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Review

Deciphering the Role of Functional Ion Channels in Cancer Stem Cells (CSCs) and Their Therapeutic Implications

Running Title: Ion channels signalling in CSCs

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Abstract

Cancer remains a leading global health challenge, with recent artificial intelligence (AI) and machine learning (ML) technologies enabling more accurate predictions of its future impact. Conventional treatments like surgery, radiotherapy, and chemotherapy have advanced with the emergence of targeted and immunotherapy approaches. However, therapeutic resistance and relapse remain major barriers to long-term success in cancer treatment, often driven by cancer stem cells (CSCs). These rare, resilient cells can survive therapy and drive tumour regrowth, urging deeper investigation into the mechanisms underlying their persistence. CSCs express ion channels typical of excitable tissues, which, beyond electrophysiology, critically regulate CSC fate. However, the underlying regulatory mechanisms of these channels in CSCs remain largely unexplored and poorly understood. Nevertheless, the therapeutic potential of targeting CSC ion channels is immense, as it offers a powerful strategy to disrupt vital signalling pathways involved in numerous pathological conditions. In this review, we explore the diverse repertoire of ion channels expressed in CSCs and highlight recent mechanistic insights into how these channels modulate CSC behaviours, dynamics, and functions. We present a concise overview of ion channel-mediated CSC regulation, emphasizing their potential as novel diagnostic markers and therapeutic targets, and identifying key areas for future research.

Keywords: cancer stem cell; ion channels; cellular signalling; tumour microenvironment; ion channel-targeted therapy; cancer therapeutics

1. Introduction

Recent advancements in AI and ML have opened new avenues for predicting global cancer trends with unprecedented accuracy. Alarmingly, AI/ML-based predictive models estimate that by 2050, cancer will account for nearly thousand million new cases and approximately four hundred million deaths worldwide, positioning it as the leading cause of mortality [1]. While ongoing innovations have significantly improved cancer treatment, urgent attention is needed to address the rising burden. Fundamental research remains critical, especially in understanding cancer biology at its root. Among the emerging areas, CSCs have garnered significant attention for their role in therapy resistance, tumour initiation, and relapse [2–6].

Normal stem cells are undifferentiated or partially differentiated cells capable of self-renewal and specialization [7,8]. In mammals, key types include embryonic stem cells (ESCs) from the blastocyst and adult stem cells (ASCs) found in tissues like bone marrow and liver, which remain mostly dormant but activate for tissue repair [7]. Induced pluripotent stem cells (iPSCs), generated by reprogramming adult cells with factors such as Oct4 and Sox2, mimic ESC behaviour [7]. A distinct population, CSCs, has been identified in various tumours [7,8]. CSCs, also known as tumour-initiating cells, are a small but aggressive subpopulation within tumours [8]. CSCs can arise either from normal tissue-resident stem cells or from differentiated cancer cells that acquire stem-like traits, often influenced by signals from the tumour microenvironment [8]. The concept of CSCs, first proposed in the late 1990s, has since become a focal point of intense investigation [9,10]. Over the past decades, extensive research has sought to reveal their roles in cancer biology [11]. CSCs have been identified and extensively characterized across a wide spectrum of tumour types [11]. These cells are identified by specific surface and intracellular markers such as CD44, CD24, CD133, ALDH1, and EpCAM [8]. CSCs have been identified across numerous cancer types such as breast, colon, lung, prostate, liver, melanoma, leukaemia, head and neck, ovarian, pancreatic, and brain tumours [12]. Several key developmental pathways, including Notch, Hedgehog, and Wnt/ β -catenin, regulate CSC behavior [8]. These cells possess hallmark properties such as self-renewal, multilineage differentiation, and the unique ability to initiate and sustain tumour growth [13]. Importantly, CSCs are also endowed with a high proliferative potential, enabling them to drive tumour progression and heterogeneity. Due to these intrinsic capabilities, CSCs are increasingly recognized as the root cause of tumour recurrence and metastasis [11,14]. Even after aggressive clinical interventions such as surgical resection, radiotherapy and chemotherapy, a small population of CSCs often survives. These residual cells can evade conventional therapies, regenerate the tumour microenvironment, and ultimately lead to disease relapse [11]. Consequently, many patients experience tumour recurrence and metastasis within a few years post-treatment, emphasizing the critical role of CSCs in cancer persistence and poor long-term prognosis [5]. While CSCs share several characteristics with normal stem cells, such as the capacity for self-renewal and differentiation, they are distinguished by aberrant signalling cascades and a pronounced resistance to conventional therapies [15]. Among the diverse molecular regulators implicated in the maintenance and plasticity of CSCs, ion channels have recently emerged as fundamental modulators [16].

Ion channels, traditionally studied in the context of excitable tissues, are transmembrane proteins that regulate the selective movement of vital ions-such as calcium (Ca^{2+}), potassium (K^+), sodium (Na^+), and chloride (Cl^-)-across cellular membranes [17]. Beyond their classical roles in maintaining membrane potential and cellular excitability, ion channels profoundly influence crucial biological processes including cell proliferation, migration, apoptosis, and stemness-related signalling pathways [18]. Recent findings suggest that the dysregulation of specific ion channel families play a crucial role in maintaining the CSC phenotype, supporting their survival, invasiveness, and resistance to therapy [16]. Therefore, it is essential to gain a clear understanding of the ion channel expression profiles in CSCs and their regulatory roles in CSC fate and function, as this knowledge could pave the way for future research aimed at effectively combating cancer. Although a few reviews have discussed ion channels in CSCs, most focus on individual channel type. To the best of our knowledge, this is the first comprehensive review that encompasses a broad spectrum of ion channels expressed across various CSC types and their associated functions. We explore the wide range of ion channels found in CSCs and shed light on recent discoveries regarding their roles in controlling CSC behaviour, functional properties, and cellular dynamics. Special emphasis is placed on acid-sensing ion channels (ASICs) and aquaporin (AQP) channels, which, despite their significant roles in regulating CSC fate and function, have not been comprehensively reviewed until now.

