Calcium ion (Ca\(^{2+}\)) is a ubiquitous and versatile signaling molecule controlling a wide variety of cellular processes, such as proliferation, cell death, migration, and immune response, all fundamental processes essential for the establishment of cancer. In recent decades, the loss of Ca\(^{2+}\) homeostasis has been considered an important driving force in the initiation and progression of malignant diseases. The primary intracellular Ca\(^{2+}\) store, the endoplasmic reticulum (ER), plays an essential role in maintaining Ca\(^{2+}\) homeostasis by coordinating with other organelles and the plasma membrane. Here, we discuss the dysregulation of ER-centered Ca\(^{2+}\) homeostasis in cancer, summarize Ca\(^{2+}\)-based anticancer therapeutics, and highlight the significance of furthering our understanding of Ca\(^{2+}\) homeostasis regulation in cancer.

The features of intracellular Ca\(^{2+}\) homeostasis

Calcium ion (Ca\(^{2+}\)) serves as a universal secondary messenger, involved in diverse biological processes such as proliferation, cell death, migration, and immune response [1]. Despite changes of Ca\(^{2+}\) regulation in cancer having been recognized for a long time, this area of research has only recently gained traction [2]. Accumulating evidence now demonstrates that dysregulated Ca\(^{2+}\) homeostasis is an essential driver of cancer initiation and progression and also influences the treatment responses of cancer patients [3]. The increased interest in this field is attributed to our in-depth understanding of the cellular mechanisms responsible for achieving Ca\(^{2+}\) homeostasis, as well as the successful application of specific Ca\(^{2+}\) signal-targeted therapies, for example, in cardiovascular and neuronal diseases [4,5]. Consequently, Ca\(^{2+}\) signaling has become a highly attractive target for the development of novel anticancer drugs [6].

Playing an essential role in cell fate regulation, it is not surprising that Ca\(^{2+}\) signaling is rigorously regulated by a complex set of components, including Ca\(^{2+}\) pumps, channels, and exchangers [2]. These Ca\(^{2+}\)-regulating ‘toolkits’ are distributed at plasma or intracellular organelle membranes, acting to maintain a low concentration of cytosolic free Ca\(^{2+}\) against steep gradients of extracellular and organelle sequestered Ca\(^{2+}\). The ER is the primary site of Ca\(^{2+}\) storage [1], along with additional stores like the Golgi and, more recently, lysosomes [7,8]. The Ca\(^{2+}\) concentration within mitochondria is relatively low under resting conditions. Nonetheless, upon activation by diverse stimuli or signaling events, almost all organelles are involved in orchestrating a complex response in order to maintain Ca\(^{2+}\) homeostasis or transmit Ca\(^{2+}\) signal [1]. As the major Ca\(^{2+}\) store, the ER is central to such a response. The regulation of Ca\(^{2+}\) homeostasis and Ca\(^{2+}\) signaling has been extensively reviewed elsewhere [2,3]. Here, we focus on our recent understanding of ER-centered Ca\(^{2+}\) homeostasis regulation and its association with cancer.
Achieving organelle calcium homeostasis

ER and ER-plasma membrane communications in calcium homeostasis

The ER plays a central role in protein and lipid synthesis and is also the largest intracellular Ca\(^{2+}\) reservoir [9]. The high Ca\(^{2+}\) concentration provides the optimal environment for the activity of local enzymes required for physiological functions of the ER, whilst contributing to the maintenance of low cytosolic Ca\(^{2+}\) under resting conditions. Upon stimulus, the ER releases Ca\(^{2+}\), which facilitates the rapid transmission of Ca\(^{2+}\) signals, leading to distinctive biological outcomes, such as proliferation and cell death [1,3].

