and normal cell functions, one challenge in drug development targeting these Ca^{2+} signaling proteins is to identify their cancer specific properties. Moreover, it is also important to identify a set of the channels that contribute to the tumor development in a given patient tissue. Structure-based rational design of more potent, more specific and less off-target compounds targeting Ca^{2+} channels/transporters/pumps will likely provide promising leads for novel cancer treatment in the coming years.

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