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REVIEW

Calcium channels as pharmacological targets for cancer therapy

Xiaozhen Liu[1] · Changyun Feng[2] · Li Yan[1] · Jili Cao[3] · Xinping Zhu[3] · Mingqian Li[3] · Guizhi Zhao[4]

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Abstract
Ca^{2+}, as critical second messengers in biological processes, plays a pivotal role in the regulation of diverse cellular signaling pathways. The dysregulation of calcium signaling is intricately linked to the progression of various cancers. The capacity of Ca^{2+} to modulate cell death and proliferation, along with its potential for pharmacological manipulation, presents a promising avenue for the development of novel cancer therapeutics. This review provides a comprehensive overview of the classification of Ca^{2+} channels and their mechanisms of action in oncogenesis, explores the application of Ca^{2+} blockers in cancer treatment, and underscores the importance of conducting further clinical trials.

Keywords Calcium channels · Cancer therapy · Pharmacological targets

Introduction

The incidence of cancer is rising annually, rendering it a significant threat to human health. Calcium ions (Ca^{2+}) are ubiquitous multifunctional signaling molecules that play critical roles in various physiological functions of cancer cells, regulating processes such as cell proliferation, migration, apoptosis, and immune responses. The maintenance of Ca^{2+} homeostasis within and between cells is crucial for normal cellular function. This homeostasis is tightly regulated by a complex array of components, including Ca^{2+} pumps, ion channels, and ion exchangers [1]. These Ca^{2+} regulatory mechanisms are located on the plasma membrane or intracellular organelle membranes, functioning to maintain low cytoplasmic free Ca^{2+} concentrations and counteract the steep Ca^{2+} gradient between the extracellular environment and organelles [2]. Disruption of Ca^{2+} homeostasis is considered a critical factor in the pathogenesis and progression of various diseases, including cancer, and influences treatment outcomes and survival prognosis in cancer patients. In recent years, the aberrant expression of Ca^{2+} channels, which play a critical role in regulating Ca^{2+} homeostasis, has been increasingly implicated in the pathogenesis of cancer.

This review synthesizes the latest findings concerning the involvement of Ca^{2+} channels in oncogenesis, encompassing their functional roles in cancer cell behavior, the underlying mechanisms of Ca^{2+} signaling in malignant cells, and the prospects and challenges associated with targeting Ca^{2+} channels using blockers as therapeutic interventions. We systematically examine the contributions and potential mechanisms of various Ca^{2+} channel types in facilitating cancer cell proliferation, invasion, and migration. Additionally, we evaluate the therapeutic potential of Ca^{2+} channel blockers and propose future research directions for their application in cancer treatment.

Xiaozhen Liu and Changyun Feng have contributed equally to this work.

✉ Mingqian Li
limingqian613@163.com

✉ Guizhi Zhao
35509790@qq.com

1 Department of Medical and Radiation Oncology, Linyi People's Hospital, Linyi 276000, China

2 Department of Pediatrics, Linyi Maternal and Child Health Hospital, Linyi 276000, China

3 Zhejiang Key Laboratory of Disease-Syndrome Integration for Cancer Prevention and Treatment, Tongde Hospital of Zhejiang Province Afflicted to Zhejiang Chinese Medical University (Tongde Hospital of Zhejiang Province), Hangzhou 310012, Zhejiang, China

4 The Integrated Traditional Chinese and Western Medicine School of Clinical Medicne (Tongde Hospital of Zhejiang Province), Zhejiang Chinese Medical University, Hangzhou 310012, Zhejiang, China

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Classification of Ca^{2+} channels

Calcium channels encompass various types, including transient receptor potential (TRP) channels, voltage-gated calcium channels (VGCCs), mitochondrial calcium channels, store-operated calcium channels (SOCCs), and calcium-activated channels [3].

TRP channels, a category of non-selective cation channels, were initially discovered in Drosophila phototransduction mutants and have since garnered substantial research interest. This family is categorized into six subfamilies: TRPAnkyrin (TRPA), TRPCanonical (TRPC), TRPMelastatin (TRPM), TRPMucolipin (TRPML), TRPPolycystic (TRPP), and TRPVanilloid (TRPV) [3]. Research indicates that TRP channels exhibit extensive tissue distribution and diversity, playing a variety of critical roles in mammals [4, 5]. Among the 28 human members of this channel superfamily, four subfamilies—TRPC, TRPV, TRPM, and TRPA—are implicated in cancer cell invasion behavior. Certain members of the TRPC, TRPM, and TRPV subfamilies are functionally linked to phenotypic and structural cellular changes essential for mechanotransduction in cell migration and tumor metastasis [6]. Humanized 3D representations of selected TRP family members are provided in Fig. 1.

The VGCC family comprises several subtypes, including L-type (CaV1.1–1.4), N-type (CaV2.2), P/Q-type (CaV2.1), R-type (CaV2.3), and T-type (CaV3.1–3.3) channels [3]. This family is integral to the process of excitation-coupling, facilitating mechanisms such as excitation–contraction coupling in skeletal and cardiac muscles, excitation-secretion coupling, and excitation-transcription coupling [19]. Excessive neuronal Ca^{2+} influx via VGCCs can initiate various cellular damage pathways, including oxidative stress, proteasome dysfunction, mitochondrial damage, neuroinflammation, apoptosis, and autophagy [20]. Notably, the L-type and T-type channels have been extensively investigated in the context of cancer, where they are implicated in tumor drug resistance and progression [3]. Figure 2 presents humanized 3D representations of selected VGCC family members.

Mitochondrial calcium channels are categorized into the outer membrane voltage-dependent anion channel (VDAC) family and the inner membrane channels, which include the mitochondrial calcium uniporter (MCU) and the mitochondrial sodium/calcium exchanger (NCLX) [3] (Fig. 3). The VDAC family consists of three subtypes—VDAC1, VDAC2, and VDAC3—that share similar structural and

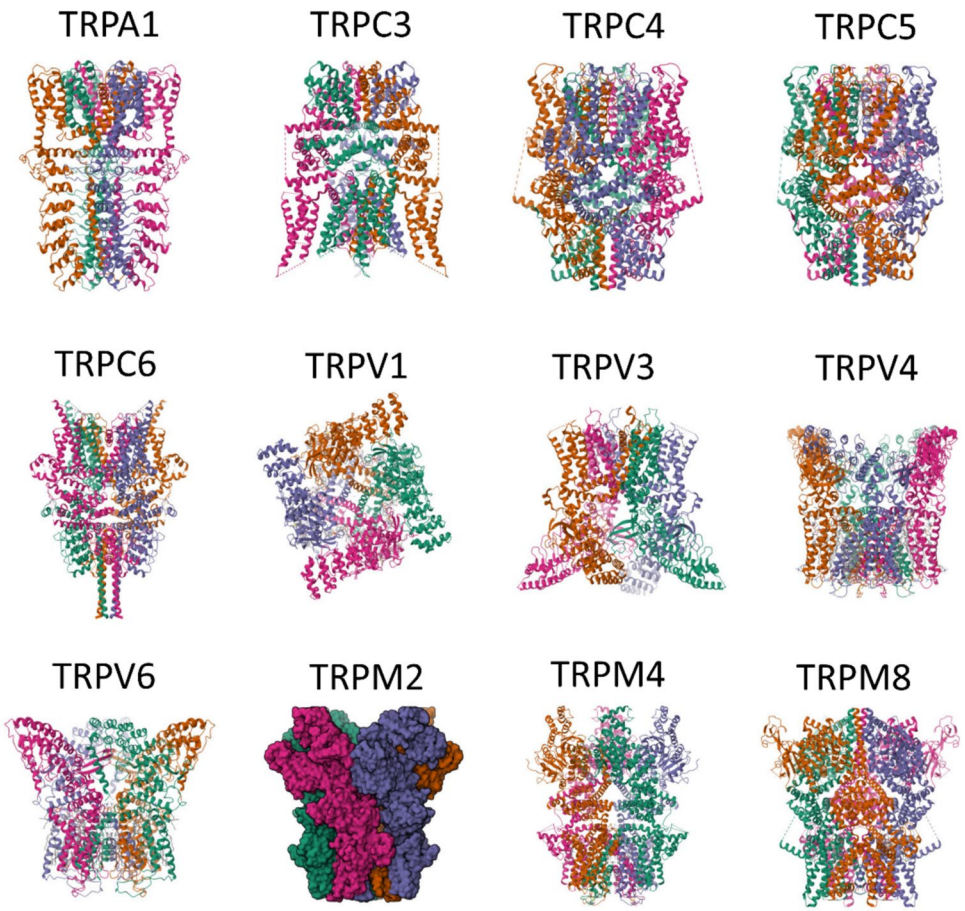

Fig. 1 Three-dimensional structure of known TRP channels. TRPA1: Structure of the TRPA1 ion channel determined by electron cryo-microscopy [7]; TRPC3: Full-length human TRPC3 in GDN [8]; TRPC4: Cryo-EM structure of the human TRPC4 in lipid nanodiscs [9]; TRPC5: Human TRPC5 apo state structure at 3 angstrom [10]; TRPC6: Cryo-EM structure of human TRPC6 at 3.8A resolution [11]; TRPV1: Cryo-EM structure of human TRPV1 in cNW11 nanodisc and soybean lipids [12]; TRPV3: Structure of human TRPV3 [13]; TRPV4: Cryo-EM structure of full-length human TRPV4 in apo state [14]; TRPV6: Cryo-EM structure of human TRPV6 in the open state [15]; TRPM2: Human TRPM2 in the apo state [16]; TRPM4: Human TRPM4 ion channel in lipid nanodiscs in a calcium-free state [17]; TRPM8: Human apo TRPM8 in a closed state (composite map) [18]