ER Ca\(^{2+}\) homeostasis is determined by a finely tuned balance of Ca\(^{2+}\) influx and outflux. Sarco(plasmic-endoplasmic type ATPases (SERCA\(_s\)) (see Glossary), the ER-resident Ca\(^{2+}\) pumps, are responsible for ER Ca\(^{2+}\) influx [9]. Whereas Ca\(^{2+}\) outflux is mediated by Ca\(^{2+}\) channels, such as inositol 1,4,5-trisphosphate receptors (IP3R\(_s\)), in response to the enhanced IP3 upon hormone or growth factor stimulation [9], or ryanodine receptors (RyR\(_s\)), in response to extracellular Ca\(^{2+}\) influx [9]. The latter process is known as Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR) [9]. In response to a reduction in Ca\(^{2+}\) concentration, the ER-resident transmembrane protein, stromal interaction molecule 1 (STIM1), is activated, which interacts with and activates the calcium release-activated calcium modulator 1 (ORAI1) channel, localized in the plasma membrane, leading to extracellular Ca\(^{2+}\) influx and the subsequent SERCA\(_2\)-mediated ER Ca\(^{2+}\) refilling, a process named store operated Ca\(^{2+}\) entry (SOCE) [9]. The transmembrane and coiled-coil domains 1 (TMCO1) transmembrane protein, localized within the ER, controls how cells restore ER homeostasis in the case of Ca\(^{2+}\) overload. TMCO1 is present as an inactive monomer under resting conditions. During ER Ca\(^{2+}\) overload, it forms a selective Ca\(^{2+}\) channel through monomer-to-tetramer transformation, leading to ER Ca\(^{2+}\) homeostasis recovery, a process known as store overload-induced Ca\(^{2+}\) release (SOICR) [10] (Figure 1A).

ER–organelle communication in calcium homeostasis

Enhanced cytosolic Ca\(^{2+}\), sourced from either the extracellular space or the ER, can trigger mitochondrial Ca\(^{2+}\) uptake [1]. The latest evidence has demonstrated that the two distinct organelles, the ER and mitochondria, are physiologically and functionally connected at multiple sites (called mitochondria-associated ER membrane (MAM)) involved in various biological processes, including regulating Ca\(^{2+}\) homeostasis [1]. Mechanistically, IP3R\(_s\) and voltage-dependent anion channels (VDAC\(_s\)) form a complex spanning the MAM, promoting mitochondrial Ca\(^{2+}\) uptake in the outer mitochondrial membrane [9]. In contrast, the Ca\(^{2+}\) influx through the inner mitochondrial membrane is mainly driven by a negative membrane potential (ΔΨ\(_m\): ~180mV) and Ca\(^{2+}\) gradient through the mitochondrial calcium uniporter (MCU) [1] (Figure 1B).

Lysosomes are typically considered as organelles that deal with intracellular waste. They are now known to be significant Ca\(^{2+}\) stores, acting as functional hubs in regulating Ca\(^{2+}\) homeostasis along with the ER [8]. An increase in local cytosolic Ca\(^{2+}\) at the ER–lysosome interface sensitizes IP3R\(_s\), thus evoking Ca\(^{2+}\) transport from the ER to lysosome [8]. The activation of nicotinic acid adenine dinucleotide phosphate (NAADP)-regulated two-pore channels (TPC\(_s\)) [11] or mucolipin (MCOLN) family of transient receptor potential (TRPML) [12] on lysosomes can elicit a local ER Ca\(^{2+}\) release in a process similar to CICR [13] (Figure 1C).

The ER coordinates with other organelles in maintaining Ca\(^{2+}\) homeostasis (Figure 1). Upon stimulation, Ca\(^{2+}\) signal is activated and the subsequent biological outcomes are determined by the magnitude, frequency, and localization of Ca\(^{2+}\) flux, processes linked to carcinogenesis.

Glossary

Adriamycin: a chemotherapeutic agent that acts as an oxidative stress mediator to promote oxidative stress-induced apoptosis.

Ca\(^{2+}\)-induced Ca\(^{2+}\) release (CICR): a process whereby Ca\(^{2+}\) influx across plasma membranes can trigger ER Ca\(^{2+}\) release by activating ryanodine-sensitive receptors.

Celastrol: a topoisomerase II inhibitor with neuroprotective and anti-inflammatory properties. It can inhibit SERCA and induce autophagy by mobilization of cytosolic Ca\(^{2+}\).

