**Biophysics Reports**

REVIEW

*Special Topic - CALCIUM SIGNALING*

# Ca²⁺ homeostasis: a potential target for cancer therapies

**Min Su**[1,2,#], **Shanliang Zheng**[1,2 ✉ #], **Hao Liu**[1,2], **Tie-Shan Tang**[3,4,5], **Ying Hu**[1,2 ✉]

1 School of Life Science and Technology, Harbin Institute of Technology, Harbin 150001, China
2 Key Laboratory of Science and Engineering for the Multi-modal Prevention and Control of Major Chronic Diseases, Ministry of Industry and Information Technology, Department of Medicine and Health, Zhengzhou Research Institute of Harbin Institute of Technology, Zhengzhou 450000, China
3 State Key Laboratory of Membrane Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China
4 Beijing Institute for Stem Cell and Regenerative Medicine, Beijing 100101, China
5 University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing 100101, China

**Abstract**    Calcium ions (Ca²⁺) play a crucial role as secondary messengers in both excitable and non-excitable cells. A complex system of proteins and molecules involved in calcium handling allows Ca²⁺ signals to be transduced. In cancer cells, mutations, aberrant expression, and dysregulation of these calcium handling toolkit proteins disrupt the normal Ca²⁺ flux between extracellular space, cytosol, endoplasmic reticulum and mitochondria, as well as the spatio-temporal patterns of Ca²⁺ signalling. This leads to the dysregulation of calcium-dependent effectors that control key signaling pathways involved in cancer cell proliferation, survival and invasion. Although there has been progressing in understanding the remodelling of calcium homeostasis in cancer cells and identifying key calcium transport molecules that promote malignant phenotypes, much work remains to be done to translate these fundamental findings into new tools for diagnosing and treating cancer by targeting Ca²⁺ homeostasis.

**Keywords**    Calcium homeostasis, Cancer, Therapy

## INTRODUCTION

As the most versatile second messenger *in vivo*, calcium ions (Ca²⁺) are involved in a wide variety of cellular and physiological processes, including proliferation, cell death, migration, gene transcription, muscle contraction, *etc*. (Fiorio Pla and Gkika 2020). Notably, accumulating evidence over the past decade has shown that dysregulation of Ca²⁺ homeostasis is an important driving force in malignant transformation, tumour progression and angiogenesis (Marchi *et al.* 2020). Here, we focus on advances in the understanding of Ca²⁺ signalling behaviour and its role in tumour initiation, progression and treatment.

Under physiological conditions, Ca²⁺ concentrations in cells are maintained in a stable state with a gradient difference of Ca²⁺ by a series of Ca²⁺ channels and pumps. The cytosolic Ca²⁺ concentration needs to be maintained at a low level (~100 nmol/L), approximately $10^4$-fold lower than the extracellular milieu (Marchi *et al.* 2020). In addition to the exchange with the extracellular Ca²⁺, there are also several Ca²⁺ storage sites within the cell, such as the endoplasmic reticulum (ER) (~0.5 mmol/L) (Kim *et al.* 2021), Golgi (~200 μmol/L) (Lissandron *et al.* 2010), lysosomes (~500 μmol/L) (Zhong *et al.* 2017) and mitochondria (~100–200 nmol/L) (Giorgi *et al.* 2018b). Under the control of a complex set of Ca²⁺ pumps, channels, and exchangers

---

# Min Su and Shanliang Zheng contributed equally to this work.

✉ Correspondence: zhengshanliang@hit.edu.cn (S. Zheng), huying@hit.edu.cn (Y. Hu)

distributed at either plasma membrane or organelle membranes, changes in cytosolic $Ca^{2+}$ or $Ca^{2+}$ transport between organelles are perceived as specific signals to activate downstream responses that affect cell fate.

Intracellular $Ca^{2+}$ homeostasis is controlled by $Ca^{2+}$ release from organelles or influx from extracellular spaces. ER-located $Ca^{2+}$ channels, inositol 1,4,5-trisphosphate receptors (IP3Rs) or ryanodine receptors (RyRs), are responsible for ER $Ca^{2+}$ release in response to elevated IP3 levels following hormone or growth factor stimulation or increased extracellular $Ca^{2+}$ influx (Zheng *et al.* 2023). In response to ER $Ca^{2+}$ depletion, the ER-resident protein stromal interaction molecule 1 (STIM1) is activated and subsequently interacts with and activates the plasma membrane-resident $Ca^{2+}$ channel ORAI1, leading to extracellular $Ca^{2+}$ influx, a process termed store-operated $Ca^{2+}$ entry (SOCE) (Benson and Trebak 2023). On the other hand, sarcoplasmic endoplasmic reticulum-type $Ca^{2+}$ ATPases (SERCAs), which are ER-resident $Ca^{2+}$ pumps, are able to pump cytosolic $Ca^{2+}$ back into the ER. During ER $Ca^{2+}$ overload, the ER $Ca^{2+}$ channel protein transmembrane and coiled-coil domains 1 (TMCO1) can be activated to release $Ca^{2+}$ into the cytosol by forming a $Ca^{2+}$ selective channel through monomer-to-tetramer transformation, a process termed store overload-induced $Ca^{2+}$ release (SOICR) (Fig. 1A) (Sumitomo 2016).

In addition to the modulation of cytosolic $Ca^{2+}$ to maintain intracellular $Ca^{2+}$ homeostasis, $Ca^{2+}$ transports between organelles, mainly ER-mitochondria or ER-lysosome, are also essential. For example, the mitochondria-associated ER membrane (MAM) is the interface between the ER and mitochondria and is involved in several biological processes, mainly by modulating ER-mitochondrial $Ca^{2+}$ transport (de Ridder *et al.* 2023). It has been shown that ER-resident IP3R and mitochondria-localized voltage-dependent anion channels (VDACs) form the $Ca^{2+}$ passage to transport $Ca^{2+}$ from the ER to mitochondria, resulting in enhanced mitochondrial $Ca^{2+}$ uptake across the mitochondrial outer membrane (Sander *et al.* 2021). The subsequent $Ca^{2+}$ influx into the mitochondria was enforced by a $Ca^{2+}$ gradient through the mitochondrial calcium uniporter (MCU) located across the inner mitochondrial membrane (Fig. 1B) (Murphy and Steenbergen 2021). In addition, it is worth noting that ER can replenish their $Ca^{2+}$ stores from the lysosomes through the activation of two different pathways: the nicotinic acid adenine dinucleotide phosphate (NAADP)-evoked activation of two-pore channels (TPC) or the activation of mammalian mucolipin TRP channel subfamily (TRPML1) (Capel *et al.* 2015; Marchant *et al.* 2022; Rosato *et al.* 2021). There are numerous calcium-exchange pathways that play a crucial role in the regulation of calcium homeostasis that have not been enumerated in this review (Fig. 1C).

In short, normal cells maintain calcium homeostasis and modulate calcium signalling through a complex and interconnected system that operates in different cellular compartments. This system allows $Ca^{2+}$ to act as a second messenger while preventing its potentially harmful effects. Conversely, cancer cells exhibit a number of abnormalities in this machinery, providing an opportunity for the development of innovative therapeutic agents, as discussed below (Zheng *et al.* 2023).