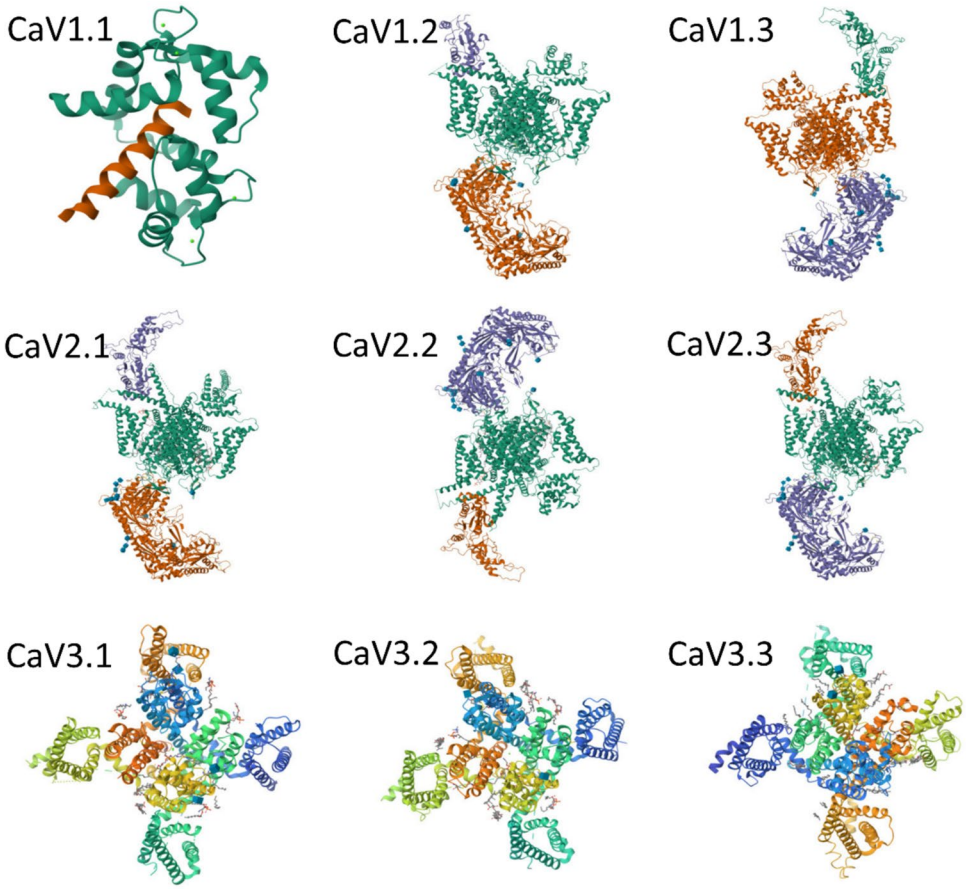

Fig. 2 Three-dimensional structure of known voltage-gated calcium channels. CaV1.1: Calmodulin complexed with CaV1.1 IQ peptide [21]; CaV1.2: Cryo-EM structure of human high-voltage activated L-type calcium channel CaV1.2 (apo) [22]; Cav1.3: Human L-type voltage-gated calcium channel Cav1.3 at 3.0 Angstrom resolution [23]; CaV2.1: PQ type calcium channel [24]; Cav2.2: Human N-type voltage-gated calcium channel Cav2.2 at 3.1 Angstrom resolution [25]; Cav2.3: Human R-type voltage-gated calcium channel Cav2.3 at 3.1 Angstrom resolution [26]; Cav3.1: Cryo-EM structures of apo and antagonist-bound human Cav3.1 [27]; Cav3.2: Cryo-EM structure of apo state human Cav3.2 [28]; CaV3.3: Cryo-EM structure of human low-voltage activated T-type calcium channel CaV3.3 (apo) [29]

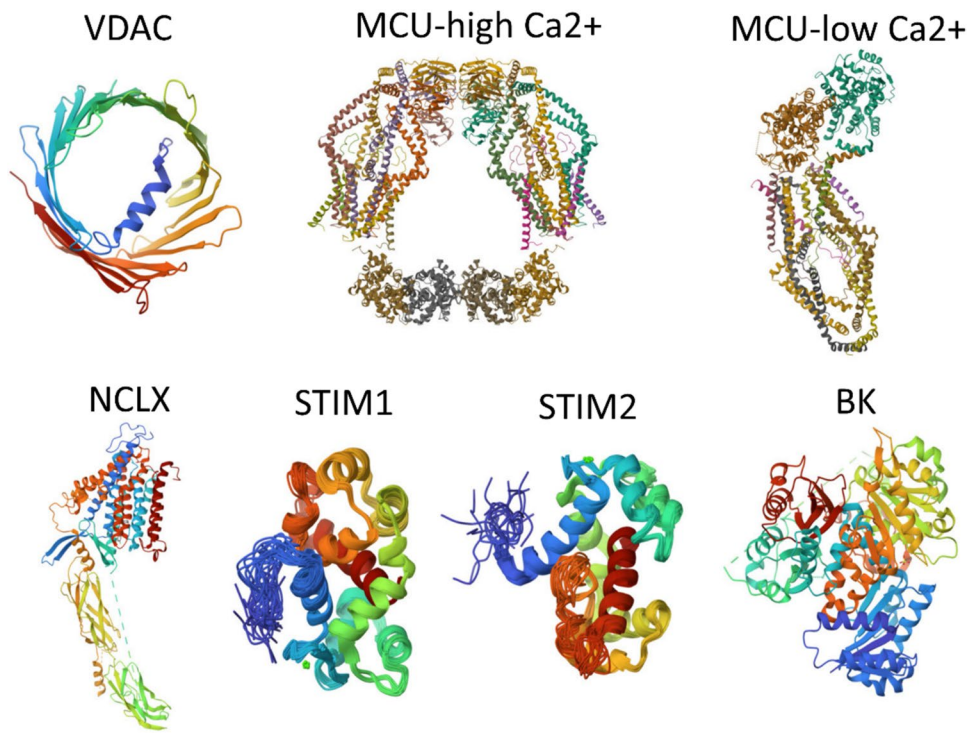

Fig. 3 Other known three-dimensional structures of calcium channels. VDAC: Structure of the human voltage-dependent anion channel [44]; MCU-high Ca2 + : Cryo-EM structure of mitochondrial calcium uniporter holocomplex in high Ca2 + [45]; MCU-low Ca2 + : Cryo-EM structure of mitochondrial calcium uniporter holocomplex in low Ca2 + [45]; NCLX: structure of human sodium-calcium exchanger NCX1 [46]; STIM1: NMR structure of calcium-loaded STIM1 EF-SAM [47]; STIM2: NMR structure of calcium-loaded STIM2 EF-SAM [48]; BK: Crystal Structure of the Human BK Gating Apparatus [49]

functional characteristics. VDAC1 is situated on the outer mitochondrial membrane and plays a pivotal role in mediating metabolic interactions between mitochondria and the cytoplasm. It also engages with proteins that are integral to cellular metabolism, apoptosis, and survival pathways [30]. VDAC2 is classified as an anti-apoptotic protein and, similar to VDAC3, functions as a sensor of oxidative stress [31]. MCU is critical in mitochondrial dysfunction and exhibits tissue-specific behaviors, influencing various aspects of metabolic function. It regulates processes such as Ca^{2+} dynamics, mitochondrial Ca^{2+} uptake, adenosine triphosphate (ATP) production, oxidative stress, and apoptosis [32]. Structural abnormalities in the MCU can result in Ca^{2+} imbalances, impacting malignant cellular phenotypes, including proliferation, invasion, and metastasis [33]. The coordinated activity of Ca^{2+} uptake via the MCU and efflux through the NCLX modulates intracellular Ca^{2+} signaling. The mitochondrial Ca^{2+} efflux pathway via NCLX serves as a critical regulatory node linking autophagy regulation and nutrient restriction [34]. NCLX is capable of activating the Ca^{2+}-dependent PYK2-SRC-STAT3-IL-6 signaling pathway. The downregulation of NCLX results in elevated mitochondrial Ca^{2+} levels, thereby increasing the sensitivity of cancer cells to chemotherapeutic agents [35].

The SOCC system comprises stromal interaction molecule (STIM) and Orai proteins (Fig. 3). STIM1 and STIM2 are multi-domain, single-channel transmembrane proteins located in the endoplasmic reticulum membrane, which detect fluctuations in Ca^{2+} concentrations within the endoplasmic reticulum and convey cellular signals to the Orai1 channel [36]. The Orai family of mammalian ion channel-forming proteins consists of three members: Orai1, Orai2, and Orai3, encoded by homologous genes [37]. Orai1 is the principal component responsible for store-operated calcium entry (SOCE), playing a crucial role in regulating various physiological and pathological processes, and has been extensively studied in the context of carcinogenesis [38]. In mammalian cells, two isoforms of Orai1 have been identified: the full-length variant Orai1 α and the truncated form Orai1 β, the latter of which lacks the N-terminal 63 amino acids. Orai1 α demonstrates greater sensitivity to Ca^{2+}-dependent rapid inactivation compared to Orai1 β [39]. Orai1 α and Orai1 β exhibit comparable effects on SOCE in cancer cells, facilitating cyclooxygenase (COX) activation and mammosphere formation [40].