2. AI-Based Generative Prediction of Near-Future Global Cancer Cases

As we deepen our understanding of cancer biology through cellular and molecular insights, particularly the role of CSCs and their regulation by ion channels, it becomes equally important to complement this knowledge with predictive tools that can forecast the future problem of disease. Recent breakthroughs in AI and ML offer powerful methods to model complex datasets and anticipate global cancer trends. This chapter integrates such computational approaches to reinforce the urgency of developing targeted cancer therapies, including those focused on CSC-specific molecular features such as ion channels.

We employed AI and ML to predict global cancer trends. Data were sourced from <https://ourworldindata.org/grapher/number-of-people-with-cancer>. Using Generative Adversarial Networks (GANs) and Long Short-Term Memory (LSTM) networks, we enhanced datasets for forecasting future global cancer cases. GANs simulated patient data over 30 years, with real and generated data refined via a discriminator network. LSTM predicted mutation trends using both historical and AI-generated data. The dataset was split 80/20 for training and testing, respectively, to evaluate the LSTM model's forecasting accuracy. In generative adversarial networks (GANs) for generating time series data, the generator and comparator (or discriminator) units work in a dynamic, adversarial process [19]. The generator and comparators units are described as follows

The input and output of the generator are described by Equation 1 and Equation 2 respectively.

$$z \sim p_z [z] \quad [1]$$

$$\hat{x} = G[z; \theta_g] \quad [2]$$

Where p_z and θ_g are the distribution of the latent noise and trainable parameter of the generator. The comparator unit evaluates whether an input time series 'x' is real $x \sim p_{data} [x]$ or synthetic $x = G [z]$. The input to the comparator is the output of the generator which is described in the equation. The output of the comparator is described as follows:

$$D [x; \theta_d] \in [0, 1] \quad [3]$$

Using data from published literature (Table 1) from the past thirty years, along with the above-mentioned method, we predicted global cancer trends for the next 20 years (Table 1 and Figure 1). The sharp projected increase in cancer cases indicating the urgent need for advanced therapeutic strategies and improved management. These AI-generated projections serve as a clarion call for more precise and targeted interventions. Given the rising global cancer burden, it becomes increasingly important to identify molecular vulnerabilities unique to CSCs, such as ion channels. In the following section, we explore into the expression patterns and functional roles of various ion channels in CSCs, aiming to uncover critical insights that could guide future research and pave the way for innovative therapeutic strategies.

Table 1. Global cancer case (1990–2022).**Table 1: Global cancer cases (1990-2022)**

Data sourced from *Our World in Data*. Available at: <https://ourworldindata.org/grapher/number-of-people-with-cancer>.

Year	Total number of cancer cases worldwide
1990	34,360,540
1991	35,390,696
1992	36,512,770
1993	37,747,870
1994	39,001,560
1995	40,316,636
1996	41,514,652
1997	42,465,280
1998	43,503,172
1999	44,746,916
2000	46,118,044
2001	47,526,044
2002	48,844,000
2003	50,283,612
2004	51,811,810
2005	53,702,332
2006	55,358,980
2007	57,071,324
2008	58,970,052
2009	60,740,120
2010	62,496,960
2011	64,144,148
2012	65,627,804
2013	67,197,640
2014	69,032,910
2015	70,864,680
2016	72,892,820
2017	74,874,984
2018	77,034,940
2019	79,046,540
2020	80,030,290
2021	81,863,256
2022	20,000,000

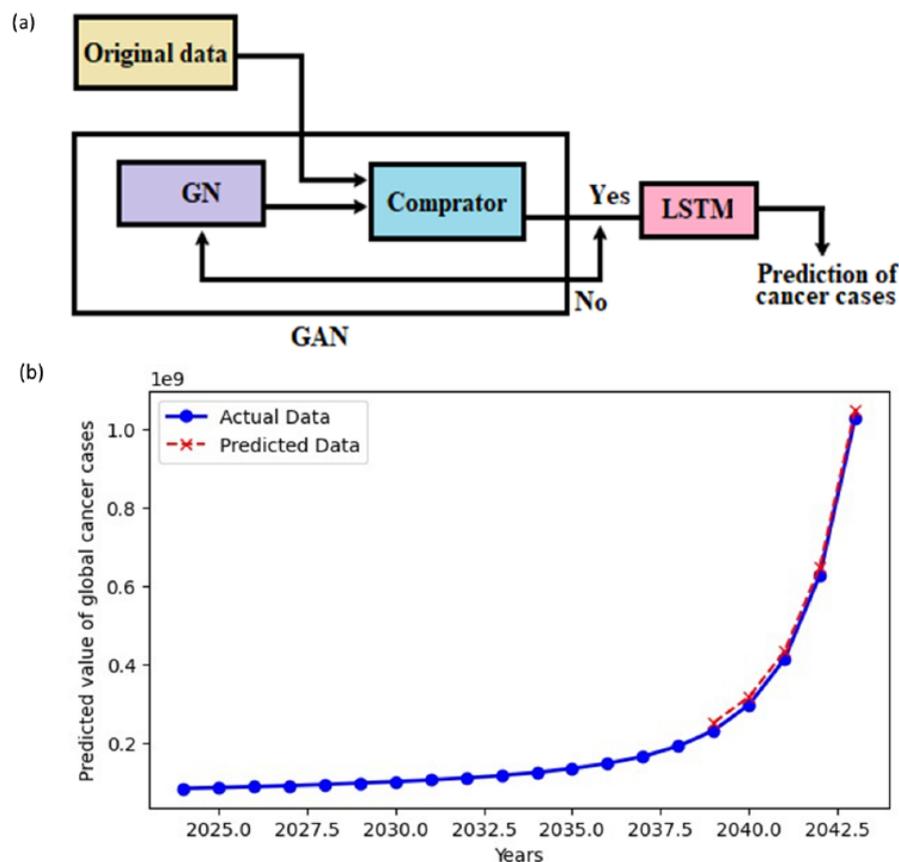


Figure 1. Forecasting global cancer incidence with an AI Model. (a) Flowchart illustrating the use of GAN and LSTM networks for forecasting cancer cases. (b) An AI model predicting the future global burden of cancer, showing projected trends over the next 20 years. The fine-tuned model parameters for predicting region-wise prostate cancer cases are as follows: number of epochs = 200, look-back value = 3, number of LSTM units = 50, optimizer = Adam, loss function = MSE, and final loss = 0.002.