## Ca²⁺ HOMEOSTASIS DYSREGULATION AND CARCINOGENESIS IN CLINICAL SETTINGS

Cancer progression may be influenced by abnormal $Ca^{2+}$ influx. Clinical evidence suggests that hypercalcaemia is often associated with the occurrence of malignant cancer. This condition has been shown to promote the growth and spread of gastric, oesophageal (Anderson *et al.* 2019), cervical (Lei *et al.* 2022), breast (Das *et al.* 2020) and colorectal cancers (Anderson *et al.* 2019) and has been considered a hallmark of end-stage disease. In colorectal cancer, the intestine has the ability to absorb significant amounts of calcium through specific ion channels, leading to hypercalcaemia in many patients. Many recent findings suggest that even a small increase in intracellular calcium signalling may contribute to the development and progression of colorectal cancer, while sustained calcium influx and overload can lead to tumour cell death (Villalobos *et al.* 2017). This dual function of calcium signalling adds complexity to the understanding of colorectal cancer and may offer new avenues for clinical intervention. In addition, in prostate cancer, non-small cell lung cancer and colon cancer, moderate levels of $Ca^{2+}$ contribute to tumour progression, while excessive cytoplasmic $Ca^{2+}$ levels also cause cell death by stimulating downstream $Ca^{2+}$-dependent sensors (Cui *et al.* 2017; Silvestri *et al.* 2023).

In addition to cytosolic $Ca^{2+}$ homeostasis, organellar $Ca^{2+}$ homeostasis is also critical for tumour development and progression. For example, low levels of $Ca^{2+}$ in mitochondria contribute to the growth of colon and non-small cell lung cancers by controlling energy production. Conversely, excessive $Ca^{2+}$ accumulation in the mitochondria can also trigger cell death (Cui *et al.* 2017).

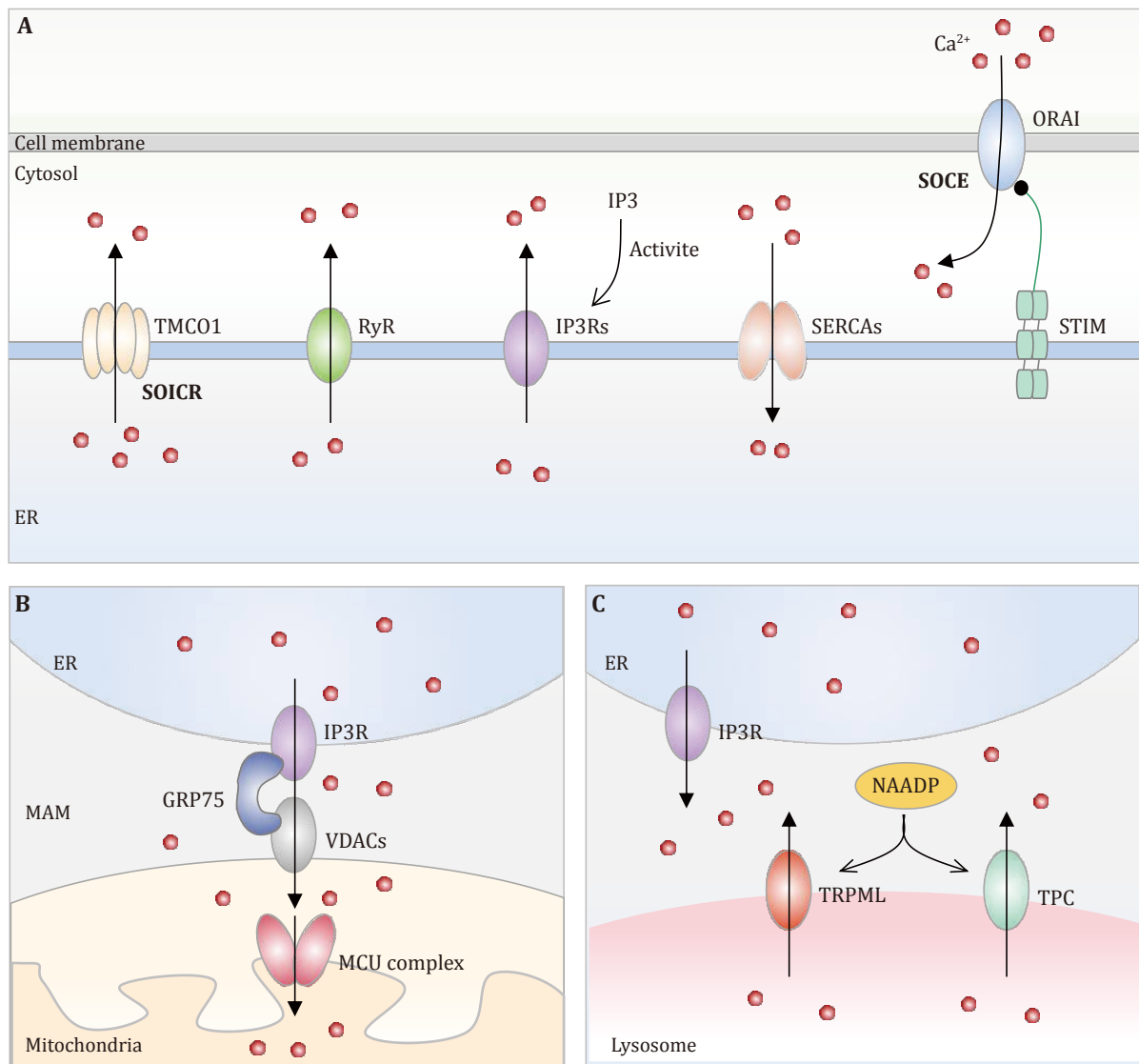In conclusion, changes in $Ca^{2+}$ fluxes affect a complex

**Fig. 1** A graphical representation of calcium homeostasis attainment. **A** ER-Cytosol-Plasma membrane communications. ER-resident calcium pump proteins SERCAs are responsible for transporting Ca$^{2+}$ from the cytosolic into the ER. IP3Rs, or RyRs mediate the release of calcium from the ER in response to the increased IP3 following hormone or growth factor stimulation, or increased cytosolic Ca$^{2+}$ levels. When ER Ca$^{2+}$ concentration is reduced, STIM can be activated to interact with and activate plasma membrane-localized Ca$^{2+}$ channel ORAI1, leading to extracellular Ca$^{2+}$ being influx and the subsequent SERCA-mediated ER Ca$^{2+}$ refilling. Nevertheless, during ER Ca$^{2+}$ overload, the TMCO1 can be stimulated to release Ca$^{2+}$ into the cytosol by forming a selective Ca$^{2+}$ channel through monomer-to-tetramer transformation, a process termed SOICR. **B** ER-Mitochondria communications. The ER and mitochondria are interconnected both structurally and functionally through a specialized microdomain known as the MAM. Within MAMs, several proteins such as Grp-75, VDAC1, and IP3R play a crucial role in regulating Ca$^{2+}$ release from the ER and an efficient mitochondrial Ca$^{2+}$ uptake. **C** ER–lysosome communications. Lysosomal Ca$^{2+}$ depletion initiates the IP3R-mediated Ca$^{2+}$ release from ER and subsequent lysosome Ca$^{2+}$ refilling through the Ca$^{2+}$ transporter or Ca$^{2+}$/H$^+$ exchanger (CAX). Furthermore, ER can restore Ca$^{2+}$ from the lysosomes through the stimulation of two distinct mechanisms: the activation of TPC by NAADP, or the activation of TRPML1

network of intrinsic (*e.g.* metabolism, redox homeostasis) and extrinsic (*e.g.* antigen presentation, danger signalling) processes in cancer cells, which in turn influence malignant transformation, tumour growth, and responses to therapy (Marchi *et al.* 2020; Monteith *et al.* 2017). Therefore, it is crucial to improve our understanding of the mechanisms by which perturbation of Ca$^{2+}$ homeostasis leads to tumour progression.

## CALCIUM HOMEOSTASIS DISRUPTION AND CANCER HALLMARKS

The role of $Ca^{2+}$ signalling in carcinogenesis and clinical status of cancer has been evidenced by the fact that altered $Ca^{2+}$ homeostasis has been implicated in multiple cancer pathological processes. Further mechanistic study reveals that calcium homeostasis disruption can influence tumour growth, cancer cell death, metastasis and anti-immunity by modulating $Ca^{2+}$ channels or pumps (Marchi *et al.* 2020) (Fig. 2).

