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STIM1 in tumor cell death: angel or devil?

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Stromal interaction molecule 1 (STIM1) is involved in mediating the store-operated Ca^{2+} entry (SOCE), driving the influx of the intracellular second messenger calcium ion (Ca^{2+}), which is closely associated with tumor cell proliferation, metastasis, apoptosis, autophagy, metabolism and immune processes. STIM1 is not only regulated at the transcriptional level by NF-κB and HIF-1, but also post-transcriptionally modified by miRNAs and degraded by ubiquitination. Recent studies have shown that STIM1 or Ca^{2+} signaling can regulate apoptosis, autophagy, pyroptosis, and ferroptosis in tumor cells and act discrepantly in different cancers. Furthermore, STIM1 contributes to resistance against antitumor therapy by influencing tumor cell death. Further investigation into the mechanisms through which STIM1 controls other forms of tumor cell death could aid in the discovery of novel therapeutic targets. Moreover, STIM1 has the ability to regulate immune cells within the tumor microenvironment. Here, we review the basic structure, function and regulation of STIM1, summarize the signaling pathways through which STIM1 regulates tumor cell death, and propose the prospects of antitumor therapy by targeting STIM1.

FACTS

- STIM1 is one of the major molecules that constitute CRAC, which is a channel that drives Ca^{2+} influx for SOCE function and is closely associated with tumor cell proliferation, metastasis, death, and immunity.
- STIM1 can be regulated at the transcriptional level by PI3K-SGK1-P300-NF-κB and CaMKKII-P300-HIF-1 signaling pathways, as well as post-transcriptionally modified by various miRNAs and also directly degraded by ubiquitination.
- Apoptosis, autophagy, pyroptosis, ferroptosis, and cuproptosis are classical forms of programmed cell death, while STIM1 has the ability to influence the occurrence of these cell deaths in tumor cells.
- STIM1 strengthens antitumor therapy by potentiating tumor cell death and antitumor immunity by enhancing the proliferation, activation, and memory of immune cells.
- The identification of effective new drugs that target STIM1 to enhance tumor cell death is a promising direction for future antitumor therapy.

OPEN QUESTIONS

- What are the various pathways through which STIM1 influences tumor cell death in different types of cancers?
- How can STIM1 regulate resistance to antitumor therapy and tumor immunity by affecting cell death?
- What are the potential future applications of targeting STIM1 for the treatment of human tumors?

INTRODUCTION

Calcium ion (Ca^{2+}) is a vital intracellular second messenger. A variety of cellular activities are controlled by changes of intracellular Ca^{2+} concentration, such as cell proliferation, apoptosis, metabolism, and immunity [1–4]. In nonexcitable cells such as tumor cells, the major route for the extracellular Ca^{2+} influx through the plasma membrane (PM) is the Ca^{2+} release-activated Ca^{2+} channel (CRAC), which mediates the store-operated Ca^{2+} entry (SOCE). The function of SOCE has been extensively studied, but its regulatory mechanisms remained a mystery until 2005 [5] and 2006 [6] when stromal interaction molecule 1 (STIM1) and Orai1 were identified as key molecules that maintain SOCE function. STIM1 is a transmembrane protein that spans the endoplasmic reticulum (ER) membrane, with its N-terminal anchored to the ER membrane and its C-terminal located in the cytosol [7], while Orai1 is a protein located on the PM that is highly selective for Ca^{2+} [8]. When the Ca^{2+} pool of the ER is depleted, STIM1 senses the signal and oligomerizes, followed by STIM1 translocation to the PM to activate Orai1 at the ER-PM junction, thereby activating CRAC and SOCE and causing Ca^{2+} influx [9]. In addition to activating Orai1, STIM1 can also activate Orai2 and Orai3 in mammals to produce I_{CRAC}, although with less efficiency [10]. It is worth noting that the canonical TRP (TRPC) channels, along with STIM1 and Orai1, are involved in SOCE [11]. Guido et al. demonstrated that junctate, a single transmembrane protein located in the ER, can mediate SOCE by recruiting the ER junctions even in the absence of the STIM1 protein [12]. These findings suggest that SOCE can be triggered without specifically targeting the STIM1 protein, offering a new approach for cancer therapy.

Recently, it has become increasingly clear that STIM1 is involved in regulating the occurrence, development, invasion, and metastasis of a variety of cancers. In these processes, tumor cell death

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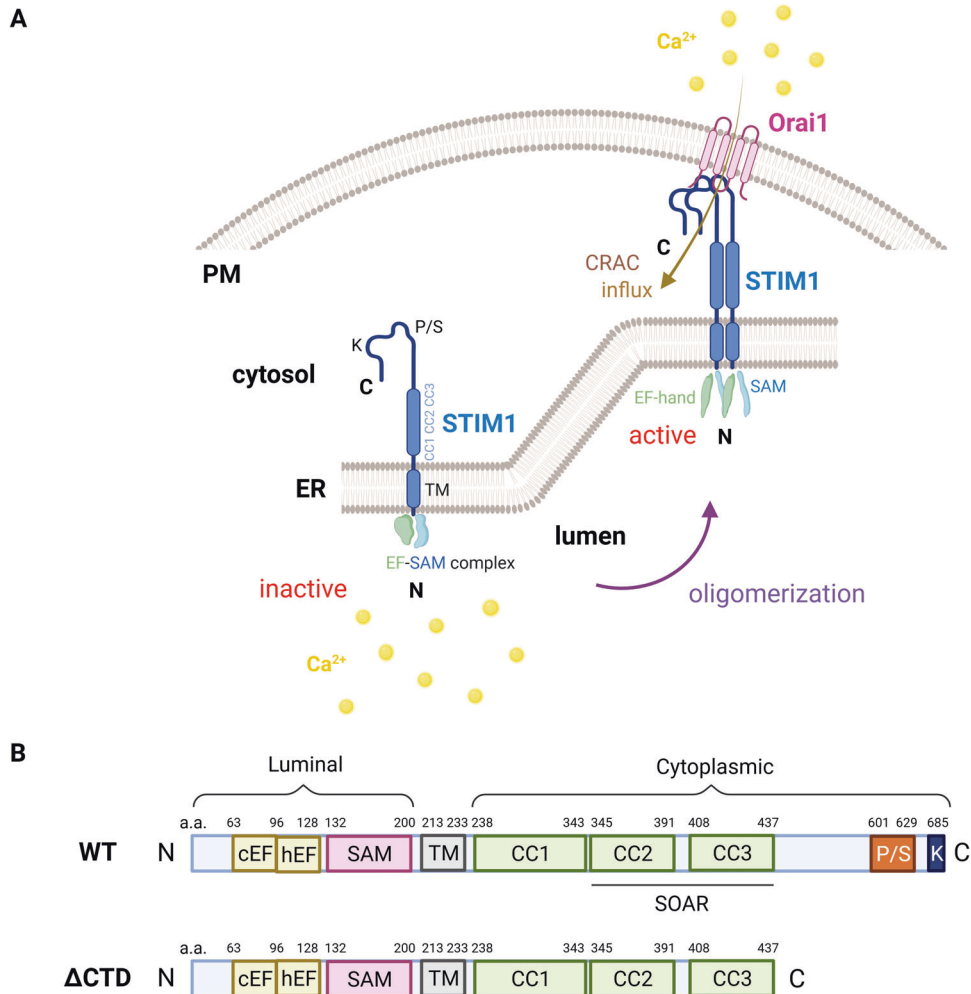
Fig. 1   Location and structure of STIM1. A STIM1 is localized primarily in the ER membrane, with a small fraction in the PM. Orai1 is a plasma membrane protein with four membrane-spanning regions and intracellular N and C-terminus. When Ca^{2+} in the ER lumen is depleted, the EF-SAM complex disintegrates. Subsequently, STIM1 oligomerizes and translocates to the PM, then binds to Orai1 on the PM, which activates CRAC and causes Ca^{2+} influx. **B** The domains of STIM1 are predicted. Starting at the N-terminal, STIM1 includes a canonical EF-hand (nEF), a hidden EF-hand (hEF) and sterile-a motif (SAM) domains on the luminal side. On the cytosolic side are overlapping coiled-coil (CC) and serine–proline-rich (S/P) and lysine-rich (K) domains.

plays a crucial role. Cell death can be classified as accidental cell death (ACD) and regulated cell death (RCD) according to whether it is regulated by genes [13–15]. Recently, compelling evidence indicates the induction of tumor cell death can enhance the effects of antitumor immunotherapy [16–18], and that STIM1-induced tumor cell death can alleviate the resistance to antitumor therapy [19–21].

In this context, we review the discovery, structure, and activation process of STIM1, the upstream signaling pathways regulating STIM1, summarize the functions of STIM1 on tumor cell death and the pathways through which STIM1 reverses resistance to antitumor therapy by affecting tumor cell death, and the key role of STIM1 in tumor immunity. Finally, we discuss the clinical applications of STIM1 and future prospects.

STIM1: DISCOVERY, STRUCTURE, AND ACTIVATION
Discovery of STIM1
In 2005, Parekh AB and Putney JW Jr proposed that four main types of Ca^{2+} channels exist in the cell membrane and the store-operated channels (SOC) is considered to be the most primitive pathway for Ca^{2+} entry into cells [22]. Although STIM was first discovered by Parker in 1996 [23], its functions were not clear.

Roos identified STIM1 as the molecular basis for the composition of thapsigargin (TG)-dependent Ca^{2+} influx and CRAC channels, by suppressing multiple genes in *Drosophila* S2 cells by RNA interference (RNAi) [5].