Calcium-activated channels are categorized into two types: calcium-activated chloride channels and calcium-activated potassium channels [3] (Fig. 3). Calcium-activated chloride channels are constituted by the protein anoctamine 1 (ANO1) or TMEM16A, which is activated in various cancers and contributes to cancer cell proliferation [41]. Calcium-activated potassium channels play a crucial role in regulating interspike intervals and spike-frequency adaptation, serving as fundamental modulators of neuronal excitability. These channels include large-conductance calcium-activated potassium (BK) channels, as well as small-conductance (SK) and intermediate-conductance (IK) calcium-activated potassium channels [42]. Additionally, these channels are implicated in the regulation of essential processes in cancer cells [43].

Effects of Ca^{2+} channels on cancer

Alterations in Ca^{2+} concentration within the human body are associated with various cancers, including breast, lung, esophageal, gastric, colon cancers, and gliomas, among others [50–55]. Evidence from preclinical and clinical trials indicates that modifications in Ca^{2+} signaling are pivotal in the molecular reprogramming that drives cancer progression [56]. Increased intracellular Ca^{2+} levels can facilitate the proliferation and metastasis of cancer cells and are regarded as a marker of advanced-stage disease [57]. In contrast to most normal cells, the aberrant expression or modified activity of specific Ca^{2+} channels in certain cancers contributes to cancer initiation and progression. This occurs through mechanisms that influence tumor angiogenesis, epithelial-to-mesenchymal transition (EMT), immune response, cancer stem cells (CSCs), and the sensitivity of tumors to treatment.

Tumor angiogenesis

Under hypoxic conditions, tumor angiogenesis is facilitated by the secretion of various growth factors that enhance endothelial cell proliferation, tube formation, and migration, ultimately resulting in tumor angiogenesis [58]. The formation of tumor blood vessels is a critical physiological requirement for cancer cell proliferation and metastasis. Ca^{2+} signaling plays a pivotal role in tumor angiogenesis, as alterations in intracellular Ca^{2+} levels regulate key nuclear and cytoplasmic events involved in the initiation and progression of angiogenesis in endothelial cells. TRPV3, TRPV4, and Orai1 are significant contributors to this process (Fig. 4).

TRP channels are key regulatory factors in tumor angiogenesis and represent novel targets for anti-angiogenesis and vascular normalization therapies [58]. Specifically, TRPV3 modulates tumor angiogenesis via the hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) signaling pathway. The downregulation of TRPV3 expression can lead to reduced levels of Ca^{2+}, HIF-1α, and VEGF proteins in cancer cells. Furthermore, the absence of HIF-1α can lead to a reduction in the expression and secretion of VEGF. The lack of TRPV3 results in increased proliferation, tube formation, and migration of human umbilical vein endothelial cells, thereby inhibiting the proliferation of

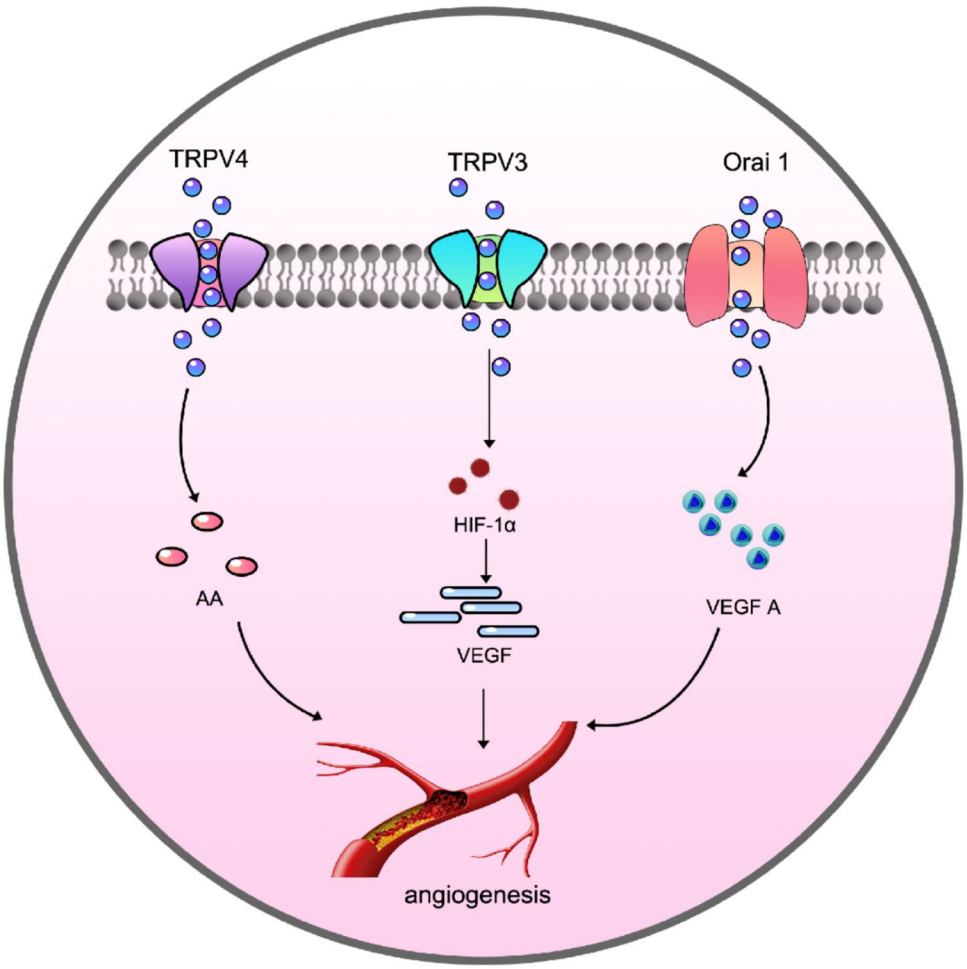

Fig. 4 The related mechanisms of TRPV3, TRPV4, and Orai1 in tumor angiogenesis. TRPV4 facilitates tumor angiogenesis by regulating AA; TRPV3 modulates tumor angiogenesis via the HIF-1α and VEGF signaling pathway, and HIF-1α can induce the expression and secretion of VEGF. Orai1 is positive correlated with VEGFA, and plays a role in modulating the tumor angiogenesis

xenograft tumors [59]. Moreover, TRPV4 is crucial in regulating the migration of endothelial cells derived from human breast cancer (BTEC) cells. Silencing TRPV4 expression completely abolished the migration capacity of BTEC induced by arachidonic acid (AA), suggesting that TRPV4 facilitates tumor angiogenesis through the regulation of AA. Concurrently, AA induces actin remodeling in BTEC, which increases TRPV4 expression in the cytoplasmic membrane, thus promoting tumor angiogenesis and growth [60]. However, some studies have reported contrasting findings. Due to the altered mechanosensitivity of tumor endothelial cells to extracellular matrix stiffness, these cells exhibit abnormal angiogenesis and increased migration, accompanied by reduced TRPV4 expression and function. The absence of TRPV4 has been associated with an increase in vascular density and diameter, alongside a reduction in pericyte coverage, thereby facilitating tumor progression. Notably, the administration of the TRPV4 small molecule activator GSK1016790A in conjunction with the anticancer drug cisplatin in murine models has been shown to significantly inhibit tumor growth by promoting vascular maturation [61]. Furthermore, a correlation has been identified between the gene expression levels of Orai1 and angiogenesis-related genes, specifically VEGFA and NF-KB1, in colon cancer tissues. Among these, Orai1 exhibits a significant positive correlation with VEGFA expression, suggesting that Orai1 may play a role in modulating the tumor microenvironment and angiogenesis [62].

Epithelial-to-mesenchymal transition

EMT can enhance the expression of genes associated with cell proliferation, invasion, and migration, thereby contributing to tumor progression [63]. The extracellular signaling factors that initiate EMT programs necessitate a second messenger to convey their effects to target cells, with Ca^{2+} signaling being capable of modulating certain tumor cells to acquire invasive phenotypes via the EMT pathway [63, 64]. The Ca^{2+} signaling pathway and EMT are involved in the metastasis of breast cancer through their interaction and are, to some extent, regulated by epigenetic mechanisms. The activation of EMT can influence Ca^{2+} concentration, and reciprocally, Ca^{2+} signaling can modulate the expression of EMT-related markers [65]. Certain members of the TRP

family and the calcium-activated chloride channel family play significant roles in the EMT process, although their effects may vary between promotion and inhibition (Fig. 5).