Cisplatin: a chemotherapy drug that can induce apoptosis; it is approved for treatment of cancers such as bladder, lymphoma, cervical, and lung cancers.

Inositol 1,4,5-trisphosphate receptors (IP3R\(_s\)): an ER Ca\(^{2+}\) channel that can release ER Ca\(^{2+}\) to mitochondria or lysosomes; its isoforms include IP3R1, IP3R2, and IP3R3.

Mitochondria-associated endoplasmic reticulum membrane (MAM): the connected sites of ER and mitochondria that are involved in some biological processes, such as regulation of Ca\(^{2+}\) homeostasis.

Oxaliplatin: a cytotoxic chemotherapy drug that can induce a rise in intracellular Ca\(^{2+}\) by stimulating Ca\(^{2+}\) influx.

Sarcoplasmic-endoplasmic type ATPases (SERCA\(_s\)): an ER Ca\(^{2+}\) pump that can refill the ER from cytosol; its isoforms include SERCA1, SERCA2, and SERCA3.

Store operated Ca\(^{2+}\) entry (SOCE): a major method of Ca\(^{2+}\) entry for nonexcitable cells. When the ER Ca\(^{2+}\) is depleted, STIM1 can recruit and bind with ORAI to influx the extracellular Ca\(^{2+}\) and refill the ER by SERCA.

Store overload-induced Ca\(^{2+}\) release (SOICR): a process that can release ER overloaded Ca\(^{2+}\) to mitochondria or maintain the ER Ca\(^{2+}\) homeostasis.

Thapsigargin (TG): a potent, noncompetitive inhibitor of the SERCA, which acts as an ER stress inducer to promote ER stress-induced apoptosis.

Transmembrane and coiled-coil domains 1 (TMCO1): an ER Ca\(^{2+}\) channel that can be activated during ER Ca\(^{2+}\) overload, to recover the ER Ca\(^{2+}\) homeostasis.

Tumor necrosis factor α (TNF-α): a pleiotropic proinflammatory cytokine known for its ability to induce cell death in target cells.
Figure 1. A graphic summary of calcium homeostasis achievement. (A) Endoplasmic reticulum (ER) and ER–plasma membrane communications. ER-resident Ca$^{2+}$ pump proteins sarcoplasmic-endoplasmic type ATPases (SERCA) transport Ca$^{2+}$ from the cytoplasm into the ER. Ca$^{2+}$ channel proteins inositol 1,4,5-trisphosphate receptors (IP3Rs) mediate ER Ca$^{2+}$ release, in response to the enhanced IP3, a mediator of the GPCR or growth factor signaling. Another family of ER-resident channel proteins, RyRs, is sensitive to the changes of cytosolic Ca$^{2+}$ that is activated by cytosolic Ca$^{2+}$ flux, a process named Ca$^{2+}$-induced Ca$^{2+}$ release (CICR). In the case of ER Ca$^{2+}$ concentration reduction, stromal interaction molecule (STIM) is activated, which subsequently interacts with and activates plasma membrane-localized Ca$^{2+}$ channel ORAI1, leading to extracellular Ca$^{2+}$ being influxed and the subsequent SERCA-mediated ER Ca$^{2+}$ refilling, a process named store operated Ca$^{2+}$ entry (SOCE). Whereas when ER Ca$^{2+}$ is overloaded, transmembrane and coiled-coil domains 1 (TMCO1) is activated and it mediates ER Ca$^{2+}$ release, a process called store overload-induced Ca$^{2+}$ release (SOICR). (B) ER–mitochondria communications. ER and mitochondria are physically and functionally connected with each other by a

(Figure legend continued at the bottom of the next page.)
Disturbed organelle Ca\textsuperscript{2+} homeostasis and tumorigenesis

Given their key roles in Ca\textsuperscript{2+} homeostasis, the expression and activity of Ca\textsuperscript{2+} pumps, channels, and exchangers are frequently altered in human cancers [3]. Table S1 (in the supplemental information online) provides a summary of differential isoform expression and cancer type-specific dysregulation of Ca\textsuperscript{2+} homeostasis. This dysregulation in turn leads to increased cell proliferation, migration, resistance to apoptosis, and immune evasion, which are discussed in further detail later.