Structure of STIM1
STIM encodes a dimeric type I transmembrane protein with two homologs in mammals, STIM1 and STIM2. STIM1 is located in the region of human chromosome 11p15.5 [23, 24]. STIM1 consists of three distinct components: the N-terminal located in the lumen of the endoplasmic reticulum (ER), the cytoplasmic chain, and the C-terminal that is soluble in the cytosol [25]. The N-terminal portion includes a canonical EF-hand (cEF), a hidden (hEF) EF-hand, and a sterile α motif (SAM). The cytoplasmic chain region is composed of three coiled-coil (CC) domains known as CC1, CC2, and CC3. CC1 and the SAM domain are connected by a transmembrane domain (TM). In addition, the STIM-Orai-activating region (SOAR), also referred to as the CRAC-activating domain (CAD), is comprised of fragments from CC2 and CC3. Besides, the C-terminal segment is composed of Pro/Ser-rich region and Lys-rich region [7, 26] (Fig. 1A). In the last decade, the STIM1 structural domain and its conformational changes during activation have been better understood by NMR spectroscopy and X-ray crystallography [26–29].
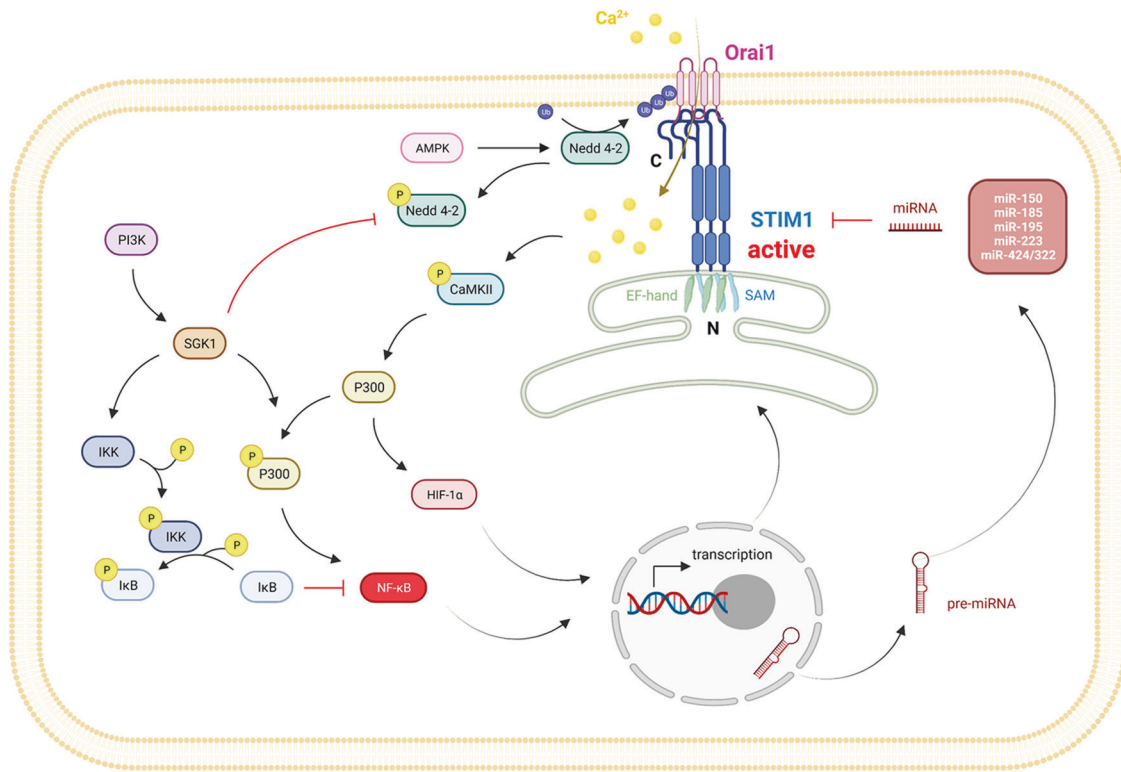
Fig. 2 Upstream regulatory pathways of STIM1. The transcriptional levels of STIM1 and Orai1 can be modulated by multiple signaling pathways, including PI3K-SGK1-NF-κB and CaMKII-P300-HIF-1α axes. In addition, the ubiquitination of Orai1 can be triggered by AMPK-Nedd4-2. At the level of post-transcriptional modification, the expression levels of STIM1 in a variety of tumors are suppressed by a variety of miRNAs, such as miR-150, miR-185, miR-195, miR-223, and miR-424/322.

Activation of STIM1

STIM1 performs two main functions: first, it has the ability to sense precise changes in the concentration of Ca^{2+} (100–400 μM) in the ER lumen [30], and second, it conveys this signal to Orai1 on PM and activates SOCE.

When cells are at rest condition, the cEF-hand of STIM1 is responsible for binding to ER luminal Ca^{2+} and the hEF-hand maintains the stability [31]. When G protein-coupled receptors (GPCRs) or protein tyrosine kinase-linked receptors (PTKRs) on the PM are activated by hormones and growth factors, they bind to the corresponding phospholipase C (PLC) isoforms, resulting in 1,4,5-trisphosphate (InsP3) and diacylglycerol (DAG), respectively. Subsequently, InsP3 binds to InsP3R on the ER membrane, causing the release of Ca^{2+} [2]. When the Ca^{2+} concentration in the ER lumen falls below 300 μM (Hill coefficient approximately equal to 4), it separates from the cEF-hand of STIM1, thereby destabilizing the EF-SAM complex and leading to STIM1 oligomerization [32]. Immediately afterward, STIM1 translocates to the ER-PM junction sites and physically interacts with Orai1, opening the CRAC channel and causing Ca^{2+} entry [30, 33]. Furthermore, reliable experiments have declared that the cytosolic C-terminus of STIM1 is the key domain for opening the Orai1 channel [34] (Fig. 1B). Through the induction of cellular mutations and subcellular localization, crucial functions of STIM1 in constituting CRAC channels and SOCE activation have been progressively elucidated.

Isoforms of STIM1

To date, three splicing variant isoforms of STIM1 have been identified and studied. The first isoform, known as STIM1L, was discovered in 2011 and is specifically expressed in the brain and heart of mice, cardiomyocytes of neonatal rats, and skeletal muscle cells of humans. STIM1L is generated through alternative splicing of exon 11. Its C-terminal region, along with an additional

106 residues, forms a permanent actin-binding domain (ABD), resulting in a significant increase in the rate and frequency of SOCE activation [35]. The second isoform, referred to as STIM1A or STIM1β, was discovered in 2020 and is highly expressed in astrocytes, heart, kidney, and testis. It is formed by the insertion of an extra 31 amino acid residues at position 491 in the C-terminal of STIM1 [36]. Xie et al. found that STIM1β, which is upregulated in glioblastoma, can enhance the function of SOCE by acting as a potent activator of the Orai1 channel [37]. On the other hand, full-length STIM1A functions to negatively regulate SOCE and I_{CRAC}, but it enhances NFAT translocation by reducing cAMP degradation [38]. Another variant, STIM1B, was discovered in 2021 and is highly abundant in the central nervous system (CNS). STIM1B is generated by inserting a specific motif into the cytoplasmic region of STIM1, which allows it to be specifically targeted. Experimental results have shown that STIM1B exhibits a slow recruitment to the ER-PM junctions, leading to a decrease in both the rate and peak of SOCE, as well as a reduction in I_{CRAC} [39].

THE UPSTREAM REGULATORY PATHWAYS OF STIM1

STIM1/Orai is the fundamental component of CRAC channels and plays an important role in the regulation of intracellular Ca^{2+} homeostasis mediated by SOCE. Various intracellular signals affect intracellular Ca^{2+} concentrations by regulating STIM1/Orai (Fig. 2).

For instance, transcription factor nuclear factor kappa B (NF-κB) has been shown to increase the mRNA and protein levels of STIM1 and Orai1 [40–42]. Further experiments demonstrated that the transcriptional promotion of STIM1 and Orai1 by NF-κB is achieved through the binding of p65 to the S1 and O2 regions of their promoters, respectively. Moreover, studies demonstrated that subunits p65/p50 or p65/p52 of NF-κB enhance the migratory capacity of HEK293 cells through transcriptional activation of

Table 1. Functions of STIM1 in tumor cell death.

Type of cell death	Cancer	The effect of STIM1/Ca^{2+}	Reference
Apoptosis	Pancreatic cancer	Inhibit	[19]
	Gastric cancer	Inhibit	[68]
	Triple-negative breast cancer	Inhibit	[69]
	Head and neck squamous cell carcinoma	Inhibit	[70]
	Prostate cancer	Promote	[71]
Autophagy	Acute promyelocytic leukemia	Promote	[74–76]
	Gastric cancer	Promote	[77]
	Hepatocellular carcinoma	Promote	[78, 79]
	Prostate cancer	Promote	[80, 81]
Pyroptosis	Non-small cell lung cancer	Promote	[85]
	Colon cancer	Promote	[87]
Ferroptosis	Non-small cell lung cancer	Promote	[89]
	Pancreatic ductal adenocarcinoma	Promote	[91]

STIM1 and Orai1 [43]. Our earlier study reported that hypoxia-inducible factor-1 (HIF-1) could transcript STIM1 to enhance the SOCE in hepatocellular carcinoma (HCC) cells [44].

In addition to regulating the transcriptional levels of STIM1 and Orai1, Keil found that Plenty of SH3's (POSH), an E3 ubiquitin ligase, could directly ubiquitinate STIM1 and initiate its degradation, thereby reducing intracellular Ca^{2+} [45]. Similarly, studies have shown that neuronal precursor cells expressed developmentally downregulated 4-2 (Nedd4-2), also an E3 ubiquitin ligase, was able to ubiquitinate and degrade Orai1, resulting in Orai1 not being activated by STIM1 to perform SOCE functions [46]. In terms of regulating Nedd4-2, Almaca et al. found that AMPK could activate it [47, 48], and later Nurbaeva et al. also reported high expression of STIM1 and Orai1 in the dendritic cells (DCs) of AMPK-deficient mice [49].

Serum and glucocorticoid inducible kinase 1 (SGK1) are a downstream target of phosphatidylinositol 3-kinase (PI3K) signaling [50–52]. Experiments have shown that the transcription levels of STIM1 and Orai1 in SGK1-deficient mice were significantly lower than those in the control group [53]. In addition, SGK1 can phosphorylate Nedd4-2, thereby reversing the reduction the influx of Ca^{2+} [46]. Overall, SGK1 facilitates cell migration, mast cell degranulation, and platelet aggregation by up-regulating STIM1/Orai1 and thereby promoting SOCE function [54, 55].