In breast cancer, the expression of TRPC1 is significantly associated with the expression of genes related to EMT, with elevated expression observed in basal B breast cancer cell lines [66]. Furthermore, TRPC1 inhibitors have been shown to attenuate transforming growth factor beta 1 (TGF-β1)-induced tumor EMT by modulating the Ras/Raf1/ERK signaling pathway [67]. Similarly, in ovarian cancer, TRPM7 expression exhibits a negative correlation with E-cadherin expression and a positive correlation with the expression of vimentin, N-cadherin, and Twist. Silencing TRPM7 can inhibit the EMT process and tumor metastasis in ovarian cancer by reducing the activation of the calcium-dependent PI3K/AKT pathway [68]. In lymph node-positive basal breast cancer, TRPV4 is linked to EMT-related gene ontology and is associated with poor relapse-free survival. TRPV4 plays a critical role in the Ca^{2+} influx phase of breast cancer cells induced by epidermal growth factor, an EMT inducer. The selective pharmacological activation of TRPV4 can upregulate various EMT markers in breast cancer cells [69]. Additionally, the absence of TRPV6 can compromise the integrity of breast epithelial cells, resulting in abnormal morphology of mammary spheroids in three-dimensional culture [70]. The expression level of TRPV6 is significantly associated with the levels of common EMT markers, including vimentin, slug, snail, N-cadherin, and β-catenin, while it is inversely correlated with the expression level of E-cadherin [70]. These findings suggest that TRP channels may play critical roles in the mesenchymal invasion of cancer cells and contribute to cancer progression through this mechanism. Calcium-activated chloride channel A2 (CLCA2) has been shown to inhibit EMT via the p38/JNK/ERK signaling pathway, thereby promoting apoptosis in cancer cells [71]. Furthermore, the overexpression of the tumor suppressor CLCA4 can impede the occurrence of EMT through the PI3K/AKT signaling pathway, influencing the expression patterns of EMT markers and thus preventing cancer cell invasion and migration [72]. Conversely, the overexpression of tweety homolog 3 (TTYH3), a member of the calcium-activated chloride channels family, can induce EMT in cancer cells by upregulating the expression of N-cadherin and vimentin via the Wnt/β-catenin pathway

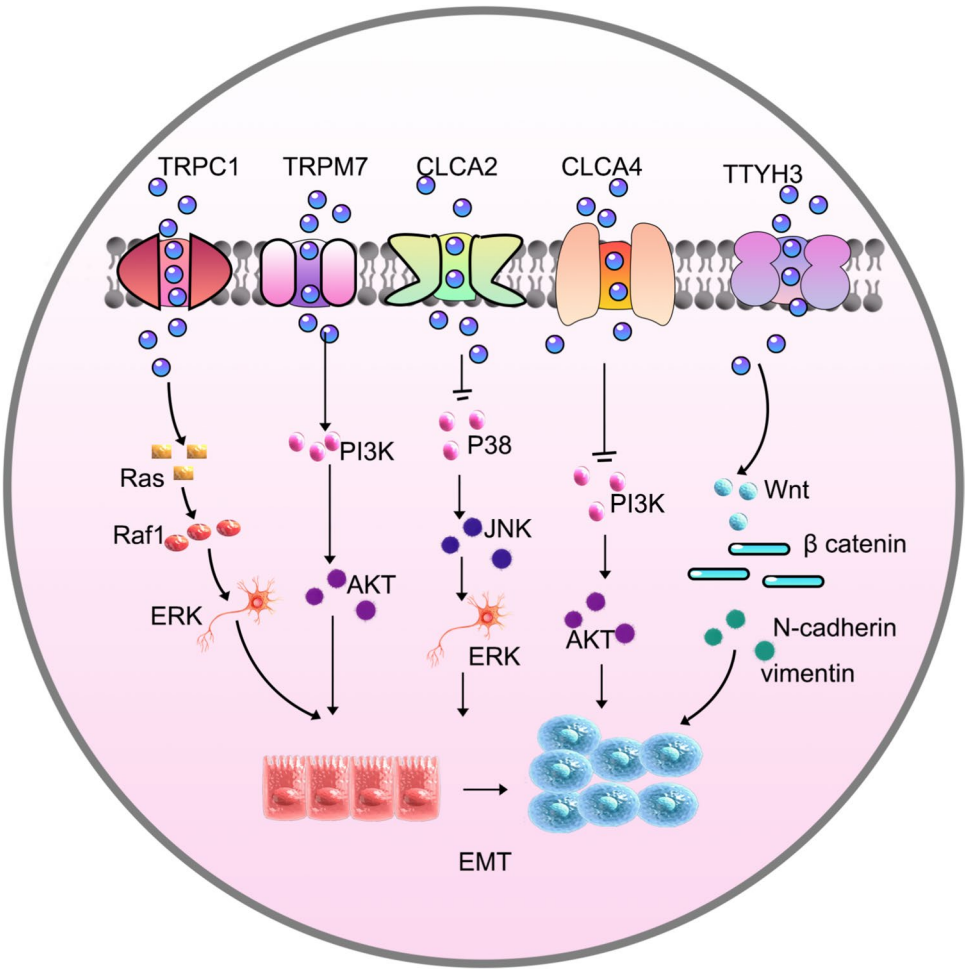

Fig. 5 The related mechanisms of TRPC1, TRPM7, CLCA2, CLCA4, and TTYH3 in the process of EMT. TRPC1 can induce tumor EMT by modulating the Ras/Raf1/ERK signaling pathway. TRPM7 can facilitate the EMT process by inducing the activation of the calcium-dependent PI3K/AKT pathway. CLCA2 inhibits EMT via the p38/JNK/ERK signaling pathway. CLCA4 can impede the occurrence of EMT through the PI3K/AKT signaling pathway. TTYH3 can induce EMT in cancer cells by upregulating the expression of N-cadherin and vimentin via the Wnt/β-catenin pathway

[73]. This indicates that calcium-activated chloride channels play a significant role in the EMT process, although the effects—either promoting or inhibitory—vary among different channel members.

Immunity response

The tumor microenvironment has emerged as a critical determinant in cancer progression and development. The presence of infiltrating immune cells within this microenvironment serves as a prognostic indicator for tumor response to therapeutic interventions and patient outcomes [74]. Ionic channels, located on the surfaces of various immune cells, have been implicated in the regulation of immune cell activation, motility, and effector functions. Specifically, Ca^{2+} channels are pivotal in the cytotoxic activity of immune cells against tumor cells [75]. Within this context, TRPV1 and TRPM8 are instrumental in modulating T cell immunity, whereas the calcium-activated potassium channel KCa3.1 and TRPA1 play distinctive roles in the function of macrophages and natural killer (NK) cells. Additionally, Orai1 represents a significant target for the modulation of programmed death-ligand 1 (PD-L1) immune checkpoint blockade. The principal regulatory mechanisms are depicted in Fig. 6.

T cells, as integral components of the adaptive immune system, facilitate the interaction between adaptive and innate immunity. The TRP channel-mediated Ca^{2+} influx is essential for the activation of T cell functions [58]. In comparison to activated T cells, the surface expression of TRPV1 is markedly elevated during immunosuppression, suggesting that TRPV1 plays a crucial role in the processes of immune activation and immunosuppression [76]. Furthermore, interferon-gamma (IFNγ) is essential for anti-tumor defense through cytotoxic mechanisms, and activation of TRPV1 has been shown to reduce IFNγ secretion. Inhibition of TRPV1 expression can lead to decreased secretion of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) in the supernatant of cultured mouse leukocytes [77]. Notably, the use of nanoparticles to block TRPV1 channels can prevent hyperthermia-induced Ca^{2+} influx and subsequent nuclear translocation of heat shock factor 1 (HSF1). This blockage inhibits the degradation of tumor stroma via the TGF-β pathway, thereby facilitating the infiltration of

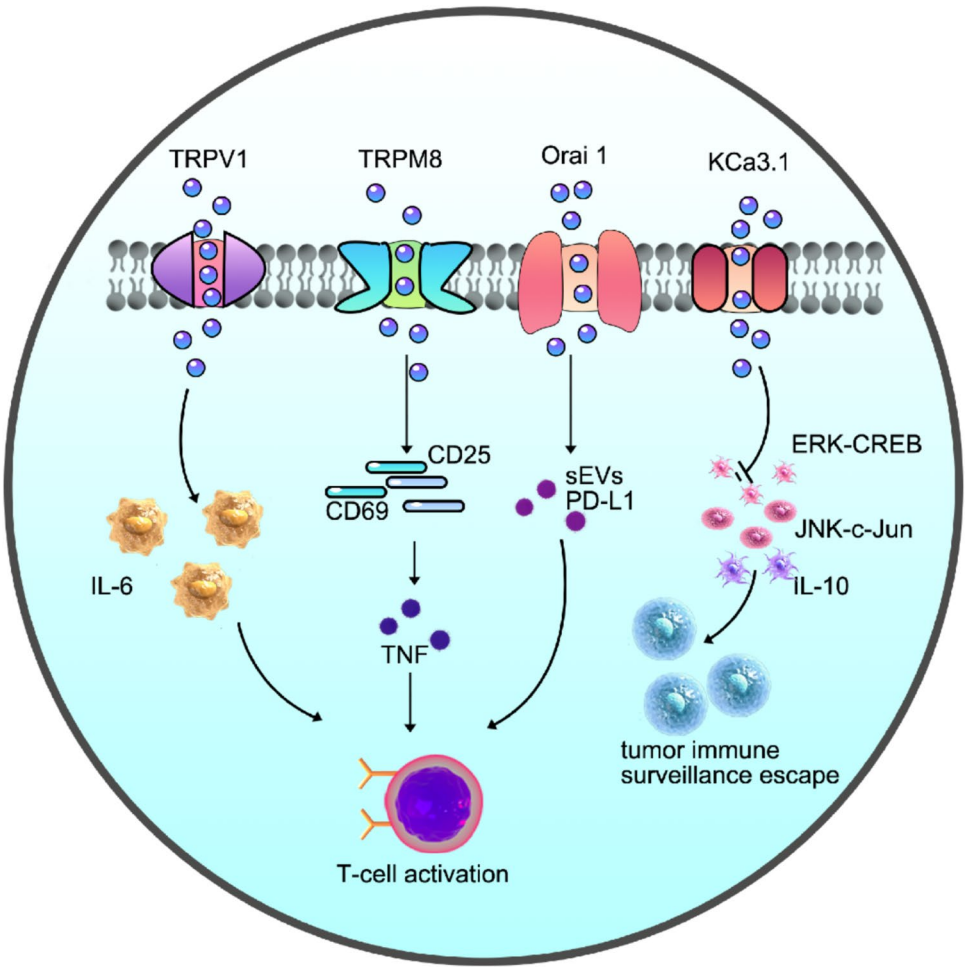

Fig. 6 The related mechanisms of TRPV1, TRPM8, Orai1and KCa3.1 in the process of tumor immunity. TRPV1 can regulate tumor immunity by mediating the secretion of IL-6. TRPM8 increases the expression levels of CD25 and CD69, as well as the promotion of TNF secretion. Orai1 induces the release of sEV and activates PD-L1, and further regulates T cell immune function. KCa3.1 may inhibit IL-10-mediated tumor immune surveillance evasion, by attenuating their production via the ERK-CREB and JNK-c-Jun signaling pathways