Disturbed organelle calcium homeostasis and cell proliferation

Under physiological conditions, Ca\textsuperscript{2+} signaling is controlled in a cell cycle-dependent manner. Some IP3R family members have been linked to cell senescence [14,15]. Although it remains to be determined whether these mechanisms directly confer carcinogenesis sensitivity, IP3R knockout in thymocytes was found to decrease proliferation and suppress the development of acute lymphoblastic leukemia [16]. Among the three IP3R family proteins, IP3R3 expression is frequently upregulated in cancers (Table S1 in the supplemental information online). Genetic or pharmacological inhibition of IP3R3 significantly reduces cancer cell proliferation [17–19], implying IP3R3 is a potential therapeutic target to reduce cancer cell growth.

The association between SOCE and proliferation has also been established. A potent SOCE inhibitor, RP4010, produces a dramatic antiproliferation effect by inducing G0/G1 arrest in esophageal cancer [20]. Whereas knocking down STIM1 in cervical cancer cells arrests cell cycle progression at S and G2/M phases [21], suggesting that the SOCE components may act by controlling distinct cell cycle checkpoints, in a context-dependent manner.

The low-level, constitutive Ca\textsuperscript{2+} transfer from ER to mitochondria is critical for cancer cell survival and proliferation [22,23]. Mitochondrial Ca\textsuperscript{2+} accumulation activates Ca\textsuperscript{2+}-sensitive dehydrogenases of the tricarboxylic acid cycle and is thus critical for the biosynthetic and bioenergetic needs of cancer cells [23,24]. The involvement of MAM in regulating cell proliferation is exemplified by ER-resident IP3R (as discussed earlier) and additionally by mitochondrial VDAC1 in lung cancer [25] and the MCU in colorectal cancer [26,27]. Dysregulated Ca\textsuperscript{2+} homeostasis has been shown to promote cell proliferation with a high energy expenditure, which provides potential vulnerable targets in cancer cells under metabolic stress [24,28].

Disturbed organelle calcium homeostasis and resistance to cell death

A moderate Ca\textsuperscript{2+} signal is essential for cell proliferation, while massive cytosolic Ca\textsuperscript{2+} influx or mitochondrial Ca\textsuperscript{2+} overload triggers cell death [29]. SERCAs have been recently shown to protect cancer stem cells (CSCs) from glucose starvation-induced apoptosis by limiting cytosolic Ca\textsuperscript{2+} sourced from the ER [30]. We have reported that the SOICR channel protein TMCO1 promotes tumor growth and protects colon cancer cells from staurosporine-induced apoptosis, by limiting cytosolic Ca\textsuperscript{2+} dynamics [31]. Another study reported that TMCO1 inhibits tumor growth in urinary bladder urothelial carcinoma, but whether this effect is related to its ER Ca\textsuperscript{2+} regulatory activity remains to be determined [32]. It is possible that TMCO1 has a Ca\textsuperscript{2+}-independent function, or it acts differentially in cancer cells in a context-dependent manner. Undoubtedly, researching the actions of TMCO1 in additional cancer cells will further guide TMCO1-targeted anticancer therapies.