MicroRNAs (miRNAs) are involved in post-transcriptional regulation of gene expression [56]. Recently, miRNAs have been revealed to regulate STIM1 in various tissues by post-transcriptionally modifying the 3'-untranslated region (3'-UTR) of STIM1 mRNA. On the one hand, in normal cells, such as in intestinal epithelial cells, miR-195 competes with the RNA-binding protein HUR to bind the 3'UTR of STIM1 mRNA, rendering it unstable and thus inhibiting cell migration [57]. In addition, in vascular smooth muscle cells (VSMC), miR-424/322 prevents VSMC proliferation and tissue repair by impairing STIM1 and cyclin D1 [58]. On the other hand, in cancer cells, such as colorectal cancer (CRC) cells, miR-185 blunts the expression of STIM1, thereby suppressing the metastasis and invasion of CRC [59]. Moreover, in luminal non-aggressive MCF7 breast cancer cells, miR-223 and miR-150 decline the expression of STIM1, but the impact of this regulation on breast cancer remains unexplored [60].

Taken together, the transcriptional, post-transcriptional modification, and translation levels of STIM1 and Orai1 are regulated by multiple signaling pathways during tumorigenesis, progression, and metastasis in different organs. Moreover, STIM1 and Orai1 can be directly degraded by ubiquitination. Targeting these specific signaling molecules is a potential strategy for antitumor therapy.

THE FUNCTIONS OF STIM1 IN TUMOR CELL DEATH

Since the discovery of STIM1, its roles in platelet aggregation [52], allergic reactions [61], autoimmune diseases [62], tumor cell death [63], and T-cell differentiation [64] have been continuously investigated. Tumors are diseases characterized by an imbalance between cell proliferation and death. Cells die in disparate patterns in response to specific stimuli, and acquired defects in cell death signaling pathways are a feature of tumors. The aim of various antitumor treatments is to interfere with and block the process of proliferation and metastasis of tumor cells, thereby inducing the death of tumor cells. Therefore, it is crucial to clarify the mechanisms of tumor cell death in order to optimize antitumor treatment measures. Here, the tumor cell deaths regulated by STIM1 and their mechanisms are summarized (Table 1).

STIM1 regulates tumor cell apoptosis

Apoptosis is a PCD whose basal function is to maintain tissue homeostasis [65]. Cancer is considered to be a disease of excessive cell proliferation, promoting apoptosis of tumor cells can effectively suppress tumor progression [66]. Ca^{2+} have been shown to regulate apoptosis in various tumors, whereas the mechanisms are elusive [67].

In most types of tumors, STIM1 attenuates apoptosis. For instance, in pancreatic cancer, STIM1 and Orai1 exert an inhibitory effect on apoptosis. Apoptosis of pancreatic cancer cells induced by chemotherapeutic agents such as 5-fluorouracil (5-FU) and gemcitabine can be enhanced by blocking STIM1 and Orai1 [19]. In gastric cancer, downregulation of STIM1 also promotes apoptosis [68]. Besides, Chakraborty's study showed that phemindole could delay STIM1 translocation to PM in Triple-negative breast cancer (TNBC) cells, thereby reducing its binding to Orai1, causing ER stress and inducing apoptosis [69]. STIM1 is not only highly expressed in breast cancer, but also displays increased expression in 89% of head and neck squamous cell carcinoma (HNSCC). Li's study presented that reducing intracellular Ca^{2+} concentration by suppressing STIM1 expression in HNSCC could accelerate ER stress-related cell death, such as apoptosis [70].

However, in prostate cancer (PCa), STIM1 plays an opposing role. Flourakis found that Orai1-induced Ca^{2+} entry is a major factor contributing to the apoptosis of PCa cells. Transfection of mutants R91W and L273S in PCa cells LNCaP, which impair Orai1 function, would reduce SOCE and thus protect LNCaP cells from TG-induced apoptosis [71].

In summary, targeting tumor cell apoptosis is a promising strategy for antitumor therapy. However, there is a large
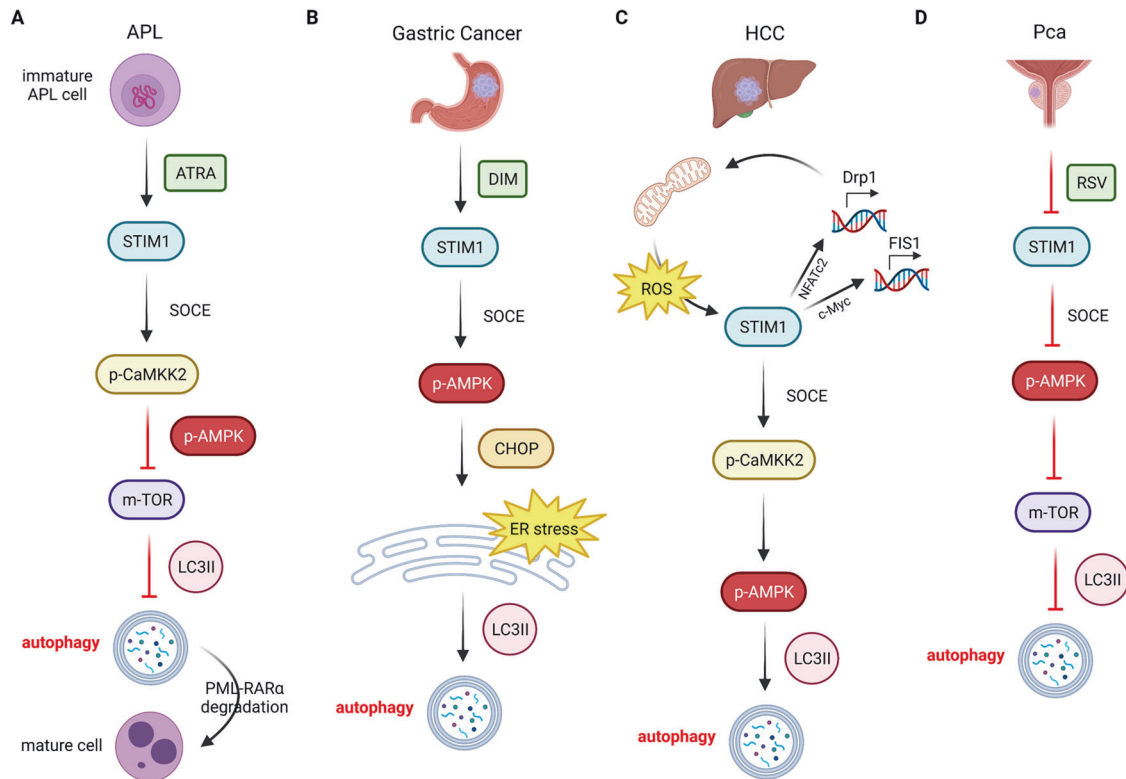
Fig. 3 Schematic representation of the mechanism by which STIM1 regulates the AMPK signaling pathway through SOCE to induce autophagy in four types of tumor cells. A In APL, ATRA upregulates p-CaMKK2 and P-AMPK through activation of STIM1, which in turn inhibits mTOR expression, leading to autophagy. Subsequent degradation of PML-RARα oncoprotein allows APL to undergo granulocyte differentiation and thus transform into a mature state. **B** DIM is used to trigger autophagy in gastric cancer cells. The mechanism is that DIM raises STIM1-mediated SOCE, followed by upregulation of p-AMPK expression, and then induces ER stress via CHOP signaling. **C** In HCC, a positive feedback loop is formed between mitochondrial fission and the cytoplasmic Ca^{2+} signaling pathway. On the one hand, STIM1 induces autophagy by elevating the expression of p-CaMKK2 and p-AMPK; on the other hand, STIM1 promotes ROS production by mitochondrial fission through the transcriptional activation of Drp1 and FIS1 by NFATc2 and c-Myc, which in turn upregulates STIM1. **D** RSV has the ability to foster PCa autophagy, which, unlike other tumors, is dependent on blocking the expression of STIM1, thereby activates p-AMPK and inhibits the mTOR pathway.

heterogeneity in the effects of STIM1 in different tumors, which may be related to their discrepant cell types and signaling pathways. Therefore, the molecular mechanisms of STIM1 regulation of apoptosis need to be investigated differentially for distinct tumor types.

STIM1 promotes tumor cell autophagy
Autophagy is the process of isolating cytoplasm and organelles into autophagosome, which is transported to lysosome for proteolysis [72]. The essence of autophagy is to maintain the energy homeostasis of the cell and the organism [73]. Studies in the last decade have shown that STIM1 plays an important role in the induction of autophagy in tumor cells.

For acute promyelocytic leukemia (APL), a non-solid tumor, all-trans retinoic acid (ATRA) is the first-line option for its treatment [74]. Previous studies have demonstrated that ATRA induces autophagy during granulocyte differentiation in APL patients, however, the upstream mechanism is unclear [75]. Merhi demonstrated that ATRA activates autophagy through the SOCE/calmodulin-dependent protein kinase kinase 2 (CAMKK2)/AMPK signaling axis, and these molecules could be potential targets to enhance the anti-cancer effects of ATRA [76] (Fig. 3A).

STIM1 can also regulate autophagy in solid tumors such as gastric cancer via AMPK. Ye found that 3,3'-Diindolylmethane (DIM) enhanced p-AMPK-CHOP-mediated ER stress through upregulation of STIM1-mediated SOCE, which in turn promoted autophagy in gastric cancer cells [77] (Fig. 3B). In addition, Huang

et al. demonstrated that in HCC cells, the NF-κB pathway activated by increased reactive oxygen species (ROS) can upregulate STIM1, thereby activating SOCE function. The increased intracellular Ca^{2+} further promotes the expression of dynamin-related protein 1 (Drp1) and mitochondrial fission 1 (FIS1) via nuclear factor of activated T-cells 2 (NFATc2) and c-myc, thereby causing mitochondrial fission [78]. Furthermore, increased intracellular Ca^{2+} also stimulates the CaMKK/AMPK pathway, which leads to autophagy in HCC [79] (Fig. 3C). In contrast, Selvaraj's experiments showed that resveratrol (RSV) activated AMPK by inhibiting STIM1, which in turn downregulated the V-akt murine thymoma viral oncogene homolog (AKT)/mammalian target of rapamycin (mTOR) signaling axis and ultimately promoted autophagy in PCa cells [80]. Furthermore, targeting the AKT-mTOR signaling pathway, Kondratskyi's study elucidated that ML-9, an inhibitor of STIM1 and AKT, could promote autophagy in PCa cells by downregulating mTOR expression [81] (Fig. 3D). Besides, ML-9 has the effect of enhancing the anti-cancer activity of docetaxel, but its molecular mechanism remains to be investigated.