anti-tumor drugs and immune cells into highly fibrotic and immunosuppressive pancreatic cancer tissue. This approach enhances the efficacy of hyperthermia treatment across various primary, metastatic, and recurrent tumors [78]. Consequently, nanoparticle-mediated TRPV1 blockade has the potential to restore thermal immunotherapy, offering tumor eradication and immune memory effects. Furthermore, the cold-sensitive TRPM8 channel plays a pivotal role in the activation of T cells. Activation of TRPM8 acts synergistically with T cell receptor stimulation, resulting in increased expression levels of CD25 and CD69, as well as the promotion of pro-inflammatory cytokine TNF secretion. However, inhibiting TRPM8 expression does not impede the activation of T cells stimulated by the T cell receptor. While inhibition of TRPM8 expression during T cell activation may lead to reduced cell proliferation and phenotypic alterations, it does not compromise cell viability [79]. It has been established that TRPM8 functions as a calcium channel, and its activation can be leveraged to elicit effective immune responses.

Macrophages are versatile immune cells that play a pivotal role in metabolic regulation induced by mechanical stimulation. Tumor-associated macrophages (TAMs) are the predominant cells recruited within the tumor microenvironment [80]. The activation of the calcium-activated potassium channel KCa3.1 may inhibit IL-8-induced tumorigenicity and metastasis, as well as IL-10-mediated tumor immune surveillance evasion, by attenuating their production from TAMs via the ERK-CREB and JNK-c-Jun signaling pathways [81].

Natural killer (NK) cells constitute approximately 5% to 15% of the total circulating lymphocyte population. The activation of TRPA1 represents a significant regulatory signal for NK cells, enhancing NK cell-mediated cytotoxicity against melanoma cells and modulating prolonged NK cell-mediated cytotoxicity by promoting NK cell survival. Furthermore, TRPA1 agonists have potential as therapeutic agents to augment the immune system's response to tumors [82]. Additionally, KCa3.1 is expressed in roughly one-quarter of resting NK cells, and its expression level can increase threefold following activation with IL-15 and IL-2. Targeted inhibition of KCa3.1 expression has been shown to enhance NK cell cytotoxicity [83].

In recent years, the strategy of blocking immune checkpoints has garnered significant attention in cancer research as a means to counteract immune evasion by tumor cells. Notably, the expression of PD-L1 in various tumor cells has emerged as a pivotal breakthrough in cancer therapy. Suppressing the expression of TRPV2 has been shown to decrease PD-L1 levels in gastric cancer cells, thereby inhibiting the interaction between PD-L1 and programmed death-1 (PD-1). Clinical sample analyses have revealed a positive correlation between TRPV2 and PD-L1 expression, with a marked reduction in the 5-year overall survival rate among patients exhibiting high TRPV2 expression and PD-L1 positivity [53]. Furthermore, PD-L1 can be transported to its functional site via local diffusion or through small extracellular vesicles (sEVs). Studies have demonstrated that sEV release in tumor cells is dependent on Ca^{2+}, and silencing the Orai1 gene reduces both sEV release and Ca^{2+} signaling [84]. Consequently, Ca^{2+}-dependent proteins within the secretion pathway and the Orai1 channel have become critical targets for elucidating and modulating the blockade of the PD-L1 immune checkpoint.

Cancer stem cells

CSCs are pivotal in the proliferation, invasion, and progression of cancer due to their capacity to differentiate into diverse forms and functional states of tumor cells, thus representing a significant focus of contemporary research [85]. Beyond merely reducing tumor volume, targeting CSCs is essential for the complete eradication of cancer, minimizing the risk of recurrence, and enhancing patient survival rates [86]. Various members of the TRP channels, VGCCs, SOCCs, and calcium-activated chloride channels contribute distinctively to this process (Fig. 7).

Specifically, different TRP channel members are integral to the physiological and pathological mechanisms of CSCs across various cancer types. Notably, the expression of TRPC6 is markedly elevated in triple-negative breast cancer (TNBC) tissues compared to estrogen receptor-positive breast cancer tissues [87]. The population with high TRPC6 expression exhibits a greater proportion of CSCs than those with low TRPC6 expression, with TRPC6-mediated calcium signaling being crucial for maintaining the CSC state. The wild-type TRPC6 is essential for mammosphere formation and plays a causal role in the CSCs of TNBC [87]. Furthermore, TRPC3 is overexpressed in TNBC cells and can be activated by lysophosphatidic acid, thereby facilitating the self-renewal of CSCs [88]. TRPC3 also activates the NF-κB signaling pathway through the induction of Ca^{2+} influx. The upregulation of TRPC3 expression in mesenchymal stem cells significantly enhances NF-κB activity, thereby inducing the proliferation, migration, and invasion capabilities of mesenchymal stem cell-derived cancer-associated fibroblasts (MT CAFs), ultimately promoting cancer progression and influencing patient prognosis [89]. In the context of esophageal CSCs, similar findings have been observed with TRPV2 channels, which are gated by the lipid ligand lysophosphatidylcholine [90, 91]. TRPV2 regulates calcium-mediated calpain activation and the subsequent cleavage of the adhesion protein talin, as well as the organization of F-actin. Its activity is sufficient to confer tumor cells with invasive and migratory potential, and it is directly associated with both local and distant metastasis of malignant tumors [92]. Conversely, TRPV2 expression and activation

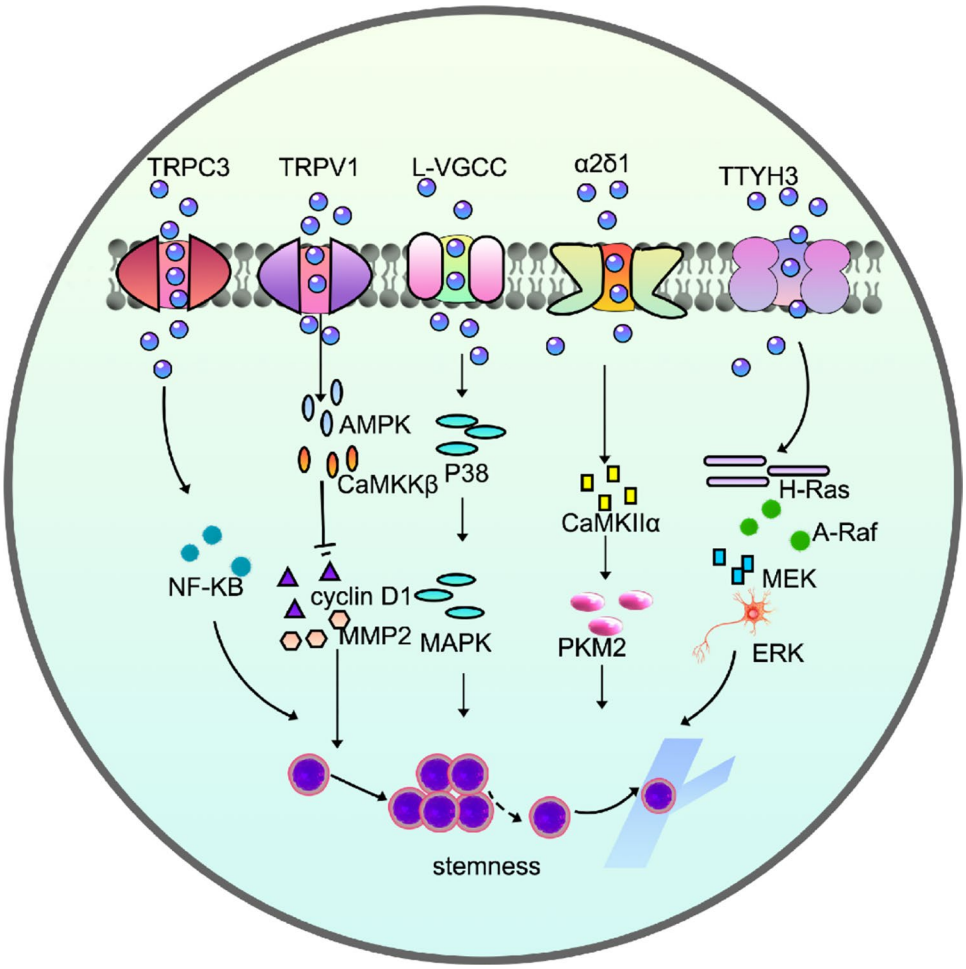

Fig. 7 The related mechanisms of TRPC3, TRPV1, L-VGCC, α2δ1 and TTYH3 in regulating tumor stemness. TRPC3 expression significantly enhances NF-κB activity, thereby inducing the proliferation, migration, and invasion capabilities of tumor cells. TRPV1 overexpression leads to the activation of AMPK and CaMKKβ phosphorylation, and a reduction in the expression of cyclin D1 and MMP2, and lead to the loss of cells stemness. L-type VGCCs can initiate the activation of p38-MAPK signaling pathway, thereby promoting cancer stemness. The VGCC auxiliary subunit α2δ1, facilitating the promotion of cancer stemness through the activation of CaMKIIδ-mediated PKM2 sequential phosphorylation. TTYH3 leads to the activation of H-Ras/A-Raf/MEK/ERK signaling pathway, and significantly promoting cancer stemness