### Calcium homeostasis disruption and tumour growth

Aberrant cell cycle progression is one of the fundamental mechanisms underlying tumourigenesis (Liu *et al.* 2022). Changes in cytosolic $Ca^{2+}$ can regulate the cell cycle by altering $Ca^{2+}$ transporters, consistent with the fact that $Ca^{2+}$ signalling is involved in the regulation of cancer cell proliferation. Chaochu Cui *et al.* reported that Orai1, as a SOCE channel protein, can regulate intracellular $Ca^{2+}$ oscillations to prevent cell cycle arrest and promote cancer cell proliferation (Cui *et al.* 2018). A novel SOCE channel inhibitor, RP4010, has been shown to mediate intracellular $Ca^{2+}$ flux to arrest the cell cycle at the $G_0/G_1$ phase, ultimately inhibiting tumour growth in oesophageal cancer (Cui et *al.* 2018). In addition, genetic inhibition of STIM1, the other member of the SOCE channel, can significantly inhibit cell proliferation by preventing cell cycle arrest at the S and G/M phases in cervical cancer (Chen *et al.* 2011). Genetic inhibition of STIM1/Orai1 or RP4010 may act as an inhibitor of SOCE-mediated $Ca^{2+}$ signalling in a context-dependent manner.

In addition, genetic silencing or pharmacological inhibition (caffeine, 2-APB and xestospongin C, XeC) of IP3R3, has been shown to inhibit cancer cell proliferation by preventing the intracellular $Ca^{2+}$ elevation (Guerra *et al.* 2019; Szatkowski *et al.* 2010; Ueasilamongkol *et al.* 2020). Similarly, it has been shown that $Ca^{2+}$-dependent lysosomal exocytosis plays an important role in cancer growth and chemoresistance (Buratta *et al.* 2020). Inhibiting this mechanism reduces the invasiveness and chemoresistance of sarcoma cells, whereas increasing lysosomal exocytosis improves invasiveness and drug resistance (Machado *et al.* 2015). TRPML1 is an important regulator of lysosomal exocytosis. Indeed, cholesterol recycling via TRPML1-mediated lysosomal exocytosis promotes the growth of oncogenic HRAS-driven cancer cells. TRPML1 deletion in cancer cells inhibits cholesterol transport from lysosome to the plasma membrane, which lowers their growth rate (Jung *et al.* 2019). These have been developed as a potential target to inhibit tumour growth.

Low-level $Ca^{2+}$ transport from the ER to the mitochondria has been shown to be essential for the maintenance of tumour growth (Cárdenas *et al.* 2016;

- • Affect cell cycle arrest by regulating intracellular $Ca^{2+}$ oscillations.
- • Stimulate the dehydrogenases of TCA by regulating mitochondrial $Ca^{2+}$ accumulation.

**Tumor growth**

- • Increase massive cytosolic $Ca^{2+}$ flux by regulating $Ca^{2+}$ channels or pumps.
- • Promote mitochondria $Ca^{2+}$-overload by regulating $Ca^{2+}$ channels

**Cell death**

**Calcium homeostasis disruption**

**Antitumor immunity**

- • Affect the function of immune cells by regulating SOCE expression.
- • Regulate PD-L1 expression, V(D)J recombination and inflammatory mediators of dendritic cells by affecting SERCA or IP3R levels.

**Cancer metastasis**

- • Promote ROS levels by regulating inter-organelle $Ca^{2+}$ flux.
- • Affect focal adhesion turnover, actomyosin formation, invadopodium assembly and ECM degradation by regulating $Ca^{2+}$ influx
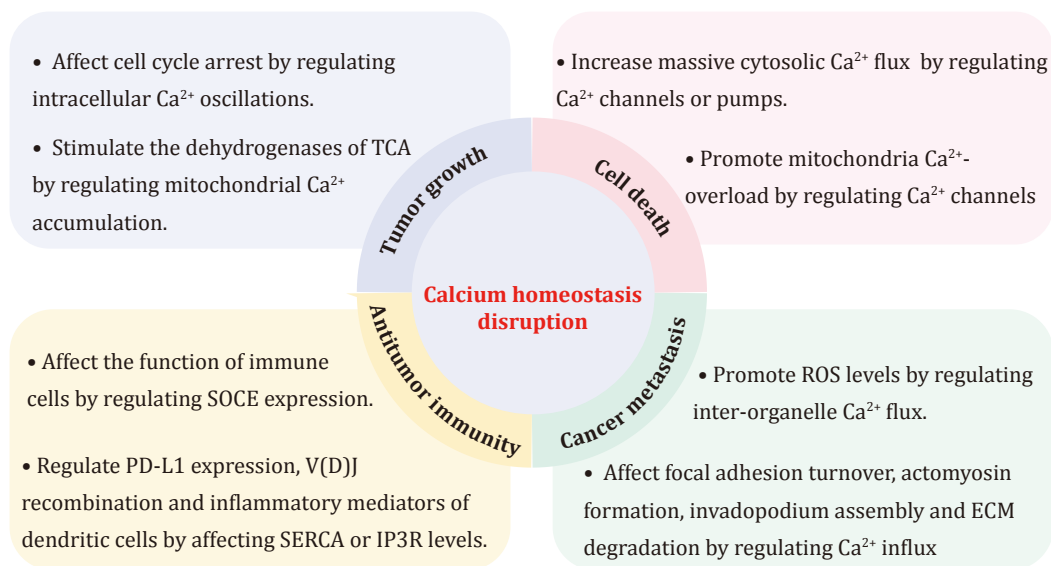
**Fig. 2** The relationship between calcium homeostasis disruption and cancer hallmarks. The examples demonstrate that disruption of calcium homeostasis is involved in mainly cancer characteristics, including tumour growth, cancer cell death, cancer metastasis, and antitumor immunity

Garbincius and Elrod 2022). The resulting mitochondrial $Ca^{2+}$ accumulation can stimulate the key dehydrogenases of the $Ca^{2+}$-regulated tricarboxylic acid cycle, suggesting that it is critical for the biosynthetic and bioenergetic needs of cancer cells (Csordás *et al.* 2018; Zhao *et al.* 2019). Consistent with the above findings, abnormal expression of MAM or MCU channels has been shown to promote cell proliferation in lung and colorectal cancers by inducing mitochondrial $Ca^{2+}$ uptake (Arif *et al.* 2014; Liu *et al.* 2020; Zeng *et al.* 2018).

**Calcium homeostasis disruption and cancer cell death**

Low levels of $Ca^{2+}$ are known to exert pro-survival functions by altering the cell cycle or promoting mitochondrial metabolism through $Ca^{2+}$-dependent stimulation of TCA (tricarboxylic acid) cycle and OXPHOS (oxidative phosphorylation), but excessive cytosolic $Ca^{2+}$ levels cause cell death (Loncke *et al.* 2021; Zheng *et al.* 2023). Indeed, increased $Ca^{2+}$ influx from extracellular space through SOCE can promote $Ca^{2+}$-induced apoptosis. Roberta Gualdani *et al.* reported that siRNA-mediated depletion of STIM1 can dramatically reduce cisplatin-induced ROS production by reducing $Ca^{2+}$ entry and subsequently induce apoptosis in non-small cell lung carcinoma cells (Gualdani *et al.* 2019). The additional members of SOCE have been shown to elicit a similar role in prostate cancer cells. Downregulation of ORAI1 can protect cancer cells from apoptosis induced by several reagents, such as thapsigargin, oxaliplatin and tumour necrosis factor α (Flourakis *et al.* 2010).