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microdomain called mitochondria-associated ER membrane (MAM). A series of protein are localized in MAMs (Grp-75, VDAC1, and IP3R) and regulate Ca\textsuperscript{2+} release from the ER and an efficient mitochondrial Ca\textsuperscript{2+} uptake. (C) ER–lysosome communications. Lysosomal Ca\textsuperscript{2+} deletion triggers IP3R-mediated Ca\textsuperscript{2+} release from ER and subsequent lysosome Ca\textsuperscript{2+} reuptake through Ca\textsuperscript{2+} transporter or Ca\textsuperscript{2+/H\textsuperscript{+}} exchanger (CA). Ca\textsuperscript{2+} released from lysosome by nicotinic acid adenine dinucleotide phosphate (NAADP)-evoked two-pore channel (TPC) activation, or the activation of TRPML1 can subsequently induce RyR-mediated ER Ca\textsuperscript{2+} release, a process similar to CICR. See also Table S1 in the supplemental information online. Abbreviations: MCU, mitochondrial calcium unipporter; ORAI1, calcium release-activated calcium modulator 1.
Increased Ca\(^{2+}\) influx mediated by SOCE is another trigger of cytosolic Ca\(^{2+}\)-induced apoptosis. Loss of STIM1 has been shown to abolish cisplatin-induced apoptosis in non-small cell lung carcinoma cells [33]. Similar effect of ORAI1 was also detected in prostate cancer cells treated with thapsigargin (TG), tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), and cisplatin/oxaliplatin [34].

At the MAM, IP3R and VDAC isoforms act in stimulus and context-dependent ways. Increased IP3R3 expression or activities [18,35] induces proliferation as well as apoptosis resistance in multiple cancer cells. Paradoxically, IP3R3 elicits proapoptotic effects in ovarian and lung cancer cells, resulting in cisplatin sensitivity by enhancing Ca\(^{2+}\) transfer from the ER to mitochondria [36]. Additionally, anti- and proapoptotic functions of IP3Rs have been assigned to IP3R3 and IP3R1, respectively, in the same cancer context [37]. Why IP3R isoforms produce such diverse functional outcomes still needs to be further explored. Similarly, VDAC1 promotes apoptosis by facilitating mitochondrial Ca\(^{2+}\) influx [38], while VDAC2 protects cells from apoptosis, possibly independently of Ca\(^{2+}\) signal transmission [38]. In line with this finding, inhibition of ER-to-mitochondria Ca\(^{2+}\) transfer has recently been proposed as a general strategy to target apoptosis in cancer cells [28].

Disturbed organelle calcium homeostasis and cancer metastasis

Metastasis is a complex multistep process, which accounts for more than 90% of cancer mortality [39]. The overexpression of SOCE components is associated with poor outcomes in patients with colorectal cancer [39]. Consistently, STIM1- and ORAI1-mediated Ca\(^{2+}\) oscillations promote cancer cell invasion by orchestrating invadopodium assembly and extracellular matrix (ECM) degradation [40]. SOCE blockade inhibits metastasis in vivo and in vitro [40,41].

Ca\(^{2+}\) flux at the MAM may also affect cancer metastasis, for example, VDAC1 promotes reactive oxygen species (ROS) production in lung cancer cells [25]. Conversely, the MCU promotes pancreatic ductal adenocarcinoma cell metastasis by activating the KEAP1-NRF2 antioxidant program [42]. A variety of Ca\(^{2+}\) channels localized in the membrane of lysosomes have been shown to regulate invasion or migration of liver, breast, and lung cancer cells, through modulating the local and global intracellular Ca\(^{2+}\)-mediated lysosomal exocytosis [5]. Whether ER–lysosome communications are involved in these processes remains to be explored. In addition to ECM remodeling, increased metastasis has been linked to angiogenesis. STIM1 or TRPML1 is able to promote angiogenesis, which possibly contributes to the increased metastasis observed in cancer cells that overexpress STIM1 or TRPML1 [21].

Disturbed organelle calcium homeostasis and cancer immunity

An increase in the intracellular Ca\(^{2+}\) concentration is required for a variety of immune responses, for which the SOCE is essential [43]. Defects in SOCE, caused by STIM1 or ORAI1 depletion, result in the dysfunction of a variety of immune cells [43]. Given the essential role of immune clearance in cancer, an increasing number of studies have established the connection between SOCE-regulated immune response and carcinogenesis. For example, mice with a STIM1 conditional knockout in CD8\(^{+}\) T cells lose their ability to engulf melanoma and colon carcinoma cells, both in vivo and in vitro [44]. Alternatively, ablation of STIM1 in mouse myeloid cells impairs crosspresentation and dendritic cell (DC) migration, leading to impaired cytotoxic T cell activation and reduced cancer cell clearance [45].