can lead to the loss of stemness and promote apoptotic cell death in hepatocellular carcinoma stem cells [93] and glioma stem cells [90]. In glioblastoma stem cells, TRPV1 has been observed to exhibit a negative correlation [94]. The TRPV1 protein is predominantly localized on the cytoplasmic membrane, and its overexpression leads to an increase in intracellular Ca^{2+} concentration, activation of adenosine mono phosphate activated protein kinase (AMPK) and calcium/calmodulin-dependent protein kinase kinases-β (CaMKKβ) phosphorylation, and a reduction in the expression of cyclin D1 and matrix metalloproteinase-2 (MMP2). TRPV1 is significantly associated with the cell cycle, and its overexpression can arrest the G1 phase, thereby inhibiting cancer cell proliferation and diminishing the invasive and migratory capabilities of cancer cells. Furthermore, TRPV1 expression is markedly downregulated in human primary gastric cancer tissues and is positively correlated with histological grading, tumor size, lymphatic metastasis, and clinical stage. Additionally, TRPV1 expression is significantly associated with established tumor proliferation and metastasis markers, such as Ki67, VEGF receptor, and E-cadherin, which critically influence patient prognosis [95].

CSCs possess Ca^{2+} channels within their cytoplasmic membranes, which can be activated by various stimuli, including the depletion of intracellular Ca^{2+} stores or changes in voltage. Notably, the upregulation of T-type and L-type VGCCs is implicated in the proliferation and invasive behavior of CSCs in glioblastoma and ovarian cancer [96–99]. The Ca^{2+} influx mediated by L-type VGCCs can initiate the activation of the Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII)-dependent p38 mitogen-activated protein kinase (MAPK) signaling pathway, thereby promoting cancer cell growth, migration, and invasion [100, 101]. The VGCC auxiliary subunit α2δ1, which encodes VGCC, has been identified as an oncogene in various cancers. Knockdown of α2δ1 results in an increased number of cells in the G1 phase, reduced cell proliferation and migration, and the induction of apoptosis [102] The protein α2δ1 is localized on the cell membrane of cancer cells, with a positive expression rate ranging from 1.5 to 3% in breast cancer, and is associated with high tumorigenic potential [103]. The protein α2δ1 influences the tumor microenvironment by modulating fibroblast activity and exhibits strong tumor initiation and self-renewal capabilities both in vitro

and in vivo. Its elevated expression sustains the properties of tumor-initiating cells and serves as an independent prognostic factor for poor outcomes in cancer patients [102, 103]. In non-small cell lung cancer (NSCLC) cell lines and clinical specimens, α2δ1 specifically identifies the tumor-initiating cell subpopulation [104]. Compared to CD133 + or CD166 + NSCLC cells, α2δ1 + cells contain a higher abundance of tumor-initiating cells. Furthermore, NSCLC tumor-initiating cells expressing α2δ1 + demonstrate resistance to conventional chemotherapy and possess the ability to form heterogeneous tumors and self-renew in NOD/SCID mice, thereby displaying characteristics akin to CSCs. Notably, antibodies targeting α2δ1 have shown significant therapeutic efficacy in NSCLC xenografts by effectively eradicating tumor-initiating cells [104]. In addition, α2δ1 is both functionally sufficient and essential, facilitating the promotion of pancreatic tumor-initiating cell characteristics and enhancing stem-like properties through the mediation of Ca^{2+} influx and the activation of CaMKIIδ-mediated the M2 isoform of pyruvate kinase (PKM2) sequential phosphorylation [105]. Additionally, small cell lung cancer cells expressing α2δ1 exhibit cancer stem cell-like traits, including tumorigenicity, self-renewal, differentiation potential, and resistance to therapy [106]. The overexpression of α2δ1 significantly enhances the sphere-forming efficiency of tumor cells, upregulates the expression of genes associated with tumor cells, and increases cell migration capability [103].

Orai1 facilitates the proliferation and tumorigenicity of breast cancer stem cell-like cells via the glycolysis pathway. Within TNBC and human epidermal growth factor receptor 2 (HER2)-positive breast cancer subtypes, Orai1 plays a crucial role in mammosphere formation and the self-renewal efficiency of breast cancer stem cells. In contrast, Orai1 does not significantly impact breast cancer stem cells derived from estrogen receptor-positive (ER +) cells or non-tumor breast stem cells [40]. Nonetheless, research indicates that silencing Orai1 RNA expression can inhibit the growth of ER + breast cancer stem cell-like cells in tumor spheroids, downregulate the expression of breast cancer stem cell markers, and subsequently suppress the growth of xenografts in mice [107]. Conversely, Orai3 enhances the proliferation and tumorigenicity of breast cancer stem cell-like cells through a glycolysis-independent mechanism. Silencing Orai3 RNA similarly inhibits xenograft growth in vivo and reduces the proliferation and stemness of breast cancer stem cell-like cells in vitro [107]. Furthermore, Orai3 is significantly enriched within the cancer stem cell population of oral/oropharyngeal squamous cell carcinoma (OSCC). The ectopic expression of Orai3 in non-tumorigenic, immortalized oral epithelial cells has been shown to promote malignant growth and enhance stem cell-like characteristics. Conversely, silencing the expression of endogenous Orai3 inhibits the cancer stem cell phenotype in OSCC. Additionally, Orai3 markedly upregulates the expression of the stemness-associated transcription factor, inhibitor of DNA binding 1 (ID1), with both Orai3 and ID1 exhibiting higher expression levels in cancer stem cells compared to non-tumor stem cells. The application of ID1 in OSCC and cells overexpressing ectopic Orai3 can abrogate the cancer stem cell phenotype [108], suggesting that Orai3 plays a pivotal role in the regulation of cancer stem cells.

TTYH3, a member of the calcium-activated chloride channel family, is involved in signal transduction processes. The downregulation of TTYH3 leads to a suppression of the H-Ras/A-Raf/MEK/ERK signaling pathway by inhibiting the phosphorylation of fibroblast growth factor receptor 1 (FGFR1). This suppression significantly reduces cancer cell proliferation and sphere formation, while also diminishing the migratory and invasive capabilities of cancer cells. TTYH3, identified as a tumor-promoting factor, is significantly correlated with reduced overall survival rates in cancer patients due to its elevated expression levels [73, 109].

Tumor treatment sensitivity

Innate and acquired drug resistance are the main reasons for the failure of tumor treatment. The interruption of Ca^{2+} signaling and defects in Ca^{2+} channels are common properties of tumor cells and can reduce sensitivity to drugs that induce cell death, thereby promoting tumor cells proliferation and metastasis [110]. These properties make Ca^{2+} signaling and channels ideal targets for reversing tumor drug resistance. The Ca^{2+} channels that affect the sensitivity of tumor treatment include TRPC6, TRPM2, and TRPV2 in the TRP family, as well as CaV1.3 in the VGCC family and the auxiliary subunit α2δ1 of VGCC.

The mitochondrial reactive oxygen species mediated by paclitaxel can induce tumor cell death and apoptosis through excessive Ca^{2+} influx [111]. Researchers have confirmed that increased expression of TRPC6 is significantly associated with paclitaxel resistance in TNBC patients [87]. It is worth noting that treating this resistant organoid with TRPC6 inhibitor BI-749327 can increase its sensitivity to paclitaxel. Following paclitaxel treatment, quantitative analysis of TRPC6 mRNA expression revealed that TRPC6 mRNA levels were approximately 13-fold higher in resistant cell populations compared to sensitive ones, with a corresponding increase in TRPC6 protein levels. This suggests that tumor cells subjected to paclitaxel treatment rely on TRPC6 expression. The TRPC6-mediated Ca^{2+} influx can suppress the epithelial splicing factor, epithelial splicing regulatory protein 1 (ESRP1), thereby promoting the expression of integrin α6B splicing variants. Both TRPC6 and α6B are capable of activating TAZ, inhibiting Myc expression, and consequently facilitating tumor cell persistence (Fig. 8). Therapeutic inhibition of TRPC6 expression enhances the