Taken together, the STIM1-SOCE-AMPK-autophagy pathway could be a potential therapeutic target for hematological cancers and solid tumors.

Function of Ca^{2+} in other types of tumor cell deaths
The mechanisms by which STIM1 regulates apoptosis and autophagy in tumor cells have been more studied while the relationship between STIM1 and other types of tumor cell deaths

(such as pyroptosis, ferroptosis, and cuproptosis) are still unclear. Recent studies have shown that calcium signaling can alter the levels of these PCDs in tumor cells, but whether STIM1 is involved requires further investigation.

Pyroptosis. Pyroptosis is caspase-1-mediated monocyte death characterized by the production of inflammasomes and caspase-11/4/5 is also activated during this process [82]. At present, the inflammasome sensors that have been extensively studied are nod-like receptor 1 (NLRP1), NLRP3, and nod-like nucleator 4 (NLRC4).

Cucurbitacin B (CuB) can induce apoptosis in tumor cells and has an inhibitory effect on the inflammatory response [83, 84]. Yuan et al. found that CuB binding to Toll-like receptor 4 (TLR4) promoted mitochondrial ROS production and intracellular Ca^{2+} accumulation through activation of the NLRP3 inflammasome complex, thereby facilitating non-small cell lung cancer (NSCLC) pyroptosis [85]. Selenoprotein has an important role in antioxidant and anti-inflammatory activities, and recent studies have shown that a certain amount of selenium intake also has a preventive effect on some tumors [86]. For example, Liu et al. showed that the selenoprotein receptor thioredoxin Reductase 3 (Txnrd3) expressed in the mouse colon and led to increased ER stress and Ca^{2+} release, which subsequently fostered the expression of NLRP3 and Gasdermin D (GSDMD) that could promote pyroptosis, thereby blunting the growth and proliferation of colon cancer cells [87].

Ferroptosis. Ferroptosis is a novel iron-dependent, lipid-reactive oxygen species (L-ROS)-induced PCD identified by Dixon in 2012 [88].

Chen et al. first found that erianin could restrain NSCLC cell proliferation and migration, and activate L-type voltage-dependent Ca^{2+} channel (LVDCC) by promoting the Ca/calmodulin (CaM) signaling pathway in NSCLC, while increasing Ca^{2+} transport and Fe^{2+} level, further promote the production of L-ROS and induce ferroptosis [89]. Mitochondria are essential for Ca^{2+} signaling and redox homeostasis [90]. Mitochondrial calcium uniporter (MCU) is an important complex that regulates Ca^{2+} homeostasis in mitochondria. MCU promotes cystine/glutamate antiporter SLC7A11 expression through activation of the Kelch-like ECH-associated protein 1-NF-E2-related factor 2 (KEAP1-NRF2) antioxidant pathway, which in turn promotes the migration, invasion and metabolic stress resistance in pancreatic ductal adenocarcinoma (PDAC) cells [91]. The relationship between the NRF2-dependent antioxidant system and the regulation of ferroptosis was also observed in melanoma. Wang et al. found that in melanoma, AMPK-mediated activation of CAMKK2 promoted NRF2 expression, thereby inhibiting L-ROS-dependent ferroptosis. Targeted inhibition of the AMPK-CAMKK2-NRF2 signaling axis could enhance the efficacy of anti-PD-1 antibody in melanoma [92]. However, whether and how STIM1 regulates ferroptosis await investigation.

Cuproptosis. Cuproptosis is the latest PCD discovered by Tsvetkov in 2022. Its mechanism is the direct binding of copper to the lipoylated components of the tricarboxylic acid (TCA) cycle, giving rise to the aggregation of lipoylated proteins, loss of iron-sulfur cluster proteins, and ultimately to proteotoxic stress and cell death [15]. The close association between Ca^{2+} with Cu^{2+} has been apprehended [93, 94], but whether Ca^{2+} is involved in the regulation of cuproptosis needs further study. Furthermore, their relationship between SOCE and cuproptosis remains unexplored.

STIM1 MEDIATES ANTITUMOR TREATMENT RESISTANCE
Over the past 20 years, targeted therapies aiming at specific genes have been proposed in some cancers and the molecular mechanisms regulating cancer development have been identified, which has revolutionized antitumor treatment strategies. Nevertheless, despite significant advances in antitumor treatment, the inevitable drug resistance is a major obstacle to improving patient prognosis.

The evasion of apoptosis is one of the characteristics of tumor cells [95] and is a crucial reason for the low efficiency of treatment. Androgens are the standard treatment for early-stage PCa, but unfortunately, PCa progresses to an androgen-independent stage characterized by apoptosis resistance [96]. Flourakis' team found in 2004 that apoptosis resistance in androgen-independent PCa cells was associated with SOCE downregulation [20]. Subsequently, in 2010, Flourakis demonstrated that the reduction in SOCE, caused by the down-regulation of Orai1, led to the suppression of calcium-dependent apoptosis [76]. Dubois et al. found that over-expression of Orai3 in PCa cells disrupted the assimilation of Orai1, resulting in a reduction in SOCE density and causing apoptosis resistance [97]. Herein, targeting STIM1/Orai1/SOCE molecules is expected to reverse the apoptosis resistance of PCa cells. By contrast, in non-solid tumors such as B lymphoma, silencing of Orai1 enhanced the pro-apoptotic effect of rituximab. This suggests that the combination of rituximab with a CRAC channel inhibitor or Ca^{2+} inhibitor may improve the outcome of patients with B lymphoma [98].

In addition to endocrine and targeted therapies, tumor cell resistance to chemotherapy has been shown to be associated with the inhibition of apoptosis by STIM1. Sun et al. found significant upregulation of STIM1 in cisplatin-resistant osteosarcoma MG63 cells. Knockdown of STIM1 in MG63 cells increased the expression of GRP78, CHOP, and ATF4d, which induced ER stress and partially restored the sensitivity of cisplatin-resistant osteosarcoma cells [21]. 5-FU is also a commonly used chemotherapeutic agent in antitumor therapy and has the effect of inducing autophagy in tumor cells [99]. Tang's study demonstrated that 5-FU caused autophagy of HepG2 cells by blocking the PI3K/AKT/mTOR signaling axis. Knockdown of Orai1 or using the SOCE inhibitor SKF96365 could further enhance the ability of 5-FU to inhibit this pathway, thereby sensitizing HepG2 cells to 5-FU treatment [100]. Therefore, in several tumors such as B lymphoma, osteosarcoma and HCC, STIM1 may protect them from escaping targeted therapy or chemotherapy. The use of Ca^{2+} or SOCE inhibitors in these tumors may partially restore their sensitivity to antitumor therapy.

STIM1 IN TUMOR IMMUNITY
Cancer consists of tumor parenchymal cells and the tumor microenvironment (TME). Enhancing the killing power of immune cells in TME can cause immunogenic cell death (ICD) of tumor parenchymal cells [18, 101]. Meanwhile, experiments in recent years have revealed that Ca^{2+} signaling is essential for lymphocyte function and that STIM1-deficient mammals develop immunodeficiency [102–104].