Massive cytosolic $Ca^{2+}$ flux, mainly from the ER, has been implicated in cancer cell death (Loncke *et al.* 2021). For example, Ki Cheong Park *et al.* showed that pharmacological inhibition of SERCA promotes $Ca^{2+}$-dependent apoptosis during glucose deprivation in cancer stem-like cells (Park *et al.* 2018). Our data also show that TMCO1, as a SOICR channel protein, is overexpressed in colon cancer cells compared with normal controls (Zheng *et al.* 2022). Increased TMCO1 reduces $Ca^{2+}$ levels in the ER store, which attenuates $Ca^{2+}$ release from the ER to the cytosol, leading to the limited cytosolic $Ca^{2+}$ dynamics upon drug treatment (TG and Stuarosporine) (Zheng *et al.* 2022). This mechanism may promote tumour growth and reduce staurosporine-induced apoptosis in colon cancer (Zheng *et al.* 2022). On the contrary, in bladder urothelial carcinoma, TMCO1 has been shown to have an opposite role, although whether its function is involved in ER $Ca^{2+}$ regulation remains to be determined (Li *et al.* 2017). It is possible that it plays a different role in different cancer cells, depending on the context.

In addition, $Ca^{2+}$ overload in the mitochondria also triggers cell death, mainly through $Ca^{2+}$ transport from the ER to the mitochondria (Beaulant *et al.* 2022). For example, Xue Y showed that IP3R3 promotes apoptosis by enhancing $Ca^{2+}$ transfer from the ER to the mitochondria, leading to the enhancement of cisplatin-induced apoptosis (Xue *et al.* 2021). Another MAM protein, VDAC1, has a similar function also by increasing mitochondrial $Ca^{2+}$ influx (De Stefani *et al.* 2012). In conclusion, the promotion of massive cytosolic $Ca^{2+}$ influx or mitochondrial $Ca^{2+}$ overload has recently been proposed as a promising strategy to induce apoptosis in cancer cells.

**Calcium homeostasis disruption and cancer metastasis**

Approximately 90% of cancer-related deaths are due to metastasis (Bakir *et al.* 2020). Metastasis consists of a number of processes, including the migration of cancer cells from their original growth sites to colonize distant organs (Gerstberger *et al.* 2023; Pastushenko and Blanpain 2019). SOCE, as a major influx route of intracellular $Ca^{2+}$, can affect focal adhesion turnover during cancer cell migration, which was an early event in cancer metastasis. Indeed, Sang Kwon Lee *et al.* reported that decreased SOCE disrupted focal adhesion turnover and actomyosin formation by impairing $Ca^{2+}$ influx in breast cancer cells (Lee *et al.* 2022). In addition, Jianwei Sun *et al.* showed that STIM1- and Orai1-mediated $Ca^{2+}$ oscillations can increase invadopodium assembly and extracellular matrix (ECM) degradation, leading to the promotion of melanoma invasion, the later event in cancer metastasis (Sun *et al.* 2014). These findings provide a mechanism and shed new light on SOCE-mediated $Ca^{2+}$ signalling in cancer cell metastasis.

In addition, cancer cell metastasis can be regulated by SERCA-mediated intracellular $Ca^{2+}$ flux. As a result, phosphorylated cofilin failed to regulate F-actin polymerisation and lamellipodium formation, thereby impairing lamellipodium-based migration (Shi *et al.* 2018).

MAM-associated proteins are also involved in cancer cell metastasis by regulating inter-organelle $Ca^{2+}$ flux. As a master gatekeeper gene that regulates $Ca^{2+}$ transport from the ER to the mitochondria, VDAC1 contributes to cell migration by promoting ROS levels produced by the electron transport chain (Arif *et al.* 2014). In addition, Xiuchao Wang *et al.* have shown that another mitochondrial protein, MCU, promotes pancreatic ductal adenocarcinoma cell migration and

invasion by activating the Keap1-Nrf2 antioxidant program (Wang *et al.* 2022).

## Calcium homeostasis disruption and antitumor immunity

SOCE-induced intracellular $Ca^{2+}$ influx is essential for antitumour immunity, as abnormal SOCE proteins lead to the dysfunction of various immune cells, including T cells, B cells, natural killer (NK) cells, dendritic cells, mast cells, macrophages and neutrophils (Xie *et al.* 2016). Carl Weidinger *et al.* have shown that SOCE in $CD8^+$ T cells is required to prevent the development of melanoma and colon cancer cells to control tumour growth (Weidinger *et al.* 2013). SOCE can regulate (cytotoxic T-lymphocyte) CTL degranulation, Fas ligand expression and TNF-α and IFN-γ production, which affect CTL cytotoxic function both *in vitro* and *in vivo* (Weidinger *et al.* 2013). In addition, antigen cross-presentation by dendritic cells (DCs) activates cytotoxic T-cell stimulation to enhance immunity against cancer (Nunes-Hasler *et al.* 2017). Deletion of SOCE impairs cross-presentation and DC migration by reducing $Ca^{2+}$ signaling (Nunes-Hasler *et al.* 2017). Alternatively, lymphocytes mediate cytotoxicity by polarized release of cytotoxic granule contents towards their target cells (Maul-Pavicic *et al.* 2011). NK cells from SOCE-deficient patients exhibited defective SOCE and severely impaired exocytosis of cytotoxic granules, leading to impaired target cell lysis by reducing SOCE-mediated $Ca^{2+}$ influx (Maul-Pavicic *et al.* 2011). These findings highlight an important role of SOCE in anti-tumour immunity and support the use of SOCE activity regulators in cancer therapy.

In addition, $Ca^{2+}$ modulators are essential for anti-tumour immunity. Jun-Kyu Byun *et al.* showed that impaired SERCA activity can reduce cellular (Glutathione) GSH levels and subsequently upregulate PD-L1 expression under glutamine-limited conditions (Byun *et al.* 2020). This has been shown to suppress T cell-mediated anti-tumour activity (Byun *et al.* 2020). SERCA2 has also been reported to regulate V(D)J recombination. For example, Chun-Chin Chen *et al.* showed that mice with SERCA2-deficient B cells have decreased ER $Ca^{2+}$ levels and increased cytosolic $Ca^{2+}$ levels, resulting in a profound block in V(D)J recombination (Chen *et al.* 2021). Alternatively, IP3R-mediated $Ca^{2+}$ mobilization can regulate NFAT activation, which suppresses cell survival and promotes the production of inflammatory mediators of dendritic cells (DC) (Marongiu *et al.* 2021). This suggests that $Ca^{2+}$ mobilization may be a promising target for anti-inflammatory therapy or immunotherapies.

## THERAPEUTIC VALUES OF TARGETING $Ca^{2+}$ HOMEOSTASIS

Chemotherapy, the basic cancer treatment, is beneficial for patients with early-stage tumours but is inevitably associated with the emergence of drug resistance during treatment (Bukowski *et al.* 2020). Therefore, elucidating the mechanism of action of chemotherapeutic drugs may provide a better basis for improving the sensitivity of chemotherapeutic drugs to improve the prognosis of patients. Although chemotherapy drugs have multiple mechanisms of action, many drugs have the function of regulating $Ca^{2+}$ homeostasis, which is achieved by regulating $Ca^{2+}$ modulators. For example, paclitaxel, cisplatin and doxorubicin, which are common chemotherapy drugs, increase the cytosolic $Ca^{2+}$ levels or promote $Ca^{2+}$ overload in mitochondria, thereby enhancing $Ca^{2+}$-induced apoptosis (Varghese *et al.* 2019).