3. Ion Channel Expression Profiles and Their Functions in CSCs

A diverse array of functional ion channels has been identified across various types of CSCs, exhibiting significant heterogeneity. CSCs exhibit a unique ion channel expression profile that distinguishes them from bulk tumour cells and normal stem cells. These ion channels span various classes, each contributing to distinct aspects of CSC biology. Through an extensive PubMed-based literature search focusing on ion channels in CSCs, we have compiled a comprehensive list of these channels, summarized in Table 1, deciphering their functional relevance and potential as therapeutic targets (Table 2 and Figure 2). The following section details specific ion channels and their involvement in CSC function.

Table 2. Ion channel expression and functions in CDCs.**Table 2: Ion channel expression and functions in CSCs**

Ion Channel Type	Specific Channels / Subtypes	Cancer Type / Model System	Functional Role in CSCs	Reference(s)
SOCE Channels	Orai channels	Breast (HER2+, TNBC), AML, OSCC, Glioblastoma	Promote self-renewal, drug resistance, glycolysis, proliferation	[8, 20-24]
	SPCA2, SK3, Kv10.1	Breast Cancer	Store-independent Ca ²⁺ entry, stemness support	[8, 20]
TRP Channels	TRPC1/3/6, TRPV1/2/4/6, TRPM7/8, TRPA1	Glioblastoma, TNBC, Breast, NSCLC, Bladder, HNSCC, Neuroblastoma	Control proliferation, chemoresistance, migration, metastasis	[26, 27, 33-40]
	TRPM7	Lung, GBM, HNSCC	Enhances stemness, EMT, invasion, survival	[33, 34, 38-40]
VGCCs	CACNG4, CACNA2D1, CACNB4	Gastric, HCC, Ovarian	Mediate proliferation, drug resistance, survival	[25, 42, 43]
	Cav1.2, Cav3.2, Cav3.1, Cav3.3	Prostate, Breast, NSCLC, Pancreatic	EMT, SNAIL, HIF-1 α , RhoA, TGF β , VEGF, PI3K/AKT/mTOR	[24-28]
Calcium Release Channels (CRCs)	RyR1, RyR3, IP3Rs	Breast, Medulloblastoma, Melanoma	ER Ca ²⁺ release, CSC enrichment, stemness marker regulation (Nanog, Oct4, CD133, PROM1)	[3]
Mechanosensitive Channels	PIEZO1, PIEZO2	Colon, AML, GBM, Breast	Regulate stemness, adhesion dynamics, tumorigenesis, Ca ²⁺ influx, EMT, immune evasion	[28-30, 44, 45]
Ion Channel Type	Specific Channels / Subtypes	Cancer Type / Model System	Functional Role in CSCs	Reference(s)
Chloride Channels	TMEM16A, Bestrophin-1, ClC-2/3/4, TMEM206, CLIC1/4	Lung, Breast, CRC, Glioma, HCC, Prostate	EGFR, MAPK, PI3K/AKT, Wnt/ β -catenin, oxidative stress, pH regulation, proliferation	[11, 46-52]
Potassium Channels	Kv1.3, Kv10.1, Kv11.1, Kir3.1, KCNK9, IKCa1, KCa1.1, KCa3.1	Prostate, Colon, Lung, Breast, Pancreatic, GBM	Regulate membrane potential, proliferation, EMT, ERK, JAK/STAT3, hypoxia	[53-58]
Sodium Channels (VGSCs)	Nav1.5	GBM, TNBC	Membrane potential, ERK activation, c-Myc, temozolomide resistance	[59-61]
ASICs	ASIC1a, ASIC3	GBM	pH sensing, necroptosis, acidic tumor suppression	[62-64]
Aquaporins (AQP)s	AQP1, AQP3, AQP4, AQP5, AQP8	Glioma, Breast, HCC, Cervical, Gastric	EMT, JAK/STAT3, CD133, autophagy, TRIM21, Wnt/ β -catenin	[65-74]

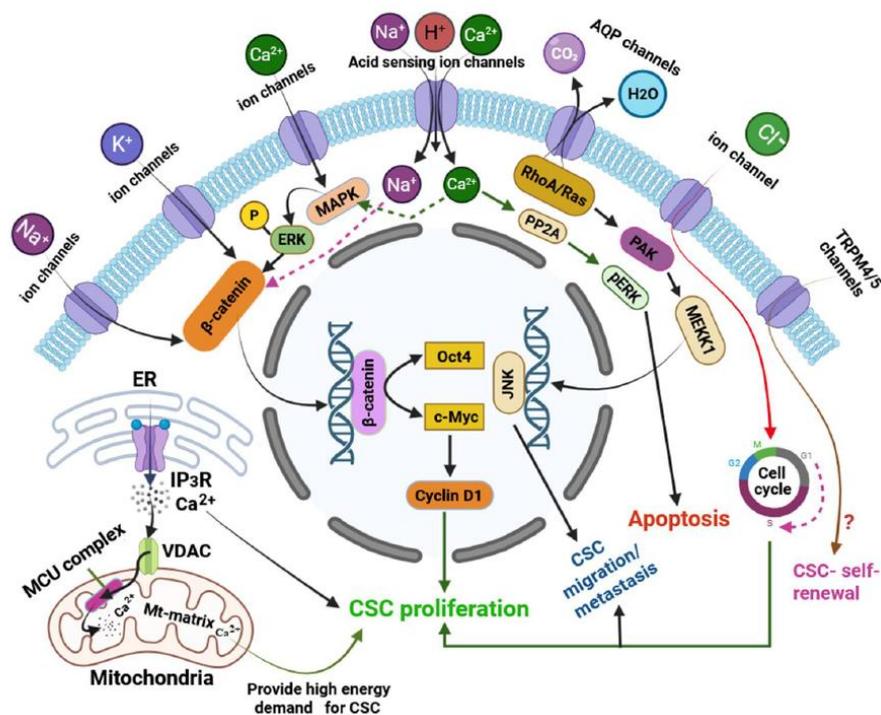


Figure 2. Fundamental ion channels in CSCs and their functional roles in maintaining stemness.