Recently, SERCA has been shown to regulate V(D)J recombination [46], and IP3R influences DC activities [47]; therefore, it is likely that Ca\(^{2+}\) modulators are commonly involved in immune responses. However, the significance of such mechanisms in cancer immunity remains unclear. It should be noted that inhibition of glutamine utilization leads to impaired SERCA activity in cancer
cells, which results in upregulation of programmed cell death protein-ligase 1 (PD-L1) expression, a representative immune checkpoint [48], suggesting that Ca\(^{2+}\) modulators may regulate immune sensitivity by a cancer cell intrinsic mechanism.

**Modulating organelle Ca\(^{2+}\) homeostasis: emerging roles of oncogenes and tumor suppressors**

The involvement of Ca\(^{2+}\) signals in carcinogenesis and metastasis has also been evidenced by the fact that classic cancer-driven events disturb Ca\(^{2+}\) homeostasis, either directly or indirectly, through modulating Ca\(^{2+}\) pumps or channels (Figures 2 and 3).

**Oncogene regulation of calcium homeostasis**

The Kirsten rat sarcoma 2 viral oncogene homolog (KRAS) is the most frequently mutated oncogene in human cancers [49]. Inhibition of ROS-modulated and transient receptor potential cation channel subfamily M (melastatin) member 8 (TRPM8)-mediated extracellular Ca\(^{2+}\) uptake, STIM1-induced SOCE, IP3R isoform switch, or SERCA2b expression at the ER are...
representative downstream events of KRAS-driven tumorigenesis [50–52]. These data suggest that modulating Ca\(^{2+}\) homeostasis may achieve clinical benefits in KRAS mutant cancers.

The B cell lymphoma 2 (BCL-2) family of proteins play essential roles in cancer, which were initially attributed to their regulation of apoptosis in mitochondria [53,54]. Later studies revealed that multiple BCL-2 proteins can localize at the ER, where they modulate ER Ca\(^{2+}\) homeostasis or influence MAM functions by directly or indirectly targeting IP3R, RyR, and VDAC1 [55–57]. These different regulatory mechanisms provide potential strategies for BCL-2 family-targeted therapies. Promisingly, peptides aiming to disrupt IP3R/BCL-2 or BCL2L10 interactions have been developed in animal models for the treatment of B cell lymphoma [58] and breast cancer [59].

The oncogene inhibitor of apoptosis-stimulating protein of p53 (iASPP) is highly expressed in various tumors, such as oral squamous cell carcinoma [60], cervical cancer [61], and ovarian cancer [62]. Previous studies indicate that iASPP mainly exerts its procancer function by inhibiting the activity of p53 [63] or promoting the activity of NRF2 [64]. Zheng \textit{et al.} revealed an unexpected function of iASPP in lowering ER Ca\(^{2+}\) content. iASPP does this by specifically stabilizing TMCO1. Mechanistically, iASPP directly binds with the ER-associated degradation E3 ligase, glycoprotein 78 (Gp78), and prevents it from binding with TMCO1, leading to a reduced Gp78-mediated TMCO1 protein degradation in colon cancers [31].

There are additional oncogenes that have been reported to regulate Ca\(^{2+}\) homeostasis, mainly by controlling the ER Ca\(^{2+}\) transporter IP3Rs, such as modulating IP3Rs stability by gamma-
butyrobetaine hydroxylase 1 (BBOX1) [35] and signal transducer and activator of transcription 3 (STAT3) [65] or inhibiting transcription by pyruvate kinase M2 (PKM2) methylation [66]. Methylated PKM2 also inhibits IP3R activity by binding with IP3Rs at ER. Akt binds and phosphates IP3R and thus inhibits its channel activities and the subsequent Ca2+ flux-induced apoptosis. Recently, the protumorigenic activity of SERCA has been linked to Notch1 [67] and Wnt signaling [68] and TRPML1 has been shown to modulate HRAS signaling, which could provide alternative therapeutic strategies to target cancer cells with specific genetic backgrounds [69] (Figure 2).