In addition to the function of chemotherapeutic drugs in regulating $Ca^{2+}$ homeostasis, the combination of $Ca^{2+}$-related regulators and chemotherapeutic drugs to kill tumours has also come to our attention. Given the important role of $Ca^{2+}$ modulators in cancer development, a number of $Ca^{2+}$ activators or inhibitors have been developed. For example, Celastrol, the curcumin analogue F36, JQ-FT and stemphol, which are SERCA inhibitors, are able to target SERCA and inhibit its activity, thereby inducing apoptosis (Fan *et al.* 2014; Ji *et al.* 2018; Roti *et al.* 2018; Xu *et al.* 2020). In addition, inhibitors that target calcium channels have also been shown to kill tumours by inhibiting cell metastasis or increasing apoptosis *in vitro* or *in vivo*, including the imidazole derivative SKF-96365 (Yang *et al.* 2009), a SOCE inhibitor, Synta66 (Waldherr *et al.* 2020), an ORAI1 inhibitor, the IP3R blocker 2-aminoethoxydiphenyl borate (2APB) (Waldherr *et al.* 2020). Moreover, the combination of some FDA-approved inhibitors with chemotherapy drugs has also shown promising effects in cancer treatments. For example, amlodipine, an FDA-approved $Ca^{2+}$ channel blocker, can significantly enhance the therapeutic response of tumor cells to gemcitabine (Principe *et al.* 2022). Alternatively, Heejin Lee reported that $Ca^{2+}$ channel inhibitors (manidipine, lacidipine, benidipine and lometzine) screened from the FDA-approved compound library show a clear inhibitory effect on the growth of ovarian (cancer stem cells) CSCs (Lee *et al.* 2020). Other chemotherapeutic agents have been shown to regulate $Ca^{2+}$ signalling and exert anti-cancer effects, although the underlying molecular mechanisms require further investigation.

Immunotherapy has become one of the most

promising tumour treatment strategies in advanced cancer (Sharma *et al.* 2017). As mentioned above, activation of $Ca^{2+}$ channels is necessary for the immune response, while dysregulation of $Ca^{2+}$ homeostasis can lead to immune cell evasion in cancer cells (Shi *et al.* 2013). Therefore, based on the research on $Ca^{2+}$ and tumour characteristics, it is reasonable to design a clinical strategy that combines the regulation of $Ca^{2+}$ homeostasis with immunotherapy to achieve better therapeutic effects. It is worth noting that an ongoing project has used nanotechnology to deliver cytotoxic doses of $Ca^{2+}$ into the tumour, followed by a combination with immunotherapy, which has so far shown promising anti-tumour effects (Zhao *et al.* 2021; Zheng *et al.* 2021) (Fig. 3).

## REMARKS

$Ca^{2+}$ homeostasis is a necessary factor in maintaining normal growth and development of normal cells (Garbincius and Elrod 2022). Intracellular $Ca^{2+}$ homeostasis requires a variety of $Ca^{2+}$ channels and transporters to be maintained (Giorgi *et al.* 2018a). It is obvious that the imbalance of $Ca^{2+}$ homeostasis caused by the abnormality of these proteins, is one of the major culprits that cause cells from a normal physiological state to a pathological state, resulting in the occurrence of various diseases, including cancer (Zheng *et al.* 2023). Regulating $Ca^{2+}$ homeostasis was a double-edged sword for cancer cells. Modulating $Ca^{2+}$ levels can promote tumour growth by interfering with cell cycle arrest. Conversely, massive cytosolic $Ca^{2+}$ or mitochondrial $Ca^{2+}$ overload promotes cell death (Marchi *et al.* 2020). It is therefore crucial to increase our knowledge of the mechanisms by which $Ca^{2+}$ modulator functions lead to such opposite cellular outcomes.

Increased understanding of the role of $Ca^{2+}$ homeostasis has greatly advanced the field of cancer, and $Ca^{2+}$-based cancer therapeutics have attracted increasing attention. Although common chemotherapeutic drugs targeting $Ca^{2+}$ have not yet been developed, more and more studies have shown that a variety of chemotherapeutic drugs can regulate $Ca^{2+}$ homeostasis and thereby affect the fate of cancer cells (Varghese *et al.* 2019). In addition, several inhibitors of $Ca^{2+}$ modulators screened from the FDA's library of compounds can be combined with chemotherapeutic drugs to kill cancer cells. These suggest that disrupting $Ca^{2+}$
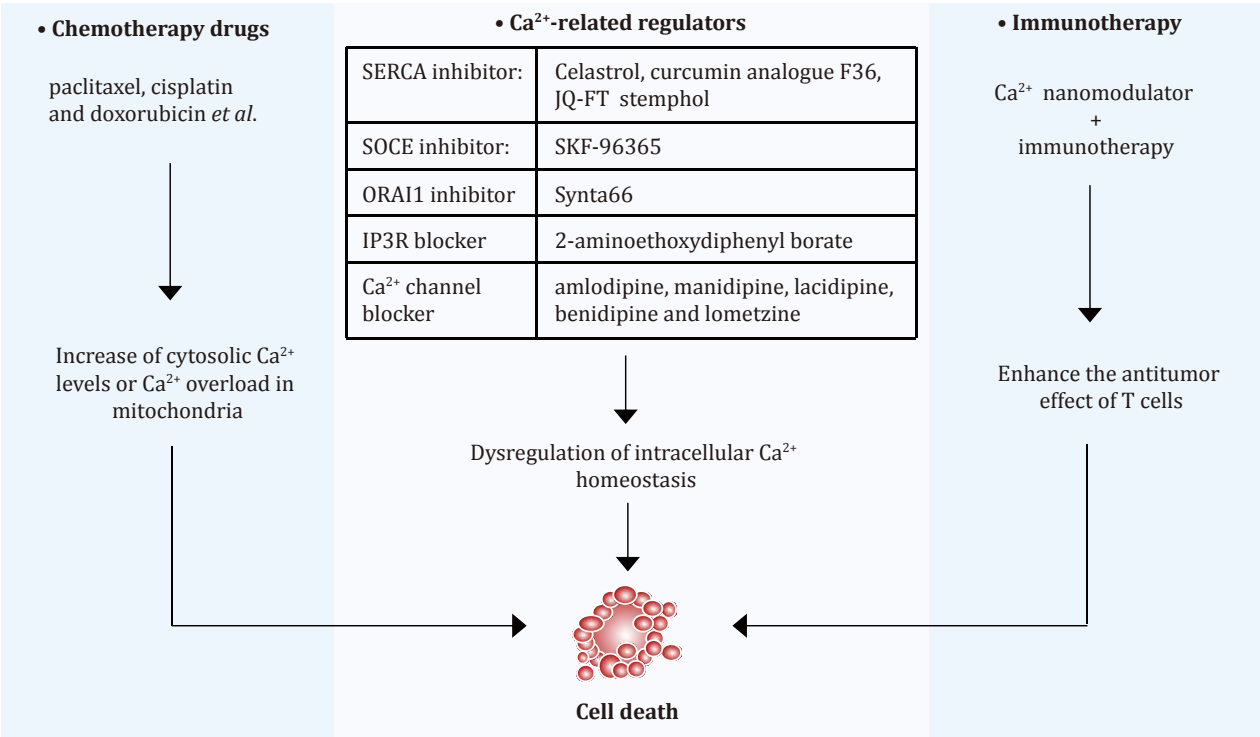


**Fig. 3** Targeting $Ca^{2+}$ homeostasis as a potential therapeutic value. Relationship between targeted calcium homeostasis and tumor therapy, which contains $Ca^{2+}$-related chemotherapy, combined-therapy and immunotherapy

homeostasis to promote cancer cell death has become a remarkable effect. What's more, $Ca^{2+}$-based therapy combined with immunotherapy has become a hot topic, while the underlying molecular mechanism needs to be further explored.

**Compliance with Ethical Standards**

**Conflict of interest** Min Su, Shanliang Zheng, Hao Liu and Tie-Shan Tang declare that they have no conflict of interest.