STIM1 and Orai1 are upregulated in T-cell-mediated immune responses and cause increased Ca^{2+} influx at the region where T cells make contact with the antigen-presenting DCs. Amplified Ca^{2+} signaling has a catalytic effect on T-cells' activation, expansion and differentiation [105]. Weidinger found that STIM1 enhanced the cytotoxic effect of $CD8^+$ T cells by increasing their FasL expression, exocytosis of perforin and granzyme B and the release of TNF-α and IFN-γ [106] (Fig. 4A). Furthermore, Shaw et al. demonstrated that STIM1 promoted CD40L expression on the surface of $CD4^+$ T cells, thereby contributing to the memory response of $CD8^+$ T cells upon reinfection [107] (Fig. 4B). In addition, STIM1 and calcineurin (CaN) synergistically activated the NFAT and PI3K-AKT-mTOR signaling pathways to stimulate naïve
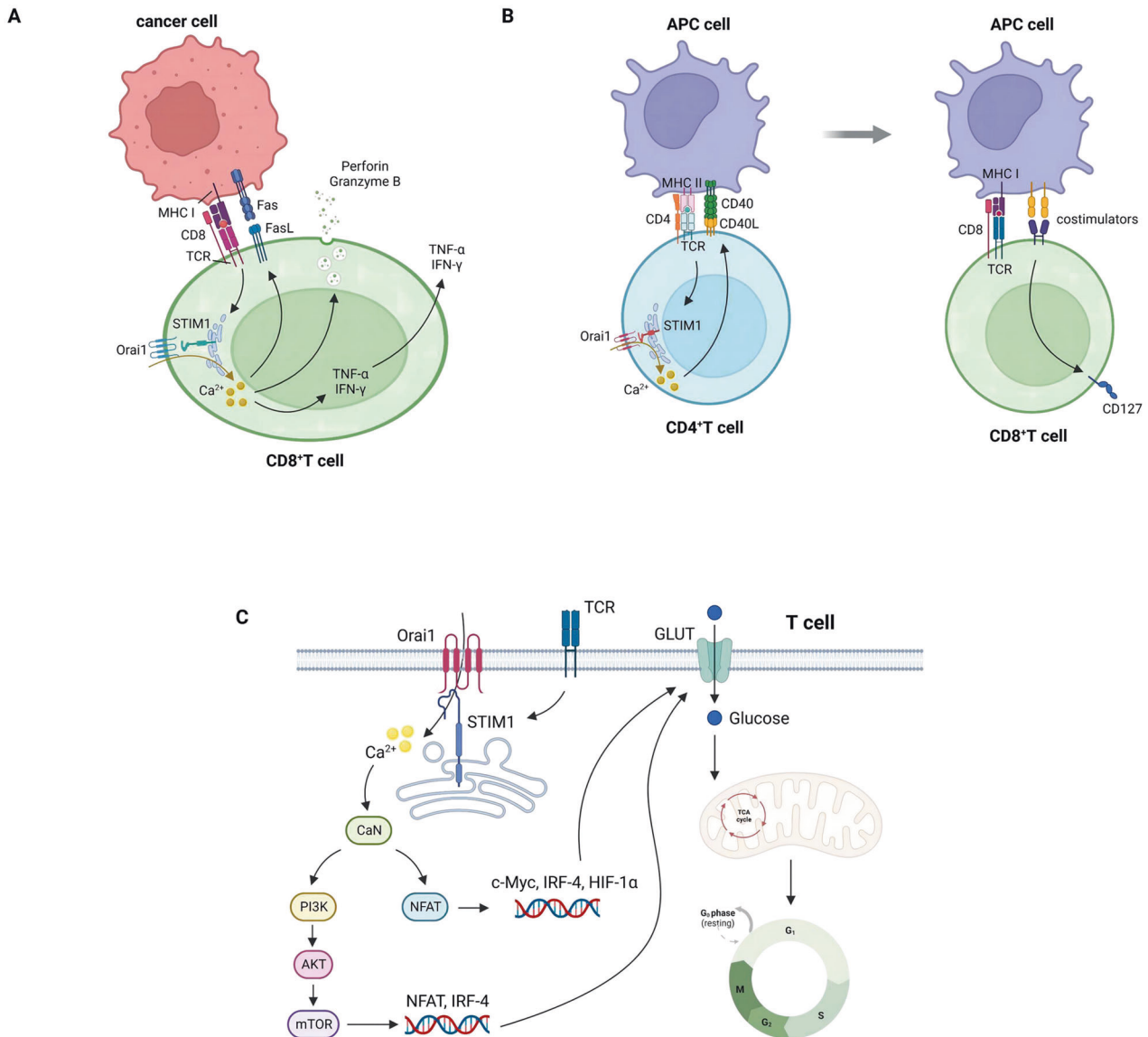
Fig. 4 **STIM1 enhances tumor killing, memory and proliferation of T cells. A** Activation of STIM1 by TCR stimulation mediates the degranulation, production of TNF-α and IFN-γ and the expression of FasL by CD8+T cells, all of which are required for their antitumor immunity. **B** The memory response function of CD8+T cells (via expression of CD127) is dependent on CD40L expression in CD4+T cells facilitated by STIM1, which in turn accelerate antigen presentation by APCs. **C** STIM1 modulates T-cell proliferation by stimulating CaN to activate PI3K-AKT-mTOR and NFAT nutrient sensing pathways to elevate glucose uptake and entry into TCA utilization.

T-cell proliferation by promoting glucose uptake and utilization [108] (Fig. 4C).

T cells are the main effector cells of adaptive immunity, while neutrophils are also key cells in the innate immune response. Studies have shown that in STIM1-deficient mice, neutrophil degranulation, phagocytosis and ROS production were completely impaired, which correlated with reduced activation of protein kinase C isoforms α and β (PKC-α and PKC-β) leading to reduced phosphorylation of oxidase subunits [109]. Immediately afterward, Clemens et al. showed that STIM1 and STIM2 synergistically regulate SOCE function in neutrophils. However, STIM1 is the main factor affecting neutrophil bactericidal function, while STIM2 regulates the secretion of TNF-α, IL-10, and IFN-γ cytokines by neutrophils through activation of NF-κB [110].

Activation of cytotoxic T cells is dependent on the presentation of antigenic by DCs, thereby activating their adaptive immune responses to harmful stimuli. Studies by Nunes-Hasler have shown that STIM1 presents selective regulation of DCs. In myeloid STIM1-deficient mice, the phagocytosis and cross-presentation of antigens by DCs is reduced. However, STIM1 is not required for the upregulation of maturation markers in mouse myeloid-derived DCs, nor does it affect their differentiation [111]. Altogether, targeting STIM1 to enhance the cytotoxic effect of T cells on tumor cells is a promising therapeutic strategy.

THERAPEUTIC POTENTIAL BY TARGETING STIM1
The prognostic significance of STIM1 and its regulation of tumor cells has been demonstrated in a variety of cancers and is a hot topic of research in the field of oncology. As STIM1 is a fundamental component of the SOCE [112], compounds that block SOCE function can also restrain STIM1 to some extent. Over the last two decades, several SOCE inhibitors have been developed to bring hope for the antitumor treatment (Table 2).

Table 2. Drugs that are effective in therapies targeting STIM1.

Drug name	Disease	Mechanism
SKF96365	Breast cancer	Suppress tumor cell metastasis
	Cervical cancer	Suppress tumor cell growth
CM4620	Acute pancreatitis and COVID-19 pneumonia	Suppress inflammation
2-APB	Cervical cancer	Suppress tumor cell proliferation and metastasis
	Hepatocellular carcinoma	Suppress tumor cell proliferation
	Colon cancer	Suppress tumor cell metastasis
2-APB analogs	Still in the research phase	Inhibit the clustering of STIM1 and inactive the SOAR domain
Thapsigargin	Prostatic cancer	Suppress tumor cell growth
Optogenetic tools	Still in the research phase	Reconstruct the modular domains of STIM1 that enable SOCE activation

SKF96365

SKF96365 was initially discovered as an inhibitor of ROC, but later studies revealed that it functions as an inhibitor of SOCE in a population of cells [113–115].

Yang et al. showed that STIM1 and Orai1 were involved in breast cancer metastasis. SKF96365 blocked STIM1 and Orai1-triggered SOCE and inhibited lung metastasis in mice with xenograft mouse model with MDA-MB-231 human breast tumor cells, suggesting that SKF96365 is a potential drug for antitumor metastasis [116]. Similarly, a study by Chen et al. found that silencing of STIM1 or use of SKF96365 reduced SOCE activity in cervical cancer SiHa cells and that tumor growth was inhibited by reduced vascularity and loss of blood supply to tumor cells in mice with subcutaneous tumor-bearing SiHa cervical cancer cells [117].

Notably, SKF96365 is not selective for CRAC channels and can also block other TRPCs [118]. Therefore, more studies on SKF96365 are needed to specifically delineate its mechanism in different types of tumor cells.

CM4620

In comparison to the non-selective SOCE inhibitor SKF96365, CM4620 is a highly selective small-molecule inhibitor of the STIM1/Orai1 complex that effectively blocks CRAC [119]. For instance, a study conducted by Waldron et al. revealed that CM4620 reduced inflammatory features and cell death signaling in cases of acute pancreatitis [120]. Furthermore, clinical trials have demonstrated that Auxora, a novel intravenous CM4620 nanoemulsion formulation, can mitigate lung inflammatory signaling and protect lung tissue from calcium-mediated damage in patients with COVID-19 pneumonia [121]. In addition, CM4620 has also shown promise in alleviating allodynia in male mice, aside from its anti-inflammatory effects [120].

While CM4620 is not currently utilized for cancer treatment, its remarkable ability to selectively inhibit STIM1/Orai1-mediated SOCE makes it highly promising for therapeutic applications in tumors with upregulated STIM1/Orai1 expression.

2-APB

2-Diphenylboranyloxyethanamine (2-APB) has a dual effect, promoting store-operated calcium entry (SOCE) at low concentrations and inhibiting SOCE at high concentrations [122]. Studies have shown that 2-APB can suppress the proliferation of cervical cancer SiHa cells [117] and HCC Huh7 cells [123], as well as restrain the metastasis of cervical [124] and colon cancer cells [125].

To specifically block SOCE, two analogs of 2-APB, DPB-162AE, and DPB-163AE, were developed in 2010 [126]. These analogs effectively inactivate STIM1 by targeting the SOAR structural domain. Among them, DPB-162AE consistently inhibits SOCE regardless of the concentration [127]. However, further clinical trials are necessary to determine the safety and efficacy of DPB-162AE in human cancers.

Thapsigargin

Tg is known for its high cytotoxicity and has been used in the treatment of rheumatic diseases, lung diseases, and female infertility [128]. Recent studies have revealed that Tg acts as a SOCE activator, inducing apoptosis by inhibiting the sarcoplasmic/endoplasmic reticulum Ca^{2+} ATPase (SERCA) pump [129]. To specifically target tumor cells, two prodrugs named G115 and G202 have been developed. These prodrugs are derived from Tg and are coupled to prostate-specific antigen (PSA). Currently, G115 and G202 are undergoing pre-clinical trials [130].

Optogenetic tools

In recent years, there has been a significant increase in the use of optogenetics in various fields of basic medicine [131]. Ma et al. have made significant advancements by developing a set of genetically encoded Ca^{2+} actuators (GECAs) that effectively control the activation of store-operated calcium entry (SOCE), leading to precise modulation of intracellular Ca^{2+} concentrations [132]. However, it is important to note that optogenetics is currently primarily employed in neurological research and its potential impact on cancer therapy is still in the early stages of exploration.

CONCLUSION AND PERSPECTIVES

In recent years, numerous studies have demonstrated the involvement of STIM1 in various aspects of cancer, including genesis, development, invasion, and metastasis. It exerts a significant influence on the fate of tumor cells. The regulation of STIM1 involves complex upstream mechanisms such as PI3K-SGK1-NF-κB, P300-HIF-1α, and miRNAs, which provide potential targets for precision antitumor therapy. Additionally, STIM1 has been found to impact tumor cell survival through various downstream signaling pathways. For instance, it promotes autophagy in different types of tumor cells via the SOCE-AMPK pathway, and enhances the self-renewal of HCC stem cells through the SOCE-NFATc2 axis. These signaling pathways hold promise for cancer intervention. However, it is important to note that the role of autophagy in cancer is paradoxical and dependent on the environmental conditions [133]. In the initial stages of tumorigenesis, autophagy plays a role in maintaining normal cellular physiology and metabolism. It enables lysosomes to break down damaged proteins and organelles, thereby exerting tumor-suppressive effects. However, as the tumor advances to a more advanced stage, nutrient scarcity and hypoxic conditions in the TME cause autophagy to support tumor survival and metastasis. Consequently, the choice to employ targeted therapies that either enhance or inhibit autophagy depends on the stage of the patient's disease [134]. In addition, the role of STIM1 in apoptosis is relatively well understood compared to other forms of tumor cell death. However, most research has only focused on observing the phenomenon without delving into the underlying molecular

mechanisms. As a result, the therapeutic targets for STIM1-induced cell death remain unclear.