The figure illustrates key membrane-bound and intracellular ion channels in CSCs, highlighting their downstream signalling pathways and collective roles in regulating ion homeostasis and CSC stemness. Several ion channels contribute to CSC maintenance and proliferation: Na^+ and K^+ channels: Activation of these channels initiates downstream signalling cascades that converge on the β -catenin pathway, ultimately upregulating the CSC-specific transcription factor Oct4 and the oncogene c-Myc, both of which are essential for CSC proliferation. Ca^{2+} channels: Ca^{2+} influx activates the MAPK signalling cascade, leading to ERK phosphorylation and subsequent activation of β -catenin-mediated transcriptional programs driving CSC proliferation [11]. Acid-sensing ion channels (ASICs): ASIC expression has been reported in various tumours and is implicated in tumour progression and metastasis [11,105]. Specifically, Ca^{2+} influx via ASIC1 activates PP2A-dependent apoptotic pathways [105], while Na^+ entry via ASICs may activate β -catenin signalling and support CSC proliferation (indicated by green and purple dashed lines in the figure). AQPs: These water channels contribute to CSC migration and metastasis through activation of the RhoA/Ras-JNK signalling axis, facilitating disease progression [126]. CLIC1: This membrane protein is crucial for CSC proliferation by regulating the cell cycle, especially by promoting the G1-to-S phase transition [52]. TRP channels: Ca^{2+} -impermeable TRPM4 and TRPM5 channels are implicated in maintaining cancer stemness. However, the molecular mechanisms underlying their roles remain largely undefined and warrant further investigation [38]. In addition to plasma membrane channels, the figure also depicts essential organelle membrane channels involved in CSC function: Mitochondrial outer membrane voltage-dependent anion channels (VDACs): These channels supply the elevated energy demand of CSCs during proliferation and metastasis. VDACs are strategically localized near the endoplasmic reticulum (ER) to acquire Ca^{2+} released via IP_3 receptors. The imported Ca^{2+} is subsequently transferred to the mitochondrial matrix through the mitochondrial calcium uniporter (MCU) complex, thus enhancing mitochondrial bioenergetics [3,92]. A portion of the IP_3 -released Ca^{2+} also directly promotes CSC stemness and proliferation [3]. All ion channels and their mechanistic roles are described in detail in the main text.

4. Calcium Ion Channels and Their Functions

Intracellular calcium dynamics play a key role in CSCs functions with multiple calcium channels-including store operated calcium entry channels (SOCE), voltage gated calcium channels (VGCC), transient receptor potential (TRP) channels, calcium release channels (CRCs) and mechanosensitive channels [3,20–30].

4.1. SOCE Channels and Their Functions

SOCE is a key mechanism for calcium influx, activated by ER calcium depletion via PLC and IP₃ signalling [8]. It involves STIM proteins (ER Ca²⁺ sensors) and Orai channels in the plasma membrane. Ca²⁺-release activated Ca²⁺-channels or CRAC channels, mainly formed by Orai proteins, mediate highly selective Ca²⁺ entry to bombard a specific downstream target [8,21,22]. Variants like Orai1 α and Orai1 β show distinct activation patterns. Dysregulation of SOCE components can disrupt calcium homeostasis, promoting tumour growth, poor prognosis, and drug resistance [8]. Beyond SOCE, Orai1 also supports alternative calcium entry pathways through interactions with secretory pathway Ca²⁺-ATPase 2 (SPCA2), small conductance calcium-activated potassium channel (SK3 or K_{Ca}2.3), and Kv10.1 channels. These interactions can sustain calcium entry and promote CSC survival and migration [8]. Using knockdown and rescue experiments in MDA-MB-231 cells, Jardin *et al* [22] showed that Orai1 is crucial for spheroid formation and self-renewal in human epidermal growth factor receptor 2 positive (HER2+) and triple-negative breast cancer stem cells (BCSCs), but not in estrogen receptor positive (ER+) BCSCs or BSCs [22]. Both Orai1 α and Orai1 β equally support SOCE, COX activation, and mammosphere formation in BCSCs [22]. Orai1 interacts with SPCA2 to drive glycolysis-dependent growth in BCSC-like cells via store-independent calcium entry (SICE), while Orai3 and STIM1 promote glycolysis-independent SOCE [20]. In Acute myeloid leukaemia (AML), Orai1-SOCE correlates with leukemic stem cell (LSC) proportion and drug resistance, indicating its utility as a biomarker [21]. Orai3 is enriched in CSCs and promotes stemness via the Orai3-ID1 (Orai3-inhibitor of DNA binding 1) axis in oral/oropharyngeal squamous cell carcinoma (OSCC) [23]. Terrie *et al* [24] demonstrated that SOC entry supports glioblastoma stem cell (GSC) maintenance, likely through CaMKII and NFAT activation, highlighting calcium's central role in stemness and tumour progression [24]. However, the precise contribution of SOC in CSCs remains to be fully defined.

4.2. TRP Channels and Their Functions

TRP ion channels, well-known for their roles in sensing physical and chemical stimuli, are increasingly recognized as important regulators of stem cell behaviour, including CSCs [26]. Several TRP family members including TRPC1/3/6, TRPV1/2/4/6, and TRPM7/8 are dysregulated during cancer progression, contributing to diverse oncogenic processes [33,34].

TRPA1 and TRPV1 are modulated by ERK signalling and transcription factor Runx1/Aml1 isoforms, influencing glioblastoma stem cell (GSC) differentiation and survival [27]. TRPC3 is frequently overexpressed in triple-negative breast cancer (TNBC), where it drives proliferation and chemoresistance via the TRPC3–RASA4–MAPK (TRP3-Ras GTPase-activating protein 4-MAPK) axis. Additionally, TRPC3 promotes NF- κ B activation in cancer-associated fibroblasts, thereby enhancing tumour growth [35]. In breast cancer, TRPV4 and TRPV6 are upregulated and facilitate calcium influx, which supports cell proliferation, angiogenesis, and tumour progression [36].