**Human and animal rights and informed consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Anderson KJ, Cormier RT, Scott PM (2019) Role of ion channels in gastrointestinal cancer. World J Gastroenterol 25(38): 5732–5772

Arif T, Vasilkovsky L, Refaely Y, Konson A, Shoshan-Barmatz V (2014) Silencing VDAC1 expression by siRNA inhibits cancer cell proliferation and tumor growth *in vivo*. Mol Ther Nucleic Acids 3(4): e159. https://doi.org/10.1038/mtna.2014.9

Bakir B, Chiarella AM, Pitarresi JR, Rustgi AK (2020) EMT, MET, plasticity, and tumor metastasis. Trends Cell Biol 30(10): 764–776

Beaulant A, Dia M, Pillot B, Chauvin M-A, Ji-Cao J, Durand C, Bendridi N, Chanon S, Vieille-Marchiset A, Da Silva CC, Patouraux S, Anty R, Iannelli A, Tran A, Gual P, Vidal H, Gomez L, Paillard M, Rieusset J (2022) Endoplasmic reticulum-mitochondria miscommunication is an early and causal trigger of hepatic insulin resistance and steatosis. J Hepatol 77(3): 710–722

Benson JC, Trebak M (2023) Too much of a good thing: the case of SOCE in cellular apoptosis. Cell Calcium 111: 102716. https://doi.org/10.1016/j.ceca.2023.102716

Bukowski K, Kciuk M, Kontek R (2020) Mechanisms of multidrug resistance in cancer chemotherapy. Int J Mol Sci 21(9): 3233. https://doi.org/10.3390/ijms21093233

Buratta S, Tancini B, Sagini K, Delo F, Chiaradia E, Urbanelli L, Emiliani C (2020) Lysosomal exocytosis, exosome release and secretory autophagy: the autophagic- and endo-lysosomal systems go extracellular. Int J Mol Sci 21(7): 2576. https://doi.org/10.3390/ijms21072576

Byun J-K, Park M, Lee S, Yun JW, Lee J, Kim JS, Cho SJ, Jeon H-J, Lee I-K, Choi Y-K, Park K-G (2020) Inhibition of glutamine utilization synergizes with immune checkpoint inhibitor to promote antitumor immunity. Mol Cell 80(4): 592–606

Capel RA, Bolton EL, Lin WK, Aston D, Wang Y, Liu W, Wang X, Burton RA, Bloor-Young D, Shade KT, Ruas M, Parrington J, Churchill GC, Lei M, Galione A, Terrar DA (2015) Two-pore channels (TPC2s) and nicotinic acid adenine dinucleotide phosphate (NAADP) at lysosomal-sarcoplasmic reticular junctions contribute to acute and chronic β-Adrenoceptor signaling in the heart. J Biol Chem 290(50): 30087–30098

Cárdenas C, Müller M, McNeal A, Lovy A, Jaňa F, Bustos G, Urra F, Smith N, Molgó J, Diehl JA, Ridky TW, Foskett JK (2016) Selective vulnerability of cancer cells by inhibition of Ca(2+) transfer from endoplasmic reticulum to mitochondria. Cell Reports 14(10): 2313–2324

Chen C-C, Chen B-R, Wang Y, Curman P, Beilinson HA, Brecht RM, Liu CC, Farrell RJ, de Juan-Sanz J, Charbonnier L-M, Kajimura S, Ryan TA, Schatz DG, Chatila TA, Wikstrom JD, Tyler JK, Sleckman BP (2021) Sarco/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) activity is required for V(D)J recombination. J Exp Med 218(8): e20201708. https://doi.org/10.1084/jem.20201708

Chen Y-F, Chiu W-T, Chen Y-T, Lin P-Y, Huang H-J, Chou C-Y, Chang H-C, Tang M-J, Shen M-R (2011) Calcium store sensor stromal-interaction molecule 1-dependent signaling plays an important role in cervical cancer growth, migration, and angiogenesis. Proc Natl Acad Sci USA 108(37): 15225–15230

Csordás G, Weaver D, Hajnóczky G (2018) Endoplasmic reticulum-mitochondrial contactology: structure and signaling functions. Trends Cell Biol 28(7): 523–540

Cui C, Chang Y, Zhang X, Choi S, Tran H, Penmetsa KV, Viswanadha S, Fu L, Pan Z (2018) Targeting Orai1-mediated store-operated calcium entry by RP4010 for anti-tumor activity in esophagus squamous cell carcinoma. Cancer Lett 432: 169–179

Cui C, Merritt R, Fu L, Pan Z (2017) Targeting calcium signaling in cancer therapy. Acta Pharm Sin B 7(1): 3–17

Das S, Clézardin P, Kamel S, Brazier M, Mentaverri R (2020) The CaSR in pathogenesis of breast cancer: a new target for early stage bone metastases. Front Oncol 10: 69. https://doi.org/10.3389/fonc.2020.00069

de Ridder I, Kerkhofs M, Lemos FO, Loncke J, Bultynck G, Parys JB (2023) The ER-mitochondria interface, where Ca(2+) and cell death meet. Cell Calcium 112: 102743. https://doi.org/10.1016/j.ceca.2023.102743

De Stefani D, Bononi A, Romagnoli A, Messina A, De Pinto V, Pinton P, Rizzuto R (2012) VDAC1 selectively transfers apoptotic $Ca^{2+}$ signals to mitochondria. Cell Death Differ 19(2): 267–273

Fan L, Li A, Li W, Cai P, Yang B, Zhang M, Gu Y, Shu Y, Sun Y, Shen Y, Wu X, Hu G, Wu X, Xu Q (2014) Novel role of Sarco/endoplasmic reticulum calcium ATPase 2 in development of colorectal cancer and its regulation by F36, a curcumin analog. Biomed Pharmacother 68(8): 1141–1148

Fiorio Pla A, Gkika D (2020) $Ca^{2+}$ channel toolkit in neuroendocrine tumors. Neuroendocrinology 110(1-2): 147–154

Flourakis M, Lehen'kyi V, Beck B, Raphaël M, Vandenberghe M, Abeele FV, Roudbaraki M, Lepage G, Mauroy B, Romanin C,

Shuba Y, Skryma R, Prevarskaya N (2010) Orai1 contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells. Cell Death Dis 1(9): e75. https://doi.org/10.1038/cddis.2010.52

Garbincius JF, Elrod JW (2022) Mitochondrial calcium exchange in physiology and disease. Physiol Rev 102(2): 893–992

Gerstberger S, Jiang Q, Ganesh K (2023) Metastasis. Cell 186(8): 1564–1579

Giorgi C, Danese A, Missiroli S, Patergnani S, Pinton P (2018a) Calcium dynamics as a machine for decoding signals. Trends Cell Biol 28(4): 258–273

Giorgi C, Marchi S, Pinton P (2018b) The machineries, regulation and cellular functions of mitochondrial calcium. Nat Rev Mol Cell Biol 19(11): 713–730

Gualdani R, de Clippele M, Ratbi I, Gailly P, Tajeddine N (2019) Store-operated calcium entry contributes to cisplatin-induced cell death in non-small cell lung carcinoma. Cancers 11(3): 430. https://doi.org/10.3390/cancers11030430

Guerra MT, Florentino RM, Franca A, Lima Filho AC, Dos Santos ML, Fonseca RC, Lemos FO, Fonseca MC, Kruglov E, Mennone A, Njei B, Gibson J, Guan F, Cheng Y-C, Ananthanarayanan M, Gu J, Jiang J, Zhao H, Lima CX, Vidigal PT, Oliveira AG, Nathanson MH, Leite MF (2019) Expression of the type 3 InsP3 receptor is a final common event in the development of hepatocellular carcinoma. Gut 68(9): 1676–1687