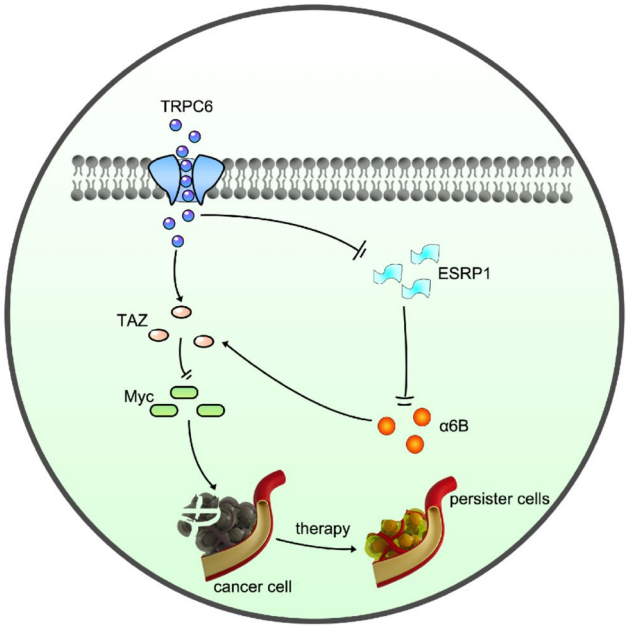

Fig. 8 The related mechanisms of TRPC6 in regulating tumor chemotherapy sensitivity. TRPC6 can suppress ESRP1, thereby promoting the expression of integrin α6B splicing variants. Both TRPC6 and α6B are capable of activating TAZ, inhibiting Myc expression, and consequently facilitating tumor cell persistence

sensitivity of TNBC cells to chemotherapy by targeting α6 integrin mRNA splicing and inducing Myc expression [87]. These findings elucidate the persistent Ca^{2+}-dependent mechanism induced by chemotherapy. Furthermore, paclitaxel treatment has been shown to upregulate TRPM2 expression in human laryngeal squamous tumor cells, and enhancing TRPM2 expression can augment the anticancer efficacy of paclitaxel [111]. The sensitivity of gastric cancer cells to cisplatin is inversely correlated with the expression of TRPV2, suggesting that TRPV2 may serve as a potential target to overcome tumor resistance to cisplatin by inducing apoptosis in tumor cells [112].

Furthermore, the expression of VGCC is upregulated in tumors, particularly the expression of CACNA1D/CaV1.3 in castration-resistant prostate cancer (CRPC). In patients with prostate cancer undergoing androgen deprivation therapy, there is an observed increase in CaV1.3 gene expression. Notably, the expression of the CaV1.3 protein is significantly elevated following treatment with the androgen deprivation therapy agent bicalutamide. The expression of the truncated 170 kDa CaV1.3 isoforms is associated with both plasma and intracellular membranes, and this variant is incapable of inducing Ca^{2+} influx upon membrane depolarization. Conversely, under androgen deprivation therapy, CaV1.3 facilitates an increase in basal cytoplasmic calcium levels and SOCE. This mechanism potentially enhances the survival and proliferation of CRPC cells undergoing anti-androgen deprivation therapy [113]. Overall, the findings corroborate that androgen deprivation therapy-specific CaV1.3 isoforms can facilitate the upregulation of SOCE in prostate cancer, potentially aiding in overcoming tumor treatment resistance.

The overexpression of α2δ1 significantly enhanced the expression of genes associated with tumor cells and demonstrated substantial resistance to radiation. Conversely, reduced expression of α2δ1 increased the radiosensitivity of A549 cells, whereas its overexpression decreased the radiosensitivity of PC9 and H1975 cells, indicating that α2δ1 expression confers resistance to radiation therapy in NSCLC cells. Additionally, α2δ1 was found to augment the efficiency of cellular DNA damage repair. Furthermore, the combination of radiation and α2δ1 monoclonal antibodies synergistically inhibited the self-renewal of cells with high α2δ1 expression, thereby enhancing the radiosensitivity of α2δ1-positive cells [114]. These results provide a theoretical foundation for the combined use of α2δ1 monoclonal antibodies and radiotherapy in the treatment of NSCLC.

Application of Ca^{2+} channel blockers in cancer treatment

Given the expression of Ca2 + channels in tumor cells and their significant roles in tumor progression and metastasis, targeting Ca2 + channels has emerged as a promising therapeutic strategy for anti-tumor treatment. Currently, the therapeutic potential of drugs targeting the Ca^{2+} channel family in cancer treatment has been recognized, with a primary focus on TRP channels and VGCC channels (Table 1). The mechanisms of action of these drugs include inhibiting tumor cell proliferation and metastasis, enhancing treatment sensitivity, reactivating tumor immune surveillance, and inducing tumor cell death.

Specifically, drugs targeting TRP channels exert antitumor effects by inhibiting tumor cell proliferation and invasion, as well as inducing apoptosis. Cannabinoids, which function as TRP channel blockers, influence tumor progression through multiple mechanisms. Firstly, cannabinoids activate cellular autophagy and modulate signaling pathways that induce apoptosis via ceramide accumulation. Secondly, cannabinoids impact tumor growth by inhibiting angiogenesis, reducing invasiveness, and modulating anti-tumor immune responses [115, 116]. Additionally, cannabinoids have demonstrated the ability to inhibit tumor cell proliferation by arresting the cell cycle [117] and can enhance the overall health of cancer patients by reducing anxiety [116]. These compounds are currently being evaluated in multiple clinical trials, with two trials actively recruiting participants (NCT06097533; NCT05629702) and four additional trials pending recruitment (NCT05754840; NCT05520294; NCT06418204; NCT06533657) (Table 2). Capsazepine

Table 1 Ca2 + channel blockers in cancer treatment (preclinical study)

Drug name	Targeted channels	Cancers	References
BI-749327	TRPC6	TNBC	[87]
Cannabinoids	TRPV1, TRPV2	Oral cancer; melanoma; glioblastoma; breast cancer; prostate cancer; colon cancer; lung cancer	[116, 117]
Capsazepine	TRPV1, TRPA1	Breast cancer; prostate cancer; oral cancer; colorectal cancer; osteosarcoma	[118–120]
MAb82	TRPV6	Prostate cancer	[121]
Manidipine	L-type calcium channel	Ovarian cancer	[98, 122]
Bendipine	L-type calcium channel	Ovarian cancer	[98]
Lacidipine	L-type calcium channel	Ovarian cancer	[98]
Diltiazem	L-type calcium channel	Breast cancer; pancreatic cancer	[124, 137]
Felodipine	L-type calcium channel	Lung squamous cell carcinoma	[127]
Fluspirilene	L-type calcium channel	Glioblastoma; prostate cancer	[128–130]
Fendiline	L-type calcium channel	Pancreatic ductal adenocarcinoma	[138]
Amlodipine	L-type calcium channel	Esophageal cancer	[139, 140]
Flunarizine	L-type calcium channel	Non-small cell lung cancer; glioblastoma	[142, 144]
Nicardipine	L-type calcium channel	Glioblastoma; prostate cancer	[143, 150]
Lercanidipine	L-type calcium channel	Non-small cell lung cancer	[147]
Nifedipine	L-type calcium channel	Colorectal cancer; ovarian cancer	[148, 149]
Lomerizine	L-type and T-Type calcium channel	Ovarian cancer	[98]
Mibefradil	L-type and T-Type calcium channel	Melanoma; glioblastoma	[132–134]
KTt-45	T-type calcium channel	Cervical cancer; breast cancer; lung cancer; lymphoma	[131]
Pimozide	T-type calcium channel	Breast cancer	[125, 126]
NNC-55-0396	T-type calcium channel	Medulloblastoma	[136]
TTA-A2	T-type calcium channel	Lung adenocarcinoma	[146]
Bepridil	Non-selective VGCC inhibitor	Ovarian cancer	[123]

Table 2 Ca2 + channel blockers in cancer treatment (clinical study)

Drugs	Clinical trials. gov ID	Official title	Research status
Mibefradil	NCT01480050	A Phase I Open Label Safety Study to Evaluate the Pharmacokinetic Profile and Tolerance of Mibefradil Dose Finding in Subjects With Recurrent High-Grade Glioma Undergoing Standard, Repeated Temozolomide Treatment	Completed
	NCT02202993	Phase I Trial of Mibefradil Dihydrochloride With Hypofractionated Re-Irradiation Therapy in Treating Patients With Recurrent Glioblastoma Multiforme (GBM)	Completed
Cannabinoids	NCT05754840	A Randomized, Double-Blind Tolerability Trial of Cannabinoids for Symptom Management in Children With Cancer: the CAN-PONC Trial	Not yet recruiting
	NCT06097533	Improvement of Quality of Life by Cannabinoids in Oncologic Patients (BEfind-Lichkeitsverbesserung Unter CANnabinoid-ExtrakTen Bei Onkologischen Patienten)	Recruiting
	NCT05629702	A Randomised Controlled Phase II Trial of Temozolomide with or Without Cannabinoids in Patients with Recurrent Glioblastoma	Recruiting
	NCT05520294	Evaluating the Effects of Cannabis Use and Circulating Cannabinoids on Tumor Infiltrating Lymphocytes in Malignant Melanoma	Active, not recruiting
	NCT06418204	Complementary Options for Symptom Management In Cancer (COSMIC): Assessing Benefits and Harms of Cannabis and Cannabinoid Use Among a Cohort of Cancer Patients Treated in Community Oncology Clinics	Not yet recruiting
	NCT06533657	A Phase 2A Study to Investigate the Safety and Preliminary Analgesic Efficacy of Oral Trichomylin® in Male and Female Participants 18 Years of Age and Above With Advanced Cancer and Moderate to Severe Cancer-Related Pain	Not yet recruiting

has been shown to suppress tumor cell proliferation and metastasis, as well as induce apoptosis, through the inhibition of TRPV1 and TRPA1 channels [118, 119]. It also exerts effects on various cancers, including breast, prostate, oral, colorectal, and osteosarcoma, by modulating the JAK/STAT and ROS-JNK-CCAAT/CHOP pathways [119, 120]. The TRPC6-specific inhibitor BI-749327 has been found to reduce mammosphere formation and significantly decrease the frequency of cancer stem cells in TNBC populations [87]. Additionally, the TRPV6 monoclonal antibody mAb82 promotes tumor cell apoptosis by activating the protease calpain, and in vivo studies have demonstrated its ability to reduce the growth of mouse xenografts and improve survival rates in mice [121]. TRP channel blockers exhibit significant potential in the treatment of cancer patients, necessitating further clinical data to substantiate their anti-tumor efficacy.