TRPM7 plays a particularly versatile role in cancer biology. It promotes metastasis in non-small cell lung cancer (NSCLC) by enhancing O-GlcNAcylation and stabilizing key oncogenic proteins such as c-Myc and caveolin-1 [33]. In lung CSCs, elevated TRPM7 expression is associated with increased levels of stemness and metastatic markers including SOX2, KLF4, CD133, Hsp90 α , uPA, and MMP2 [34]. Therapeutically, TRPM7 has emerged as a promising target [33,34]. Oridonin, a bioactive compound from *Rabdosia rubescens*, suppresses bladder cancer growth by targeting TRPM7 and inhibiting the ERK/AKT signalling pathway [37]. Interestingly, TRPM7 is unique among TRP channels in containing both an ion channel and an α -kinase domain. While its kinase domain

regulates sensitivity to Mg^{2+} and cAMP, it is dispensable for the ion channel function. In glioblastoma, TRPM7 activates STAT3 signalling to upregulate ALDH1, thus driving CSC proliferation and invasion [38]. However, further investigation is needed to delineate the specific contributions of its kinase versus channel activities in modulating STAT3, ALDH1, and Notch pathways. Moreover, TRPM7 has been reported to be critical for neuroblastoma cell migration and SNAI2-driven metastasis [39]. In head and neck squamous cell carcinoma (HNSCC), high TRPM7 expression correlates with invasiveness, cisplatin resistance, and poor prognosis. Silencing TRPM7 not only impairs tumorsphere formation but also increases chemosensitivity [40].

Tumour-initiating cells (TICs), which include CSCs, exhibit elevated calcium sensitivity compared to their differentiated counterparts, likely due to enriched expression of ion channels. In glioma-initiating cells (GICs), this sensitivity correlates with neural stem cell markers such as GRIA1, NES, and FABP7 and diminishes upon differentiation. These findings highlight calcium homeostasis as a potential vulnerability in immature, stem-like cancer cells [41].

4.3. VGCCs and Their Functions

VGCCs, composed of α , β , δ , and γ subunits, regulate calcium entry and play critical roles in cellular functions [25]. Among them, CACNG4, a γ -subunit of VGCCs has been implicated in several cancers [25]. Shiozaki *et al* [42] investigated ion channel expression in gastric cancer stem cells (GCSCs) and found elevated levels of VGCC genes, especially *CACNA2D1* and *CACNB4*, in CD44-high cells isolated from MKN74 gastric cancer cell line [42]. These GCSCs were more resistant to cisplatin but showed increased sensitivity to VGCC inhibitors, amlodipine and verapamil, which reduced tumorsphere formation and tumour growth when combined with cisplatin [42]. They also explored ion channel expression in hepatocellular carcinoma (HCC) CSCs (HepG2 line), revealing upregulation of several channel-related genes, including *CACNG4* [25]. Lee *et al* [43] reported that ovarian cancer's five-year survival rate remains low due to recurrence and drug resistance, largely driven by CSCs [43]. They investigated the effects of trimebutine maleate (TM) on ovarian CSCs using A2780-SP cells derived from A2780 ovarian cancer cells. They proved that TM showed selective toxicity to CSCs ($GI_{50} \sim 0.4 \mu M$) compared to non-CSCs ($>100 \mu M$), inducing cell cycle arrest and cell death. In mouse models, TM significantly reduced tumour growth [43]. TM targets overexpressed VGCC and calcium-activated potassium channels (BKCa) channels in CSCs, and dual inhibition of these channels further reduced cell viability and stemness markers. Although they explained that TM effectively and selectively reduces stemness and proliferation in ovarian CSCs, potentially involving Wnt/ β -catenin signalling [43], but other pathways may also play a role. Additional signalling pathways should be investigated to fully clarify TM's underlying mechanism of action.

4.4. Ca^{2+} Release Channels (CRCs)

CRCs like ryanodine receptors (RyRs) and inositol trisphosphate receptors (IP3Rs) regulate calcium flux from the endoplasmic reticulum and are increasingly linked to CSC functions [3]. RyR1 expression is elevated in chemotherapy-resistant BCSCs, where it promotes calcium release via the glutathione S-transferase omega 1 (GSTO1) pathway; blocking this channel reduces CSC markers like Nanog and tumour volume in mouse models [3]. Similarly, downregulation of RyR3 by miR-367 in medulloblastoma enhances stemness traits, including Oct4 and CD133 expression [3]. IP3Rs, though better known for roles in oncogenesis and stem cell differentiation, have also been implicated in CSC maintenance; loss of Selenoprotein K (SELENOK) impairs IP3R function in melanoma, reducing intracellular calcium and stemness gene expression such as PROM1 [3]. These findings suggest both RyRs and IP3Rs contribute to CSC maintenance, though isoform-specific effects require further study.

5. Mechanosensitive Channels and Their Functions

Recently, mechanosensitive channels have gained significant attention for their emerging role in regulating CSCs. Piezo1, a mechanosensitive, calcium-permeable ion channel, regulates focal

adhesion dynamics in normal cells by localizing to adhesions in a force-dependent manner [44]. It promotes adhesion maturation and disassembly via localized calcium influx, likely through calpain activation, in an integrin-dependent manner. However, in cancer cells, Piezo1 fails to localize to adhesions and has little effect on adhesion turnover, suggesting a tumour-associated functional shift [44]. Piezo1 supports colon cancer stem cell (CCSC) stemness via calcium/NFAT1 signalling [30]. Piezo1 knockdown reduced Yoda1-induced Ca^{2+} influx and nuclear NFAT1 protein, without affecting its mRNA. It also destabilized NFAT1 and suppressed stem-like traits, while Piezo1 overexpression increased nuclear NFAT1 and stemness. NFAT1 downregulation blocked Piezo1-driven sphere formation and gene expression [30]. In AML, PIEZO1 is upregulated and associated with better survival [29]. While activation has minimal effect, silencing PIEZO1 impairs proliferation, induces cell cycle arrest, and promotes apoptosis by disrupting DNA repair pathways [29]. In glioblastoma, exosomal circZNF800 from glioma stem-like cells promotes tumorigenesis by activating the PIEZO1/Akt pathway via miR-139-5p sponging. Silencing circZNF800 reduces GBM growth and improves survival in vivo. Exosomes from glioma stem-like cells (GSLCs) contribute to glioblastoma (GBM) aggressiveness by transferring specific circular RNAs (circRNAs) [28]. Zhang *et al* [28] identified circZNF800 as highly enriched in GSLC-derived exosomes and associated with poor prognosis in GBM patients. CircZNF800 enhances GBM cell proliferation, migration, and survival by sponging miR-139-5p, thereby activating the PIEZO1/Akt signalling pathway. Silencing circZNF800 reduced tumour growth and improved survival in a GBM mouse model [28]. PIEZO1 links cell morphology and cancer progression. In breast cancer, PIEZO1 activation via YODA1 triggers epithelial-mesenchymal plasticity (EMP), a key step in metastasis and therapy resistance, by remodelling calcium signalling in response to shape changes [45].