Tumor suppressors regulate calcium homeostasis

Tumor protein p53 (TP53) mutations are detected in approximately 50% of tumors. In addition to the localization at the nucleus or mitochondria, p53 can be localized at the ER upon chemical activation through chemotherapeutic agents, such as adriamycin, or by the oxidative stress mediator, H2O2. Following this, p53 directly binds to SERCA, altering its oxidative state, which results in increased ER Ca2+ loading. Activation of the p53-SERCA axis subsequently enhances Ca2+ flux from the ER to mitochondria, leading to enhanced apoptosis [70].

Tumor suppressors can modulate Ca2+ homeostasis by counteracting with the aforementioned oncogene functions. Bax and Bak regulate Ca2+ homeostasis by counteracting with Bcl-2 and Bcl-xl, facilitating IP3R-mediated cell death. PML recruits PP2a, which also prevents AKT-dependent phosphorylation of the IP3R [71]. Loss of phosphatase and tensin homolog (PTEN) is frequently reported in human cancers. In addition to the cytosol, PTEN directly interacts with IP3R in the ER membrane and MAMs and protects IP3R from AKT-mediated phosphorylation, promoting Ca2+ release from the ER [72]. PTEN also has a phosphorylation-independent function, competing with the ubiquitin ligase F-box and leucine rich repeat protein 2 (FBXL2) in binding with IP3R3 [73]. BRCA1-associated protein 1 (BAP1) [74] and BCL-2-related ovarian killer (BOK) [75] have also been found to stabilize IP3R, leading to increased apoptosis sensitivity. Moreover, SMARCA4/2 [36] elicits similar outcome by promoting IP3R transcription. Together, these findings point to a view that Ca2+ homeostasis dysregulation is widely involved in tumor-driven events, providing potential new therapeutic directions for tumor therapy (Figure 3).

Therapeutic value of manipulating Ca2+ homeostasis in tumor cells

Increasing our understanding of the intracellular Ca2+ signaling network has greatly advanced the field of drug design and drug application in clinics. Chemotherapy is the most often used cancer treatment, but despite initial patient benefit, drug resistance is often inevitable. Unraveling the comprehensive mechanisms of a drug’s actions may provide combination or alternative strategies to improve patient outcomes. Anticancer drugs have multiple modes of action, what’s more, many of them have common functions in regulating Ca2+ homeostasis. One example is DNA damage reagents, such as cisplatin and doxorubicin. The expression or activities of numerous Ca2+ modulators, such as IP3R, VDAC1, and RyR, are changed by drug treatments, leading to cytosolic Ca2+-induced or mitochondrial apoptosis [76]. Another example is the microtubule inhibitor, paclitaxel, which elevates cytosolic Ca2+ levels by promoting mitochondrial ROS overproduction-induced cell death [77,78], or by interfering with the function of BCL-2 at the ER [79].

In light of the aforementioned findings, carboxyamidotriazole (CAI), a Ca2+ channel blocker, was found to inhibit tumor cell proliferation, metastasis, and angiogenesis. CAI platinum-based chemotherapy prolonged the survival of patients in a trial with non-small cell lung cancer [80]. Min et al. screened an FDA-approved compound library, which led to the discovery of four voltage-gated Ca2+ channel blockers (manidipine, lacidipine, benidipine, and lomerizine) [81]. These blockers, given in combination with cisplatin, exhibited a greater inhibitory effect on the viability and proliferation of ovarian CSCs [81]. Additional chemotherapeutic drugs have been shown to
modulate Ca\(^{2+}\) signals, leading to an anticancer effect, although the underlying molecular mechanisms warrant further exploration [76].