Currently, the marketed anti-tumor agents targeting the calcium channel family predominantly focus on VGCCs. These agents generally possess the capacity to inhibit cellular proliferation and migration, as well as induce apoptosis. For instance, compounds such as manidipine, bendipine, lacidipine, and lomerizine have been shown to target ovarian cancer stem cells by inhibiting the AKT and ERK signaling pathways, thereby reducing the formation and viability of stem cell spheroids and decreasing the expression of stemness-associated signaling molecules and markers, ultimately inducing apoptosis [98, 122]. Additionally, bepridil has demonstrated the ability to reverse the EMT-like phenotype induced by TGF-β1 in ovarian cancer cells, significantly reducing the expression levels of vimentin, Snail, and β-catenin. Furthermore, bepridil diminishes the viability of ovarian cancer cells, impairs their migratory and invasive capabilities, and inhibits the growth of mouse xenograft tumors, highlighting its potential as a promising anti-tumor agent [123]. Diltiazem modulates EMT by upregulating the expression of growth differentiation factor-15 in breast cancer cells and in murine models of breast cancer, consequently diminishing cell migration, tumorigenesis, and metastasis [124]. Pimozide impedes the proliferation of breast cancer cells, promotes autophagy, and induces apoptosis through the regulation of the RAF/ERK and PI3K/AKT/MDM2 signaling pathways [125, 126]. Felodipine suppresses the growth of lung squamous cell carcinoma and hinders tumor cell proliferation and migration by modulating the nuclear factor of activated T cells, while also demonstrating synergistic anti-tumor effects in combination with PD-1 and cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) antibodies [127]. Fluspirilene inhibits the proliferation and migration of glioblastoma cell lines and induces apoptosis and cell cycle arrest at the G2/M phase by targeting the FOXM1-KIF20A axis [128, 129]. Additionally, it impedes prostate cancer progression by superoxide dismutase (SOD) activity and enhancing reactive oxygen species (ROS) production [130]. KTt-45, a T-type calcium channel blocker, exhibits cytotoxic effects on various cancer cell lines, including those of cervical, breast, lung, and lymphoma origins, with a notably stronger selective toxicity toward cervical cancer cells. This compound has emerged as a potential anti-tumor agent by inhibiting cervical cancer cell proliferation and inducing mitochondrial-dependent apoptosis [131].

Additionally, certain VGCC blockers have been shown to enhance treatment sensitivity. For instance, the L-type and T-type calcium channel blocker mibefradil can inhibit the migration and invasion capabilities of melanoma cells both in vitro and in vivo. It also promotes differentiation and apoptosis in melanoma cells, reduces resistance to BRAF inhibitors, and offers a potential targeted therapeutic strategy for melanoma with drug-resistant BRAF^V600E mutations [132, 133]. Furthermore, mibefradil can synergistically interact with radiation and the chemotherapeutic agent temozolomide to impede the growth of glioblastoma stem cells [134]. Notably, mibefradil has progressed to phase I clinical trials (Table 2). The study identified as NCT01480050 investigated the pharmacokinetic profile and dose tolerance of mibefradil in patients with recurrent high-grade glioma undergoing treatment with temozolomide, with the findings published in 2017 [135]. The data showed that the maximum tolerated dose of Mibefradil is 87.5 mg/p.o. q.i.d. The dose limiting toxicity mainly includes sinus bradycardia and an increase in alanine aminotransferase/aspartate aminotransferase. The steady-state maximum plasma concentration of the maximum tolerated dose is 1693 ± 287 ng/mL. Thus in patients with high-grade gliomas, Mibefradil and temozolomide are well tolerated at the maximum tolerated dose. Another study, NCT02202993, assessed the use of mibefradil in conjunction with hypofractionated re-radiation therapy for the treatment of recurrent glioblastoma multiforme. Although this study has been completed, its results have not yet been disseminated. NNC-55-0396, an analog of mibefradil, has been shown to enhance the sensitivity of medulloblastoma cells to vincristine when either compound is incorporated into the treatment regimen [136]. In ovarian cancer therapy, the combination of manidipine with HER4 inhibitors such as poziotinib, as well as with cisplatin or paclitaxel, demonstrates a synergistic effect, thereby augmenting the therapeutic efficacy [98, 122]. Furthermore, diltiazem, when used in combination with 5-fluorouracil (5-FU) or gemcitabine, synergistically decreases cell viability, induces cell cycle arrest, and promotes apoptosis in pancreatic cancer cells, thus enhancing the sensitivity of these cells to 5-FU or gemcitabine treatment [137]. The addition of fendiline may also increase the sensitivity of pancreatic ductal adenocarcinoma to gemcitabine, visudyne, or tivantinib [138]. Amlodipine exerts its inhibitory effect on EMT by inducing endoplasmic reticulum stress, which

consequently diminishes the migratory capacity of esophageal cancer cells and promotes apoptosis, thereby reducing the formation of tumor spheroids [139, 140]. Additionally, it enhances the anti-tumor efficacy of doxorubicin in gastric cancer by inhibiting the ERK/MAPK and TGF-β signaling pathways [141]. Flunarizine exhibits resistance to gefitinib, particularly in non-small cell lung cancer cells harboring the epidermal growth factor receptor (EGFR) T790M mutation [142]. Both flunarizine and nicardipine potentiate the cytotoxic effects of temozolomide on glioblastoma multiforme by inhibiting autophagy and inducing apoptosis [143, 144]. The T-type calcium channel blocker TTA-A2 forms a stable complex with the anticancer agent paclitaxel at the T-type calcium channel binding site [145]. As an adjuvant, TTA-A2 reduces chemotherapy resistance in lung adenocarcinoma cells to paclitaxel, thereby enhancing its anti-cancer efficacy [146]. However, a mutual antagonistic interaction occurs when these two drugs are co-administered; thus, sequential treatment is recommended to mitigate this antagonism [145]. These studies introduce novel therapeutic strategies for addressing tumor drug resistance, highlighting the significance of calcium ion blockers in cancer treatment. Furthermore, Ca^{2+} signaling is pivotal in modulating the transcription of PD-L1. Ca^{2+} channel blockers have been shown to decrease PD-L1 expression both in the cytoplasm and on the cell surface in a dose-dependent manner. Specifically, lercanidipine has been demonstrated to continuously downregulate IFN-γ-mediated PD-L1 transcription within 24 h, thereby augmenting the cytotoxic function of T cells [147]. Nifedipine, an L-type Ca^{2+} channel blocker, has been observed to induce apoptosis in colorectal and ovarian cancer cells in a concentration-dependent manner [148], as well as inhibit the proliferation and metastasis of colorectal cancer cells [149]. Additionally, nifedipine reduces PD-L1 expression on colorectal cancer cells and PD-1 expression on $CD8^+$ T cells, thereby reactivating the tumor's immune surveillance mechanisms, which may enhance or potentiate the effectiveness of PD-1-based anti-tumor immunotherapy [149].

Conclusion

The role of Ca^{2+} channels in the initiation and progression of cancer, as well as the regulation of Ca^{2+} signaling within cancer cells, has consistently been a focal point in oncological research. This review examines the involvement of Ca^{2+} channels in cancer, highlighting their influence on tumorigenesis, cell proliferation, invasion, metastasis, and apoptosis. Emphasis is placed on elucidating the mechanisms by which Ca2 + channels contribute to cancer pathophysiology. These channels impact cancer development through various mechanisms, including tumor angiogenesis, EMT, CSC characteristics, tumor immune response, and treatment sensitivity. The comprehensive analysis presented herein offers novel insights into the physiological and pathological roles of Ca^{2+} channels in cancer, suggesting innovative approaches for therapeutic intervention. Furthermore, the review provides an overview of recent advancements in the clinical application of Ca^{2+} channel blockers, detailing successful case studies and addressing current challenges in clinical trials. Researchers are diligently working to develop more specific Ca^{2+} channel blockers in order to minimize side effects on normal cells and enhance the targeting and efficacy of treatments. However, the majority of these drugs have only been examined at the cellular and animal levels, lacking validation through clinical trials. With the advancement of in-depth studies on the mechanisms of cellular Ca^{2+} homeostasis and the successful application of therapies targeting specific Ca^{2+} signals, Ca^{2+} channels are emerging as promising targets for tumor therapy, representing a novel approach in cancer research. Nonetheless, the anti-tumor mechanisms of Ca^{2+} channel blockers require further comprehensive investigation and analysis. As our understanding of the role of Ca^{2+} channels in cancer deepens and interdisciplinary collaboration continues to strengthen, it is anticipated that more precise and effective cancer treatment strategies will be developed, offering new hope to cancer patients. This field presents both significant challenges and opportunities.

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Declarations

Conflicts of interest The authors declare no conflicts of interest.

Informed consent Not applicable.

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