To date, drugs such as SKF96365, CM4620, 2-APB, and their analogs have been studied as potential therapeutic agents for preventing tumor development by blocking STIM1 or SOCE. However, most of their effects have only been demonstrated in animal experiments, and further clinical trials are needed to assess their safety, efficacy, and determine the appropriate dosage for administration. In addition, tumor cells often exhibit resistance to various therapies, including chemotherapy, targeted therapy, immunotherapy, and endocrine therapy, due to their apoptosis resistance. This necessitates the use of STIM1/SOCE inhibitors to overcome immunotherapy resistance in lymphoma, chemotherapy resistance in osteosarcoma and HCC, and STIM1/SOCE activators such as thapsigargin to address androgen therapy resistance in PCa. However, it is important to note that the overall impact of non-specific STIM1 inhibition on antitumor therapy remains unknown, as STIM1 also plays a role in the activation and differentiation of $CD8^+$ T cells, the secretory function of neutrophils, and the antigen-presenting role of DCs in immune cells within the TME. While the modulation of Ca^{2+} homeostasis through optogenetics is currently in the early stages of basic research, its potential applications in cardiac electrophysiology and neurology suggest that it could become a valuable tool for precision-targeted therapies. In summary, it is necessary to further investigate the specific mechanisms underlying different modes of tumor cell death. This will not only expand the range of targets for antitumor therapy but also improve the responsiveness to such therapy and enhance the killing effect of the TME. Ultimately, these advancements will lead to more effective antitumor treatments and greater health benefits for patients.

DATA AVAILABILITY
All data are included in the manuscript.

REFERENCES
1. Berridge MJ. Inositol trisphosphate and calcium signalling. Nature. 1993;361:315–25.
2. Berridge MJ. The inositol trisphosphate/calcium signaling pathway in health and disease. Physiol Rev. 2016;96:1261–96.
3. Lewis RS. Calcium signaling mechanisms in T lymphocytes. Annu Rev Immunol. 2001;19:497–521.
4. Berridge MJ. Smooth muscle cell calcium activation mechanisms. J Physiol. 2008;586:5047–61.
5. Roos J, DiGregorio PJ, Yeromin AV, Ohlsen K, Lioudyno M, Zhang S, et al. STIM1, an essential and conserved component of store-operated Ca^{2+} channel function. J Cell Biol. 2005;169:435–45.
6. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. Nature. 2006;441:179–85.
7. Grabmayr H, Romanin C, Fahrner M. STIM proteins: an ever-expanding family. Int J Mol Sci. 2020;22:378.
8. Liu X, Wu G, Yu Y, Chen X, Ji R, Lu J, et al. Molecular understanding of calcium permeation through the open Orai channel. PLoS Biol. 2019;17:e3000096.
9. Cahalan MD. STIMulating store-operated Ca(2+) entry. Nat Cell Biol. 2009;11:669–77.
10. Trebak M, Putney JW Jr. ORAI calcium channels. Physiology. 2017;32:332–42.
11. Lopez JJ, Jardin I, Sanchez-Collado J, Salido GM, Smani T, Rosado JA. TRPC channels in the SOCE scenario. Cells. 2020;9:126.
12. Guido D, Demaurex N, Nunes P. Junctate boosts phagocytosis by recruiting endoplasmic reticulum Ca2+ stores near phagosomes. J Cell Sci. 2015;128:4074–82.
13. Galluzzi L, Vitale I, Aaronson SA, Abrams JM, Adam D, Agostinis P, et al. Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018. Cell Death Differ. 2018;25:486–541.
14. Tang D, Kang R, Berghe TV, Vandenabeele P, Kroemer G. The molecular machinery of regulated cell death. Cell Res. 2019;29:347–64.
15. Tsvetkov P, Coy S, Petrova B, Dreishpoon M, Verma A, Abdusamad M, et al. Copper induces cell death by targeting lipoylated TCA cycle proteins. Science. 2022;375:1254–61.
16. White E, Lattime EC, Guo JY. Autophagy regulates stress responses, metabolism, and anticancer immunity. Trends Cancer. 2021;7:778–89.
17. Fan JX, Deng RH, Wang H, Liu XH, Wang XN, Qin R, et al. Epigenetics-based tumor cells pyroptosis for enhancing the immunological effect of chemotherapeutic nanocarriers. Nano Lett. 2019;19:8049–58.
18. Wang W, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, et al. $CD8^+$ T cells regulate tumour ferroptosis during cancer immunotherapy. Nature. 2019;569:270–4.
19. Kondratska K, Kondratskyi A, Yassine M, Lemonnier L, Lepage G, Morabito A, et al. Orai1 and STIM1 mediate SOCE and contribute to apoptotic resistance of pancreatic adenocarcinoma. Biochim Biophys Acta. 2014;1843:2263–9.
20. Vanoverberghe K, Vanden Abeele F, Mariot P, Lepage G, Roudbaraki M, Bonnal JL, et al. Ca2+ homeostasis and apoptotic resistance of neuroendocrine-differentiated prostate cancer cells. Cell Death Differ. 2004;11:321–30.
21. Sun X, Wei Q, Cheng J, Bian Y, Tian C, Hu Y, et al. Enhanced Stim1 expression is associated with acquired chemo-resistance of cisplatin in osteosarcoma cells. Hum Cell. 2017;30:216–25.
22. Prakriya M, Lewis RS. Store-operated calcium channels. Physiol Rev. 2015;95:1383–436.
23. Parker NJ, Begley CG, Smith PJ, Fox RM. Molecular cloning of a novel human gene (D11S4896E) at chromosomal region 11p15.5. Genomics. 1996;37:253–6.
24. Williams RT, Manji SS, Parker NJ, Hancock MS, Van Stekelenburg L, Eid JP, et al. Identification and characterization of the STIM (stromal interaction molecule) gene family: coding for a novel class of transmembrane proteins. Biochem J. 2001;357:673–85.
25. Stathopulos PB, Ikura M. Partial unfolding and oligomerization of stromal interaction molecules as an initiation mechanism of store operated calcium entry. Biochem Cell Biol. 2010;88:175–83.
26. Stathopulos PB, Zheng L, Li GY, Plevin MJ, Ikura M. Structural and mechanistic insights into STIM1-mediated initiation of store-operated calcium entry. Cell. 2008;135:110–22.
27. Zheng L, Stathopulos PB, Schindl R, Li GY, Romanin C, Ikura M. Auto-inhibitory role of the EF-SAM domain of STIM proteins in store-operated calcium entry. Proc Natl Acad Sci USA. 2011;108:1337–42.
28. Enomoto M, Nishikawa T, Back SI, Ishiyama N, Zheng L, Stathopulos PB, et al. Coordination of a single calcium ion in the EF-hand maintains the off state of the stromal interaction molecule luminal domain. J Mol Biol. 2020;432:367–83.
29. Cui B, Yang X, Li S, Lin Z, Wang Z, Dong C, et al. The inhibitory helix controls the intramolecular conformational switching of the C-terminus of STIM1. PLoS ONE. 2013;8:e74735.
30. Luik RM, Wang B, Prakriya M, Wu MM, Lewis RS. Oligomerization of STIM1 couples ER calcium depletion to CRAC channel activation. Nature. 2008;454:538–42.
31. Park CY, Hoover PJ, Mullins FM, Bachhawat P, Covington ED, Raunser S, et al. STIM1 clusters and activates CRAC channels via direct binding of a cytosolic domain to Orai1. Cell. 2009;136:876–90.
32. Zhou Y, Mancarella S, Wang Y, Yue C, Ritchie M, Gill DL, et al. The short N-terminal domains of STIM1 and STIM2 control the activation kinetics of Orai1 channels. J Biol Chem. 2009;284:19164–8.
33. Luik RM, Wu MM, Buchanan J, Lewis RS. The elementary unit of store-operated Ca2+ entry: local activation of CRAC channels by STIM1 at ER-plasma membrane junctions. J Cell Biol. 2006;174:815–25.
34. Penna A, Demuro A, Yeromin AV, Zhang SL, Safrina O, Parker I, et al. The CRAC channel consists of a tetramer formed by Stim-induced dimerization of Orai dimers. Nature. 2008;456:116–20.
35. Darbellay B, Arnaudeau S, Bader CR, Konig S, Bernheim L. STIM1L is a new actin-binding splice variant involved in fast repetitive Ca2+ release. J Cell Biol. 2011;194:335–46.
36. Knapp ML, Förderer K, Alansary D, Jung M, Schwarz Y, Lis A, et al. Alternative splicing switches STIM1 targeting to specialized membrane contact sites and modifies SOCE. biorxiv [Preprint] 2020. https://www.biorxiv.org/content/10.1101/2020.03.25.005199v1.
37. Xie J, Ma G, Zhou L, He L, Zhang Z, Tan P, et al. Identification of a STIM1 splicing variant that promotes glioblastoma growth. Adv Sci. 2022;9:e2103940.
38. Knapp ML, Alansary D, Poth V, Förderer K, Sommer F, Zimmer D, et al. A longer isoform of Stim1 is a negative SOCE regulator but increases cAMP-modulated NFAT signaling. EMBO Rep. 2022;23:e53135.
39. Ramesh G, Jarzembowski L, Schwarz Y, Poth V, Konrad M, Knapp ML, et al. A short isoform of STIM1 confers frequency-dependent synaptic enhancement. Cell Rep. 2021;34:108844.
40. Criollo A, Senovilla L, Authier H, Maiuri MC, Morselli E, Vitale I, et al. IKK connects autophagy to major stress pathways. Autophagy. 2010;6:189–91.
41. Shih VF, Tsui R, Caldwell A, Hoffmann A. A single NFκB system for both canonical and non-canonical signaling. Cell Res. 2011;21:86–102.
42. Lang F, Münzer P, Gawaz M, Borst O. Regulation of STIM1/Orai1-dependent Ca2+ signalling in platelets. Thromb Haemost. 2013;110:925–30.