6. Chloride Channels and Their Functions

Chloride ions, beyond their classical functions in maintaining membrane potential, cell volume, and intracellular pH, are increasingly recognized for their crucial roles in cancer biology, particularly in tumour cell proliferation, migration, and metastasis [46]. Chloride channels including calcium-activated chloride channels (CaCCs), voltage-gated chloride channels (CICs), acid-sensitive chloride channels, and intracellular chloride channels (CLICs) are deeply involved in tumorigenesis, particularly through their support of CSC proliferation, survival, invasion, and adaptation to the tumour microenvironment [46–52].

CaCCs such as TMEM16A (also known as ANO1) are overexpressed in various cancers, including lung, breast, colorectal, and gliomas. ANO1 promotes tumour growth through activation of EGFR, PI3K/AKT, and MAPK signalling pathways. In colorectal cancer (CRC), its high expression is associated with poor prognosis, and pharmacological inhibition of ANO1 suppresses tumour growth by downregulating Wnt/ β -catenin signalling [46,47]. Another CaCC, Bestrophin-1, has also been implicated in cancer progression, particularly in CRC and oral squamous carcinoma, potentially through modulation of calcium signalling and functional interaction with ANO1 [46].

CICs such as CIC-2 and CIC-3 are upregulated in gliomas and contribute to enhanced proliferation and motility. Functional assays using antisense oligonucleotides and patch-clamp studies have demonstrated their role in chloride-mediated cell volume regulation and invasive behaviour within the dense extracellular matrix of the brain [48]. CIC-3 is also overexpressed in hepatocellular carcinoma (HCC), CRC, nasopharyngeal, and breast cancers, where it facilitates tumour progression via Wnt/ β -catenin and IGF/ERK signalling. Silencing CIC-3 leads to reduced proliferation, suppressed IGF-1 signalling, and decreased tumour growth in breast cancer models [46]. CIC-4, another voltage-gated channel, supports CRC cell invasion and migration by maintaining pH homeostasis in acidic tumour microenvironments [46].

Acid-sensitive chloride channels, particularly TMEM206, are upregulated in CRC, breast, and liver cancers. TMEM206 enables tumour cells to adapt to extracellular acidosis and promotes CRC cell growth and invasion through the AKT/ERK pathway [46].

CLICs, mainly CLIC1 and CLIC4, are significantly overexpressed in several malignancies, including glioblastoma, prostate, colon, and HCC [46,49,51]. In glioblastoma, which is driven by CSCs, CLIC1 has been shown to be selectively active in CSCs but not in mesenchymal stem cells (MSCs) and is crucial for their proliferation and self-renewal [11]. It localizes to the plasma membrane during the cell cycle, where it mediates chloride flux in response to oxidative stress and pH shifts. Blocking CLIC1 disrupts these signals, effectively halting CSC growth without impacting normal stem cells [11]. Additionally, CLIC1 expression in glioblastoma stem cells (GSCs) correlates with poor prognosis, and its inhibition via RNA silencing or antibody targeting reduces proliferation, clonogenicity, and tumorigenicity both in vitro and in vivo [50–52].

7. Potassium (K⁺) Channels and Their Functions

Potassium (K⁺) channels are crucial regulators of membrane potential and cell signalling, classified into voltage-gated (Kv), inwardly rectifying (Kir), and two-pore (K2P) families [53]. In CSCs, specific K⁺ channels such as Kv1.3, KCa3.1, and voltage-sensitive human ERG (hERG, Kv11.1) regulate stemness, survival, and proliferation. Inhibition of these channels induces cell cycle arrest and reduces CSC proliferation, as observed in leukaemia models [11,54]. Similarly, K⁺ channel tetramerization domain containing 12 (KCTD12), a K⁺ channel-associated protein, serves as a prognostic marker in gastrointestinal cancer. In colorectal CSC-like cells, its expression is reduced [11]. Silencing KCTD12 boosts self-renewal and drug resistance, while its overexpression suppresses these traits, highlighting its role in regulating CSC functions and chemoresistance. [11].

Various K⁺ channels including Kv, KCa, hEag, KATP, and K2P are overexpressed in CSCs from prostate, colon, lung, and breast cancers [53]. Blocking these channels suppresses tumour growth or enhances chemotherapy response. Kv (e.g., Eag1, HERG, Kv1.3), Kir3.1, and KCa (KCa1.1, KCa3.1) are especially linked to tumour progression [53]. In glioblastoma CSCs, KCa3.1 is upregulated and exhibits stronger currents in CD133⁺ cells [54].

In prostate cancer, overexpression of IKCa1 (KCa3.1) supports proliferation. Its activity hyperpolarizes the membrane and enhances calcium influx via TRPV6, potentially driving tumour growth [55]. In glioblastoma, M2 muscarinic receptor (M2 mAChR) activation suppresses CSC proliferation and migration partly by inhibiting IKCa currents. Direct IKCa inhibition with TRAM-34 reduces CSC motility and invadopodia formation [56]. In pancreatic CSCs, Shiozaki *et al* [57] found upregulation of Kv channel genes in ALDH1A1⁺ cells from the PK59 line. Treatment with 4-aminopyridine (4-AP) selectively impaired CSC viability and reduced tumor growth in vivo. In breast cancer, multiple K⁺ channels are linked to CSC maintenance and tumor progression [58]. Kv1.3 is silenced in aggressive tumours via promoter methylation and associated with poor prognosis. Kv10.1 is elevated in invasive and TNBC, responding to astemizole. Kv11.1 (hERG1) is linked to better survival in ER-negative patients, whereas Kir3.1 correlates with metastasis in ER-positive tumours. KCNK9 (K2P) promotes migration in TNBC, while KCa1.1 and KCa3.1 are associated with higher tumour grade and metastasis [58].