Ji S, Lee J-Y, Schrör J, Mazumder A, Jang DM, Chateauvieux S, Schnekenburger M, Hong CR, Christov C, Kang HJ, Lee Y, Han BW, Kim K-W, Shin H-Y, Dicato M, Cerella C, König GM, Orlikova B, Diederich M (2018) The dialkyl resorcinol stemphol disrupts calcium homeostasis to trigger programmed immunogenic necrosis in cancer. Cancer Lett 416: 109–123

Jung J, Cho KJ, Naji AK, Clemons KN, Wong CO, Villanueva M, Gregory S, Karagas NE, Tan L, Liang H, Rousseau MA, Tomasevich KM, Sikora AG, Levental I, van der Hoeven D, Zhou Y, Hancock JF, Venkatachalam K (2019) HRAS-driven cancer cells are vulnerable to TRPML1 inhibition. EMBO Rep 20(4): e46685. https://doi.org/10.15252/embr.201846685

Kim E, Lee DM, Seo MJ, Lee HJ, Choi KS (2021) Intracellular Ca²⁺ imbalance critically contributes to paraptosis. Front Cell Dev Biol 8: 607844. https://doi.org/10.3389/fcell.2020.607844

Lee H, Kim JW, Kim DK, Choi DK, Lee S, Yu JH, Kwon O-B, Lee J, Lee D-S, Kim JH, Min S-H (2020) Calcium channels as novel therapeutic targets for ovarian cancer stem cells. Int J Mol Sci 21(7): 2327. https://doi.org/10.3390/ijms21072327

Lee SK, Kweon YC, Lee AR, Lee YY, Park CY (2022) Metastasis enhancer PGRMC1 boosts store-operated Ca²⁺ entry by uncoiling Ca²⁺ sensor STIM1 for focal adhesion turnover and actomyosin formation. Cell Rep 38(3): 110281. https://doi.org/10.1016/j.celrep.2021.110281

Lei J, Deng F, Ding H, Fu M, Xu T, Ji B, Feng L, Li M, Qiu J, Gao Q (2022) Recent developments on the roles of calcium signals and potential therapy targets in cervical cancer. Cells 11(19): 3003. https://doi.org/10.3390/cells11193003

Li C-F, Wu W-R, Chan T-C, Wang Y-H, Chen L-R, Wu W-J, Yeh B-W, Liang S-S, Shiue Y-L (2017) Transmembrane and coiled-coil domain 1 impairs the AKT signaling pathway in urinary bladder urothelial carcinoma: a characterization of a tumor suppressor. Clin Cancer Res 23(24): 7650–7663

Lissandron V, Podini P, Pizzo P, Pozzan T (2010) Unique characteristics of Ca²⁺ homeostasis of the trans-Golgi compartment. Proc Natl Acad Sci USA 107(20): 9198–9203

Liu J, Peng Y, Wei W (2022) Cell cycle on the crossroad of tumorigenesis and cancer therapy. Trends Cell Biol 32(1): 30–44

Liu Y, Jin M, Wang Y, Zhu J, Tan R, Zhao J, Ji X, Jin C, Jia Y, Ren T, Xing

J (2020) MCU-induced mitochondrial calcium uptake promotes mitochondrial biogenesis and colorectal cancer growth. Signal Transduct Target Ther 5(1): 59. https://doi.org/10.1038/s41392-020-0155-5

Loncke J, Kaasik A, Bezprozvanny I, Parys JB, Kerkhofs M, Bultynck G (2021) Balancing ER-mitochondrial Ca²⁺ fluxes in health and disease. Trends Cell Biol 31(7): 598–612

Machado E, White-Gilbertson S, van de Vlekkert D, Janke L, Moshiach S, Campos Y, Finkelstein D, Gomero E, Mosca R, Qiu X, Morton CL, Annunziata I, d'Azzo A (2015) Regulated lysosomal exocytosis mediates cancer progression. Sci Adv 1(11): e1500603. https://doi.org/10.1126/sciadv

Marchant JS, Gunaratne GS, Cai X, Slama JT, Patel S (2022) NAADP-binding proteins find their identity. Trends Biochem Sci 47(3): 235–249

Marchi S, Giorgi C, Galluzzi L, Pinton P (2020) Ca²⁺ fluxes and cancer. Mol Cell 78(6): 1055–1069

Marongiu L, Mingozzi F, Cigni C, Marzi R, Di Gioia M, Garrè M, Parazzoli D, Sironi L, Collini M, Sakaguchi R, Morii T, Crosti M, Moro M, Schurmans S, Catelani T, Rotem R, Colombo M, Shears S, Prosperi D, Zanoni I, Granucci F (2021) Inositol 1, 4, 5-trisphosphate 3-kinase B promotes Ca²⁺ mobilization and the inflammatory activity of dendritic cells. Sci Signal 14(676): eaaz2120. https://doi.org/10.1126/scisignal.aaz2120

Maul-Pavicic A, Chiang SCC, Rensing-Ehl A, Jessen B, Fauriat C, Wood SM, Sjöqvist S, Hufnagel M, Schulze I, Bass T, Schamel WW, Fuchs S, Pircher H, McCarl C-A, Mikoshiba K, Schwarz K, Feske S, Bryceson YT, Ehl S (2011) ORAI1-mediated calcium influx is required for human cytotoxic lymphocyte degranulation and target cell lysis. Proc Natl Acad Sci USA 108(8): 3324–3329

Monteith GR, Prevarskaya N, Roberts-Thomson SJ (2017) The calcium-cancer signalling nexus. Nat Rev Cancer 17(6): 367–380

Murphy E, Steenbergen C (2021) Regulation of mitochondrial Ca(2+) uptake. Annu Rev Physiol 83: 107–126

Nunes-Hasler P, Maschalidi S, Lippens C, Castelbou C, Bouvet S, Guido D, Bermont F, Bassoy EY, Page N, Merkler D, Hugues S, Martinvalet D, Manoury B, Demaurex N (2017) STIM1 promotes migration, phagosomal maturation and antigen cross-presentation in dendritic cells. Nat Commun 8(1): 1852. https://doi.org/10.1038/s41467-017-01600-6

Park KC, Kim SW, Jeon JY, Jo AR, Choi HJ, Kim J, Lee HG, Kim Y, Mills GB, Noh SH, Lee MG, Park ES, Cheong J-H (2018) Survival of cancer stem-like cells under metabolic stress via CaMK2α-mediated upregulation of sarco/endoplasmic reticulum calcium atpase expression. Clin Cancer Res 24(7): 1677–1690

Pastushenko I, Blanpain C (2019) EMT transition states during tumor progression. Trends Cell Biol 29(3): 212–226

Principe DR, Aissa AF, Kumar S, Pham TND, Underwood PW, Nair R, Ke R, Rana B, Trevino JG, Munshi HG, Benevolenskaya EV, Rana A (2022) Calcium channel blockers potentiate gemcitabine chemotherapy in pancreatic cancer. Proc Natl Acad Sci USA 119(18): e2200143119. https://doi.org/10.1073/pnas.2200143119

Rosato AS, Tang R, Grimm C (2021) Two-pore and TRPML cation channels: regulators of phagocytosis, autophagy and lysosomal exocytosis. Pharmacol Ther 220: 107713. https://doi.org/10.1016/j.pharmthera.2020.107713

Roti G, Qi J, Kitara S, Sanchez-Martin M, Saur Conway A, Varca AC, Su A, Wu L, Kung AL, Ferrando AA, Bradner JE, Stegmaier K (2018) Leukemia-specific delivery of mutant NOTCH1 targeted therapy. J Exp Med 215(1): 197–216

Sander P, Gudermann T, Schredelseker J (2021) A calcium guard in

the outer membrane: is VDAC a regulated gatekeeper of mitochondrial calcium uptake? Int J Mol Sci 22(2): 946. https://doi.org/10.3390/ijms22020946

Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A (2017) Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell 168(4): 707–723

Shi C, Cai Y, Li Y, Li Y, Hu N, Ma S, Hu S, Zhu P, Wang W, Zhou H (2018) Yap promotes hepatocellular carcinoma metastasis and mobilization via governing cofilin/F-actin/lamellipodium axis by regulation of JNK/Bnip3/SERCA/CaMKII pathways. Redox Biol 14: 59–71

Shi X, Bi Y, Yang W, Guo X, Jiang Y, Wan C, Li L, Bai Y, Guo J, Wang Y, Chen X, Wu B, Sun H, Liu W, Wang J, Xu C (2013) Ca$^{2+}$ regulates T-cell receptor activation by modulating the charge property of lipids. Nature 493(7430): 111–115

Silvestri R, Nicolì V, Gangadharannambiar P, Crea F, Bootman MD (2023) Calcium signalling pathways in prostate cancer initiation and progression. Nat Rev Urol 20(9): 524–543

Sumitomo N (2016) Current topics in catecholaminergic polymorphic ventricular tachycardia. J Arrhythm 32(5): 344–351

Sun J, Lu F, He H, Shen J, Messina J, Mathew R, Wang D, Sarnaik AA, Chang W-C, Kim M, Cheng H, Yang S (2014) STIM1- and Orai1-mediated Ca(2+) oscillation orchestrates invadopodium formation and melanoma invasion. J Cell Biol 207(4): 535–548

Szatkowski C, Parys JB, Ouadid-Ahidouch H, Matifat F (2010) Inositol 1, 4, 5-trisphosphate-induced Ca$^{2+}$ signalling is involved in estradiol-induced breast cancer epithelial cell growth. Mol Cancer 9: 156. https://doi.org/10.1186/1476-4598-9-156

Ueasilamongkol P, Khamphaya T, Guerra MT, Rodrigues MA, Gomes DA, Kong Y, Wei W, Jain D, Trampert DC, Ananthanarayanan M, Banales JM, Roberts LR, Farshidfar F, Nathanson MH, Weerachayaphorn J (2020) Type 3 inositol 1, 4, 5-trisphosphate receptor is increased and enhances malignant properties in cholangiocarcinoma. Hepatology 71(2): 583–599

Varghese E, Samuel SM, Sadiq Z, Kubatka P, Liskova A, Benacka J, Pazinka P, Kruzliak P, Büsselberg D (2019) Anti-cancer agents in proliferation and cell death: the calcium connection. Int J Mol Sci 20(12): 3017. https://doi.org/10.3390/ijms20123017

Villalobos C, Sobradillo D, Hernández-Morales M, Núñez L (2017) Calcium remodeling in colorectal cancer. Biochim Biophys Acta Mol Cell Res 1864(6): 843–849

Waldherr L, Tiffner A, Mishra D, Sallinger M, Schober R, Frischauf I, Schmidt T, Handl V, Sagmeister P, Köckinger M, Derler I, Üçal M, Bonhenry D, Patz S, Schindl R (2020) Blockage of store-operated Ca$^{2+}$ influx by Synta66 is mediated by direct inhibition of the Ca$^{2+}$ selective orai1 pore. Cancers 12(10): 2876. https://doi.org/10.3390/cancers12102876

Wang X, Li Y, Li Z, Lin S, Wang H, Sun J, Lan C, Wu L, Sun D, Huang C, Singh PK, Hempel N, Trebak M, DeNicola GM, Hao J, Yang S (2022) Mitochondrial calcium uniporter drives metastasis and confers a targetable cystine dependency in pancreatic cancer. Cancer Res 82(12): 2254–2268

Weidinger C, Shaw PJ, Feske S (2013) STIM1 and STIM2-mediated Ca(2+) influx regulates antitumour immunity by CD8(+) T cells. EMBO Mol Med 5(9): 1311–1321

Xie J, Pan H, Yao J, Zhou Y, Han W (2016) SOCE and cancer: recent progress and new perspectives. Int J Cancer 138(9): 2067–2077

Xu S-W, Law BYK, Qu SLQ, Hamdoun S, Chen J, Zhang W, Guo J-R, Wu A-G, Mok SWF, Zhang DW, Xia C, Sugimoto Y, Efferth T, Liu L, Wong VKW (2020) SERCA and P-glycoprotein inhibition and ATP depletion are necessary for celastrol-induced autophagic cell death and collateral sensitivity in multidrug-resistant tumor cells. Pharmacol Res 153: 104660. https://doi.org/10.1016/j.phrs.2020.104660

Xue Y, Morris JL, Yang K, Fu Z, Zhu X, Johnson F, Meehan B, Witkowski L, Yasmeen A, Golenar T, Coatham M, Morin G, Monast A, Pilon V, Fiset PO, Jung S, Gonzalez AV, Camilleri-Broet S, Fu L, Postovit L-M, Spicer J, Gotlieb WH, Guiot M-C, Rak J, Park M, Lockwood W, Foulkes WD, Prudent J, Huang S (2021) SMARCA4/2 loss inhibits chemotherapy-induced apoptosis by restricting IP3R3-mediated Ca$^{2+}$ flux to mitochondria. Nat Commun 12(1): 5404. https://doi.org/10.1038/s41467-021-25260-9

Yang S, Zhang JJ, Huang X-Y (2009) Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. Cancer Cell 15(2): 124–134

Zeng F, Chen X, Cui W, Wen W, Lu F, Sun X, Ma D, Yuan Y, Li Z, Hou N, Zhao H, Bi X, Zhao J, Zhou J, Zhang Y, Xiao R-P, Cai J, Zhang X (2018) RIPK1 binds MCU to mediate induction of mitochondrial Ca$^{2+}$ uptake and promotes colorectal oncogenesis. Cancer Res 78(11): 2876–2885

Zhao H, Li T, Wang K, Zhao F, Chen J, Xu G, Zhao J, Li T, Chen L, Li L, Xia Q, Zhou T, Li H-Y, Li A-L, Finkel T, Zhang X-M, Pan X (2019) AMPK-mediated activation of MCU stimulates mitochondrial Ca$^{2+}$ entry to promote mitotic progression. Nat Cell Biol 21(4): 476–486

Zhao Q, Gong Z, Li Z, Wang J, Zhang J, Zhao Z, Zhang P, Zheng S, Miron RJ, Yuan Q, Zhang Y (2021) Target reprogramming lysosomes of CD8+ T Cells by a mineralized metal-organic framework for cancer immunotherapy. Adv Mater 33(17): e2100616. https://doi.org/10.1002/adma.202100616

Zheng P, Ding B, Shi R, Jiang Z, Xu W, Li G, Ding J, Chen X (2021) A multichannel Ca$^{2+}$ nanomodulator for multilevel mitochondrial destruction-mediated cancer therapy. Adv Mater 33(15): e2007426. https://doi.org/10.1002/adma.202007426

Zheng S, Wang X, Zhao D, Liu H, Hu Y (2023) Calcium homeostasis and cancer: insights from endoplasmic reticulum-centered organelle communications. Trends Cell Biol 33(4): 312–323

Zheng S, Zhao D, Hou G, Zhao S, Zhang W, Wang X, Li L, Lin L, Tang T-S, Hu Y (2022) iASPP suppresses Gp78-mediated TMCO1 degradation to maintain Ca$^{2+}$ homeostasis and control tumor growth and drug resistance. Proc Natl Acad Sci USA 119(6): e2111380119. https://doi.org/10.1073/pnas.2111380119

Zhong XZ, Yang Y, Sun X, Dong X-P (2017) Methods for monitoring Ca$^{2+}$ and ion channels in the lysosome. Cell Calcium 64: 20–28