43. Eylenstein A, Schmidt S, Gu S, Yang W, Schmid E, Schmidt E-M, et al. Transcription factor NF-κB regulates expression of pore-forming Ca2+ channel unit, Orai1, and its activator, STIM1, to control Ca2+ entry and affect cellular functions. J Biol Chem. 2012;287:2719–30.

44. Li Y, Guo B, Xie Q, Ye D, Zhang D, Zhu Y, et al. STIM1 mediates hypoxia-driven hepatocarcinogenesis via interaction with HIF-1. Cell Rep. 2015;12:388–95.

45. Keil JM, Shen Z, Briggs SP, Patrick GN. Regulation of STIM1 and SOCE by the ubiquitin-proteasome system (UPS). PLoS ONE. 2010;5:e13465.

46. Eylenstein A, Gehring EM, Heise N, Shumilina E, Schmidt S, Szteyn K, et al. Stimulation of Ca2+-channel Orai1/STIM1 by serum- and glucocorticoid-inducible kinase 1 (SGK1). FASEB J. 2011;25:2012–21.

47. Garcia D, Shaw RJ. AMPK: mechanisms of cellular energy sensing and restoration of metabolic balance. Mol Cell. 2017;66:789–800.

48. Almaça J, Kongsuphol P, Hieke B, Ousingsawat J, Viollet B, Schreiber R, et al. AMPK controls epithelial Na(+) channels through Nedd4-2 and causes an epithelial phenotype when mutated. Pflug Arch. 2009;458:713–21.

49. Nurbaeva MK, Schmid E, Szteyn K, Yang W, Viollet B, Shumilina E, et al. Enhanced Ca2+ entry and Na+/Ca2+ exchanger activity in dendritic cells from AMP-activated protein kinase-deficient mice. FASEB J. 2012;26:3049–58.

50. Lang F, Böhmer C, Palmada M, Seebohm G, Strutz-Seebohm N, Vallon V. Pathophysiological significance of the serum- and glucocorticoid-inducible kinase isoforms. Physiol Rev. 2006;86:1151–78.

51. Lang F, Perrotti N, Stournaras C. Colorectal carcinoma cells-regulation of survival and growth by SGK1. Int J Biochem Cell Biol. 2010;42:1571–5.

52. Tai DJ, Su CC, Ma YL, Lee EH. SGK1 phosphorylation of IkappaB Kinase alpha and p300 Up-regulates NF-kappaB activity and increases N-Methyl-D-aspartate receptor NR2A and NR2B expression. J Biol Chem. 2009;284:4073–89.

53. Ali K, Bilancio A, Thomas M, Pearce W, Gilfillan AM, Tkaczyk C, et al. Essential role for the p110delta phosphoinositide 3-kinase in the allergic response. Nature. 2004;431:1007–11.

54. Sobiesiak M, Shumilina E, Lam RS, Wölbing F, Matzner N, Kaesler S, et al. Impaired mast cell activation in gene-targeted mice lacking the serum- and glucocorticoid-inducible kinase SGK1. J Immunol. 2009;183:4395–402.

55. Borst O, Schmidt EM, Münzer P, Schönberger T, Towhid ST, Elvers M, et al. The serum- and glucocorticoid-inducible kinase 1 (SGK1) influences platelet calcium signaling and function by regulation of Orai1 expression in megakaryocytes. Blood. 2012;119:251–61.

56. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136:215–33.

57. Zhuang R, Rao JN, Zou T, Liu L, Xiao L, Cao S, et al. miR-195 competes with HuR to modulate stim1 mRNA stability and regulate cell migration. Nucleic Acids Res. 2013;41:7905–19.

58. Merlet E, Atassi F, Motiani RK, Mougenot N, Jacquet A, Nadaud S, et al. miR-424/322 regulates vascular smooth muscle cell phenotype and neointimal formation in the rat. Cardiovasc Res. 2013;98:458–68.

59. Zhang Z, Liu X, Feng B, Liu N, Wu Q, Han Y, et al. STIM1, a direct target of microRNA-185, promotes tumor metastasis and is associated with poor prognosis in colorectal cancer. Oncogene. 2015;34:4808–20.

60. Kulkarni RP, Elmi A, Alcantara-Adap E, Hubrack S, Nader N, Yu F, et al. miRNA-dependent regulation of STIM1 expression in breast cancer. Sci Rep. 2019;9:13076.

61. Baba Y, Nishida K, Fujii Y, Hirano T, Hikida M, Kurosaki T. Essential function for the calcium sensor STIM1 in mast cell activation and anaphylactic responses. Nat Immunol. 2008;9:81–8.

62. Braun A, Gessner JE, Varga-Szabo D, Syed SN, Konrad S, Stegner D, et al. STIM1 is essential for Fcgamma receptor activation and autoimmune inflammation. Blood. 2009;113:1097–104.

63. Yang J, Yu J, Li D, Yu S, Ke J, Wang L, et al. Store-operated calcium entry-activated autophagy protects EPC proliferation via the CAMKK2-MTOR pathway in ox-LDL exposure. Autophagy. 2017;13:82–98.

64. Vaeth M, Kahlfuss S, Feske S. CRAC channels and calcium signaling in T cell-mediated immunity. Trends Immunol. 2020;41:878–901.

65. Bedoui S, Herold MJ, Strasser A. Emerging connectivity of programmed cell death pathways and its physiological implications. Nat Rev Mol Cell Biol. 2020;21:678–95.

66. Solary E, Dubrez L, Eymin B. The role of apoptosis in the pathogenesis and treatment of diseases. Eur Respir J. 1996;9:1293–305.

67. Pinton P, Giorgi C, Siviero R, Zecchini E, Rizzuto R. Calcium and apoptosis: ER-mitochondria Ca2+ transfer in the control of apoptosis. Oncogene. 2008;27:6407–18.

68. Liu B, Yu HH, Ye HL, Luo ZY, Xiao F. Effects of stromal interacting molecule 1 gene silencing by short hairpin RNA on the biological behavior of human gastric cancer cells. Mol Med Rep. 2015;12:3047–54.

69. Chakraborty S, Ghosh S, Banerjee B, Santra A, Adhikary A, Misra AK, et al. Phemindole, a synthetic di-indole derivative maneuvers the store operated

70. calcium entry (SOCE) to induce potent anti-carcinogenic activity in human triple negative breast cancer cells. Front Pharm. 2016;7:114.

70. Li P, Bian XY, Chen Q, Yao XF, Wang XD, Zhang WC, et al. Blocking of stromal interaction molecule 1 expression influence cell proliferation and promote cell apoptosis in vitro and inhibit tumor growth in vivo in head and neck squamous cell carcinoma. PLoS ONE. 2017;12:e0177484.

71. Flourakis M, Lehen'kyi V, Beck B, Raphaël M, Vandenberghe M, Abeele FV, et al. Orai1 contributes to the establishment of an apoptosis-resistant phenotype in prostate cancer cells. Cell Death Dis. 2010;1:e75.

72. Klionsky DJ, Emr SD. Autophagy as a regulated pathway of cellular degradation. Science. 2000;290:1717–21.

73. Kim KH, Lee MS. Autophagy-a key player in cellular and body metabolism. Nat Rev Endocrinol. 2014;10:322–37.

74. Moosavi MA, Djavaheri-Mergny M. Autophagy: new insights into mechanisms of action and resistance of treatment in acute promyelocytic leukemia. Int J Mol Sci. 2019;20:3559.

75. Djavaheri-Mergny M, Giuriato S, Tschan MP, Humbert M. Therapeutic modulation of autophagy in leukaemia and lymphoma. Cells. 2019;8:103.

76. Merhi F, Alvarez-Valadez K, Trepiana J, Lescoat C, Groppi A, Dupuy JW, et al. Targeting CAMKK2 and SOC channels as a novel therapeutic approach for sensitizing acute promyelocytic leukemia cells to all-trans retinoic acid. Cells. 2021;10:3364.

77. Ye Y, Li X, Wang Z, Ye F, Xu W, Lu R, et al. 3,3'-Diindolylmethane induces gastric cancer cells death via STIM1 mediated store-operated calcium entry. Int J Biol Sci. 2021;17:1217–33.

78. Chan DC. Mitochondrial dynamics and its involvement in disease. Annu Rev Pathol. 2020;15:235–59.

79. Huang Y, Cao H, Zhan L, Sun X, Wang G, Li J, et al. Mitochondrial fission forms a positive feedback loop with cytosolic calcium signaling pathway to promote autophagy in hepatocellular carcinoma cells. Cancer Lett. 2017;403:108–18.

80. Selvaraj S, Sun Y, Sukumaran P, Singh BB. Resveratrol activates autophagic cell death in prostate cancer cells via downregulation of STIM1 and the mTOR pathway. Mol Carcinog. 2016;55:818–31.

81. Kondratskyi A, Yassine M, Slomianny C, Kondratska K, Gordienko D, Dewailly E, et al. Identification of ML-9 as a lysosomotropic agent targeting autophagy and cell death. Cell Death Dis. 2014;5:e1193.

82. Yu P, Zhang X, Liu N, Tang L, Peng C, Chen X. Pyroptosis: mechanisms and diseases. Signal Transduct Target Ther. 2021;6:128.

83. Jayaprakasam B, Seeram NP, Nair MG. Anticancer and antiinflammatory activities of cucurbitacins from Cucurbita andreana. Cancer Lett. 2003;189:11–6.

84. Zhang M, Bian ZG, Zhang Y, Wang JH, Kan L, Wang X, et al. Cucurbitacin B inhibits proliferation and induces apoptosis via STAT3 pathway inhibition in A549 lung cancer cells. Mol Med Rep. 2014;10:2905–11.

85. Yuan R, Zhao W, Wang QQ, He J, Han S, Gao H, et al. Cucurbitacin B inhibits non-small cell lung cancer in vivo and in vitro by triggering TLR4/NLRP3/GSDMD-dependent pyroptosis. Pharm Res. 2021;170:105748.