8. Sodium (Na⁺) Channels and Their Functions

Na⁺ channels, particularly voltage-gated sodium channels (VGSCs), are membrane proteins that regulate Na⁺ influx and initiate action potentials [59]. In cancer, aberrant VGSC expression is increasingly linked to enhanced invasion, metastasis, and maintenance of CSC traits [59]. Although compounds like eicosapentaenoic acid and tamoxifen show anti-tumour effects by targeting VGSCs, their clinical use is limited due to poor subtype selectivity. However, recent efforts are focused on developing VGSC subtype-specific small molecules and peptides as promising therapeutic tools [59].

In glioblastoma stem cells (GSCs), Giannello *et al* [60] reported that VGSCs help maintain the depolarized resting membrane potential (RMP), particularly during the G0 phase, supporting stemness. Blocking VGSCs induced GSC differentiation, reduced self-renewal, increased temozolomide sensitivity, and reactivated ERK signalling, suggesting a new approach for

glioblastoma therapy [60]. TNBC, characterized by high plasticity and drug resistance, exhibits elevated activity of VGSCs [61]. Nav1.5 (SCN5A) enhances tumour cell invasion and drives epithelial-to-mesenchymal transition (EMT) [61]. Targeting VGSCs in TNBC has been linked to reduced stemness and tumour aggression [61].

9. ASICs and Their Functions

ASICs are voltage-insensitive sodium channels that detect extracellular acidity or proton levels [62]. Several ASIC subtypes, including ASIC1, ASIC1a, and ASIC3, have recently been identified in CSCs [62–64]. In glioblastoma stem cells (GSCs), which are key contributors to therapy resistance in malignant glioma, functional ASIC1a and ASIC3 channels are expressed [62]. In contrast, ASIC2, known for its anti-oncogenic role, is absent. Electrophysiological studies confirmed that ACCN2 and ACCN3 transcripts are translated into active ASIC1a- and ASIC3-containing channels. ASIC1b was present at low levels and largely non-functional [62]. Clusmann *et al* [63] found that under prolonged acidosis, ASIC1a activation induces necrotic cell death, partially through necroptosis-like pathways. They proved that inhibiting ASIC1a or knocking it out protects GSCs from acid-induced death, while activating it reduces tumorsphere formation even at neutral pH [63]. Although their findings suggest that targeting ASIC1a could be a novel therapeutic approach by exploiting the acidic tumour microenvironment to eliminate CSC, but no clear underlying mechanism has been described [63].

10. AQPs or Water Channels and Their Functions

AQP, known primarily for their roles in water and solute transport, are now recognized for their broader involvement in key CSC-related processes and their regulations [65–74]. Recent research describes the crucial role of aquaporin channels in cancer, particularly in CSCs. Several isoforms, including AQP1, AQP3, AQP4, AQP5, AQP8 and AQP9 are expressed in CSC populations [65–74]. AQP1 overexpression in rat C6 glioma CSCs enhanced cell viability and migration, potentially promoting glioma progression through transcriptional networks involving Foxo4, Maz, and E2F factors [65]. AQP3 has emerged as a key oncogenic factor across multiple cancers [66–69]. In breast cancer, AQP3 is upregulated in ER-positive invasive ductal carcinoma, where it enhances migration, invasion, and EMT. Its expression is estrogen-inducible via an estrogen response element (ERE) in the promoter. Clinically, elevated AQP3 correlates with poor differentiation, lymph node metastasis, and premenopausal status [66]. Similarly, AQP3 is highly expressed in hepatocellular carcinoma (HCC), where it correlates with advanced stage, metastasis, and poor prognosis [67]. Mechanistically, AQP3 promotes stemness by enhancing CD133 expression through activation of the JAK/STAT3 pathway, which facilitates STAT3 phosphorylation, nuclear translocation, and histone H3 acetylation at the CD133 promoter [67,68]. Additionally, Liu *et al* [69] reported that AQP3 inhibits differentiation and apoptosis in liver cancer stem cells (LCSCs) by suppressing components of the Wnt/GSK-3 β / β -catenin pathway, including β -catenin, GSK-3 β , and STAT3. Collectively, these findings position AQP3 as a key driver of cancer progression and stemness through distinct signalling mechanisms [66–69]. In glioblastoma (GBM), AQP4-loaded extracellular vesicles (EVs) influence tumour behaviour [70]. EVs containing AQP4-tetramers promote cell migration, while those with AQP4-orthogonal arrays of particles (OAPs) induce apoptosis, highlighting a novel mechanism by which AQP4 modulates the tumour microenvironment [70]. AQP5 is highly overexpressed in breast cancer, but not in normal tissue [71]. Its expression is linked to loss of polarity, increased proliferation, and poor prognosis, particularly in ER/PR-negative and HER2-positive cases. Gene amplification may drive this overexpression [72]. In gastric cancer, AQP5 serves as a surface marker of cancer stem cells (GC-CSCs), co-localizing with LGR5 [72]. It enhances growth, invasion, and tumour formation by activating autophagy and promoting ULK1 ubiquitination [72]. AQP8 is overexpressed in cervical cancer and promotes viability, migration, and EMT, while suppressing apoptosis [73]. It has been reported that AQP9 is expressed and significantly downregulated in LCSCs, and its restoration suppresses stemness by promoting reactive oxygen species (ROS) accumulation. This leads to

reduced β -catenin–TCF4 interaction and enhanced β -catenin-FOXO3a association, ultimately inhibiting LCSC self-renewal [74].