It should also be noted that an increase in intracellular Ca\(^{2+}\) does not always result in increased cancer cell death. The antimalarial drug, artemisinin, has shown its potential in the treatment of cancer by inhibiting SERCA activity. However, the transient increase of intracellular Ca\(^{2+}\) subsequently phosphorylates and activates the transcription factor hypoxia-inducible factor 1-alpha (HIF-1\(\alpha\)) through the activation of calmodulin-dependent kinase II. This in turn induces expression of glycoprotein P and thus compromises the antitumor effects of doxorubicin [82]. These data highlight the complexity of Ca\(^{2+}\) signaling and the need to increase our understanding of Ca\(^{2+}\) homeostasis in the context of cancer.

Given the fundamental roles of Ca\(^{2+}\) modulators in cancer, attempts have been made to establish reagents that will target them. Many activators and inhibitors have been developed and their potential to treat cancers has been tested. For example, pharmacological activation of the transient receptor potential vanilloid-type 4 (TRPV4) with the drug GSK1016790A reduces the viability of breast cancer in vitro [83], while the FDA-approved calcium channel blocker, amlodipine, significantly enhances the therapeutic response of tumor cells to gemcitabine chemotherapy [84].

SERCA is a promising target that is gaining attention. Celastrol stimulates Ca\(^{2+}\)-mediated autophagy, sensitizing drug-resistant cancer cell responses to apoptosis by targeting SERCA [85]. The curcumin analog, F36, also has potential to inhibit SERCA, which was reported to induce ER stress-related apoptosis in colorectal cancer [86]. Additional targeted pharmacological inhibitors have been shown to block cell migration and increase apoptosis in various cell lines or animal models, these include the imidazole derivative SKF-96365, a SOCE inhibitor [87]; Synta66, an ORAI1 inhibitor [88]; JQ-FT and stemphol, SERCA inhibitors [89,90]; and 2-aminoethoxydiphenyl borate (2APB), an IP3R blocker [88].

Immunotherapy, due to its long-lasting efficacy in the treatment of advanced solid tumors, has become one of the most promising anticancer strategies in the clinic [91]. As described earlier, Ca\(^{2+}\) channel activation is required for an immune response, while dysregulated Ca\(^{2+}\) homeostasis in cancer cells can lead to immune cell evasion [92]. It is logical, therefore, to design a therapeutic strategy to combine immune checkpoint blockades with Ca\(^{2+}\)-based treatments, to achieve better outcomes. Notably, there are current projects underway that introduce a cytotoxic dose of Ca\(^{2+}\) into tumors, in combination with immuno therapies, using nano-techniques, which are so far exhibiting promising antitumor effects in animal experiments [93,94].

**Concluding remarks**

The cellular distribution of Ca\(^{2+}\) is highly varied, represented by a 2000-fold change in concentration gradient across the ER membrane [1]. The ER, along with other organelles, assures the rapid and precise control of Ca\(^{2+}\) levels. The Ca\(^{2+}\) signal is intrinsically complex and sensitive to the spatial and temporal changes of Ca\(^{2+}\) levels. The nuanced changes of Ca\(^{2+}\) can result in dramatic functional consequences. How can Ca\(^{2+}\) signals be precisely controlled and specific cellular outcomes, such as cancer cell death, be reached without toxicity to healthy cells?

Under normal conditions, complex negative and positive feedback mechanisms warrant further exploration [76].

The fundamental roles of Ca\(^{2+}\) signals have been delineated in nonmalignant cells. How can the dysregulated Ca\(^{2+}\) homeostasis in cancer cells be specifically targeted and how can optimal outcomes be achieved through cancer cell-autonomous and nonautonomous mechanisms involved in immune modulation.

The heterogeneity of tumor cells is a long recognized and poorly understood cancer feature. Ca\(^{2+}\) modulators can be either activated or inactivated in a cancer type- and isoform-dependent manner. The underlying mechanisms controlling the paradoxical and controversial functions of Ca\(^{2+}\) modulators remain to be determined.
remain (see Outstanding questions). Despite numerous unaddressed questions in the field, a thorough and complete understanding of the regulatory mechanisms underlying Ca\textsuperscript{2+} homeostasis in cancer lies at the forefront of unlocking exciting new avenues in the development of novel cancer therapeutics.

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