86. Rayman MP. Selenium and human health. Lancet. 2012;379:1256–68.

87. Liu Q, Du P, Zhu Y, Zhang X, Cai J, Zhang Z. Thioredoxin reductase 3 suppression promotes colitis and carcinogenesis via activating pyroptosis and necrosis. Cell Mol Life Sci. 2022;79:106.

88. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev E, Gleason C, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. Cell. 2012;149:1060–72.

89. Chen P, Wu Q, Feng J, Yan L, Sun Y, Liu S, et al. Erianin, a novel dibenzyl compound in Dendrobium extract, inhibits lung cancer cell growth and migration via calcium/calmodulin-dependent ferroptosis. Signal Transduct Target Ther. 2020;5:51.

90. Vultur A, Gibhardt CS, Stanisz H, Bogeski I. The role of the mitochondrial calcium uniporter (MCU) complex in cancer. Pflug Arch. 2018;470:1149–63.

91. Wang X, Li Y, Li Z, Lin S, Wang H, Sun J, et al. Mitochondrial calcium uniporter drives metastasis and confers a targetable cystine dependency in pancreatic cancer. Cancer Res. 2022;82:2254–68.

92. Wang S, Yi X, Wu Z, Guo S, Dai W, Wang H, et al. CAMKK2 defines ferroptosis sensitivity of melanoma cells by regulating AMPK–NRF2 pathway. J Invest Dermatol. 2022;142:189–200.e8.

93. González A, Sáez CA, Morales B, Moenne A. Copper-induced activation of TRP channels promotes extracellular calcium entry and activation of CaMK, PKA, PKC, PKG and CBLPK leading to increased expression of antioxidant enzymes in Ectocarpus siliculosus. Plant Physiol Biochem. 2018;126:106–16.

94. Yadav V, Gill RA, Arif N, Gill SA, Singh VP, Ramawat N, et al. Endogenous indole-3-acetic acid and nitric oxide are required for calcium-mediated alleviation of copper oxide nanoparticles toxicity in wheat seedlings. Physiol Plant. 2021;173:2262–75.

95. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70.

96. Fixemer T, Remberger K, Bonkhoff H. Apoptosis resistance of neuroendocrine phenotypes in prostatic adenocarcinoma. Prostate. 2002;53:118–23.

97. Dubois C, Vanden Abeele F, Lehen'kyi V, Gkika D, Guarmit B, Lepage G, et al. Remodeling of channel-forming ORAI proteins determines an oncogenic switch in prostate cancer. Cancer Cell. 2014;26:19–32.

98. Vacher P, Vacher AM, Pineau R, Latour S, Soubeyran I, Pangault C, et al. Localized store-operated calcium influx represses CD95-dependent apoptotic effects of rituximab in non-Hodgkin B lymphomas. J Immunol. 2015;195:2207–15.

99. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003;3:330–8.

100. Tang BD, Xia X, Lv XF, Yu BX, Yuan JN, Mai XY, et al. Inhibition of Orai1-mediated Ca^{2+} entry enhances chemosensitivity of HepG2 hepatocarcinoma cells to 5-fluorouracil. J Cell Mol Med. 2017;21:904–15.

101. Wang Q, Wang Y, Ding J, Wang C, Zhou X, Gao W, et al. A bioorthogonal system reveals antitumour immune function of pyroptosis. Nature. 2020;579:421–6.

102. Feske S. ORAI1 and STIM1 deficiency in human and mice: roles of store-operated Ca2+ entry in the immune system and beyond. Immunol Rev. 2009;231:189–209.

103. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, et al. Whole-exome-sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. J Exp Med. 2010;207:2307–12.

104. Picard C, McCarl CA, Papolos A, Khalil S, Lüthy K, Hivroz C, et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. New Engl J Med. 2009;360:1971–80.

105. Lioudyno MI, Kozak JA, Penna A, Safrina O, Zhang SL, Sen D, et al. Orai1 and STIM1 move to the immunological synapse and are up-regulated during T cell activation. Proc Natl Acad Sci USA. 2008;105:2011–6.

106. Weidinger C, Shaw PJ, Feske S. STIM1 and STIM2-mediated Ca(2+) influx regulates antitumour immunity by CD8(+) T cells. EMBO Mol Med. 2013;5:1311–21.

107. Shaw PJ, Weidinger C, Vaeth M, Luethy K, Kaech SM, Feske S. CD4+ and CD8+T cell-dependent antiviral immunity requires STIM1 and STIM2. J Clin Investig. 2014;124:4549–63.

108. Vaeth M, Maus M, Klein-Hessling S, Freinkman E, Yang J, Eckstein M, et al. Store-operated Ca^{2+} entry controls clonal expansion of T cells through metabolic reprogramming. Immunity. 2017;47:664–79.e6.

109. Zhang H, Clemens RA, Liu F, Hu Y, Baba Y, Theodore P, et al. STIM1 calcium sensor is required for activation of the phagocyte oxidase during inflammation and host defense. Blood. 2014;123:2238–49.

110. Clemens RA, Chong J, Grimes D, Hu Y, Lowell CA. STIM1 and STIM2 cooperatively regulate mouse neutrophil store-operated calcium entry and cytokine production. Blood. 2017;130:1565–77.

111. Nunes-Hasler P, Maschalidi S, Lippens C, Castelbou C, Bouvet S, Guido D, et al. STIM1 promotes migration, phagosomal maturation and antigen cross-presentation in dendritic cells. Nat Commun. 2017;8:1852.

112. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE Jr, et al. STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol. 2005;15:1235–41.

113. Zheng CB, Gao WC, Xie M, Li Z, Ma X, Song W, et al. Ang II promotes cardiac autophagy and hypertrophy via Orai1/STIM1. Front Pharm. 2021;12:622774.

114. Chung SC, McDonald TV, Gardner P. Inhibition by SK&F 96365 of Ca2+ current, IL-2 production and activation in T lymphocytes. Br J Pharm. 1994;113:861–8.

115. Huang GN, Zeng W, Kim JY, Yuan JP, Han L, Muallem S, et al. STIM1 carboxyl-terminus activates native SOC, I(crac) and TRPC1 channels. Nat Cell Biol. 2006;8:1003–10.

116. Yang S, Zhang JJ, Huang XY. Orai1 and STIM1 are critical for breast tumor cell migration and metastasis. Cancer Cell. 2009;15:124–34.

117. Chen YF, Chiu WT, Chen YT, Lin PY, Huang HJ, Chou CY, et al. 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. 2011;108:15225–30.

118. Wong PS, Roberts RE, Randall MD. Sex differences in the role of transient receptor potential (TRP) channels in endothelium-dependent vasorelaxation in porcine isolated coronary arteries. Eur J Pharm. 2015;750:108–17.

119. Waldron RT, Chen Y, Pham H, Go A, Su HY, Hu C, et al. The Orai Ca^{2+} channel inhibitor CM4620 targets both parenchymal and immune cells to reduce inflammation in experimental acute pancreatitis. J Physiol. 2019;597:3085–105.

120. Tsujikawa S, DeMeulenaere KE, Centeno MV, Ghazisaeidi S, Martin ME, Tapies MR, et al. Regulation of neuropathic pain by microglial Orai1 channels. Sci Adv. 2023;9:eade7002.

121. Miller J, Bruen C, Schnaus M, Zhang J, Ali S, Lind A, et al. Auxora versus standard of care for the treatment of severe or critical COVID-19 pneumonia: results from a randomized controlled trial. Crit Care. 2020;24:502.

122. Prakriya M, Lewis RS. Potentiation and inhibition of Ca(2+) release-activated Ca(2+) channels by 2-aminoethyldiphenyl borate (2-APB) occurs independently of IP(3) receptors. J Physiol. 2001;536:3–19.

123. Enfissi A, Prigent S, Colosetti P, Capiod T. The blocking of capacitative calcium entry by 2-aminoethyl diphenylborate (2-APB) and carboxyamidotriazole (CAI) inhibits proliferation in Hep G2 and Huh-7 human hepatoma cells. Cell Calcium. 2004;36:459–67.

124. Chen YT, Chen YF, Chiu WT, Wang YK, Chang HC, Shen MR. The ER Ca^{2+} sensor STIM1 regulates actomyosin contractility of migratory cells. J Cell Sci. 2013;126:1260–7.

125. Wang JY, Sun J, Huang MY, Wang YS, Hou MF, He H, et al. STIM1 overexpression promotes colorectal cancer progression, cell motility and COX-2 expression. Oncogene. 2015;34:4358–67.

126. Goto JI, Suzuki AZ, Ozaki S, Matsumoto N, Nakamura T, Ebisui E, et al. Two novel 2-aminoethyl diphenylborinate (2-APB) analogues differentially activate and inhibit store-operated Ca(2+) entry via STIM proteins. Cell Calcium. 2010;47:1–10.

127. Liang X, Zhang N, Pan H, Xie J, Han W. Development of store-operated calcium entry-targeted compounds in cancer. Front Pharm. 2021;12:688244.

128. Andersen TB, López CQ, Manczak T, Martinez K, Simonsen HT. Thapsigargin-from Thapsia L. to mipsagargin. Molecules. 2015;20:6113–27.

129. Jaskulska A, Janecka AE, Gach-Janczak K. Thapsigargin-from traditional medicine to anticancer drug. Int J Mol Sci. 2020;22:4.

130. Denmeade SR, Mhaka AM, Rosen DM, Brennen WN, Dalrymple S, Dach I, et al. Engineering a prostate-specific membrane antigen-activated tumor endothelial cell prodrug for cancer therapy. Sci Transl Med. 2012;4:140ra86.

131. Fenno L, Yizhar O, Deisseroth K. The development and application of optogenetics. Annu Rev Neurosci. 2011;34:389–412.

132. Ma G, He L, Liu S, Xie J, Huang Z, Jing J, et al. Optogenetic engineering to probe the molecular choreography of STIM1-mediated cell signaling. Nat Commun. 2020;11:1039.

133. Leone RD, Amaravadi RK. Autophagy: a targetable linchpin of cancer cell metabolism. Trends Endocrinol Metab. 2013;24:209–17.

134. Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. Mol Cancer. 2020;19:12.

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