10.1. Intracellular Organelles Ion Channels and Their Functions

Intracellular organelle ion channels play essential roles in the survival and function of CSCs by regulating ion homeostasis, apoptosis, and metabolic signalling. Mitochondrial ion channels such as the mitochondrial calcium uniporter (MCU) are critical for tumour growth, influencing cell cycle progression and energy metabolism essential for CSC maintenance [75]. MCU-driven mitochondrial calcium uptake enhances breast cancer cell migration via store-operated Ca^{2+} entry; inhibition of MCU suppresses metastasis in vivo and slows tumour growth through impaired mitochondrial redox signaling [76]. Additionally, ER-resident channels like TMCO1 modulate calcium dynamics and resistance to apoptosis, contributing to CSC survival under therapeutic stress [77]. Synthetic ion transporters targeting mitochondrial and lysosomal membranes have shown potential in selectively inducing apoptosis in CSCs, revealing novel avenues for anti-CSC therapies [78]. Recently, Zheng *et al* [79] proved that circular RNA hsa_circ_0007905 is upregulated in cervical cancer (CC) and enriched in cancer stem-like cells [79]. Its knockdown impairs proliferation, invasion, self-renewal, and promotes apoptosis. Mechanistically, it sponges miR-330-5p, relieving repression of VDAC1. Restoring VDAC1 or inhibiting miR-330-5p reverses these effects. They suggested that this axis may serve as a therapeutic target in CC [79]. These findings highlight the functional significance of organellar ion channels in CSC biology and emphasize their therapeutic potential in targeting resistant cancer populations.

11. Interplay Between Ion Channels and Epigenetic Control in CSCs

Understanding ion channel expression and function in CSCs reveals their role in regulating key cellular processes. Epigenetic mechanisms further modulate these channels, affecting their expression, localization, and activity. The next section explores how this interplay supports CSC maintenance, plasticity, and therapy resistance.

CSCs, recognized as subpopulations within tumours, contribute significantly to tumour heterogeneity through both genetic and epigenetic mechanisms [80]. This heterogeneity enhances the adaptability of cancer cells, facilitating invasion and resistance to therapy [81]. Epigenetic regulation—comprising DNA methylation, histone modifications, and non-coding RNAs—maintains CSC plasticity and stemness without altering the DNA sequence [82,83]. Emerging evidence reveals a dynamic crosstalk between ion channel signalling and epigenetic machinery in CSCs [84]. Ion channels, especially those mediating calcium influx like the store-operated Ca^{2+} channel Orai1, activate intracellular cascades such as CaMKII-AKT/PI3K and MAPK pathways, which in turn upregulate EMT drivers like TWIST (TWIST related protein1 or Twist1), thereby promoting CSC-like states [85,86]. TWIST is not only central to EMT but also facilitates tumour initiation and metastasis. Epigenetic mechanisms reciprocally modulate ion channel expression; for example, DNA methylation silences Kv1.3 in colorectal cancer, impacting cellular excitability and tumour behaviour [86]. Additionally, post-translational modifications of histones—such as methylation and acetylation—govern transcription of key epithelial markers like CDH1, often repressed by the polycomb protein EZH2 [87]. In BCSCs, hyperactivation of the nuclear respiratory factor 2 (NRF2) pathway is mediated by the epigenetic reader Zinc Finger MYND-Type Containing 8 (ZMYND8), which enhances antioxidative capacity and promotes resistance to oxidative damage and ferroptosis [88]. Emerging evidence suggests that this NRF2-ZMYND8 axis modulate the expression and activity of redox-sensitive ion channels, such as TRP channels and calcium-permeable channels, thereby contributing to CSC survival, metabolic flexibility, and therapeutic resistance under oxidative stress conditions [89]. TRPM2, a member of the TRP melastatin subfamily, is highly expressed in variety of tumours and CSCs and plays a key role in protecting cell viability by modulating oxidative stress [89,90]. Interestingly, the inhibition of TRPM2 channels results in mitochondrial dysfunction, elevated ROS, and reduced levels of antioxidant cofactors such as GSH, NADPH, and NADH—effects linked to

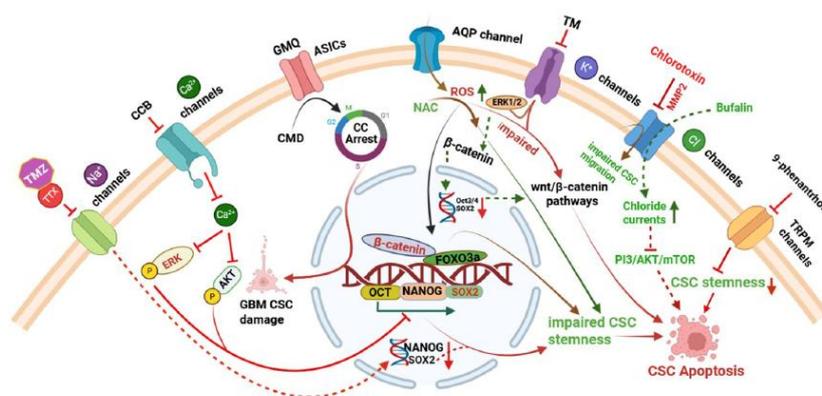
suppressed NRF2 signalling and decreased expression of its antioxidant gene targets. Importantly, TRPM2-dependent stabilization of NRF2 involves IQGAP1 and calcium signalling, pointing toward a regulatory loop where epigenetic factors like ZMYND8 may indirectly influence TRPM2 expression and function, further coordinating redox balance and stemness in CSCs [89,90]. Recent research demonstrated that mitoeepigenetic dysregulation in CSCs affects mitochondrial function and redox balance, contributing to tumour progression. Recent findings show that AIF-induced mitochondrial Ca²⁺ overload, due to impaired mitochondrial Ca²⁺ uniporter (MCU) regulation, activates calpain and retrograde signalling, enhancing oncogenic gene expression in CSCs. This ROS-Ca²⁺-calpain axis, integrated with epigenetic modulation of mitochondrial DNA, links mitochondrial dynamics to CSC survival and aggressiveness in numerous tumours [91,92]. In glioblastoma stem-like cells (GSCs), VDAC1 depletion has been shown to trigger extensive epigenetic reprogramming, leading to changes in chromatin organization and transcriptional activity. Specifically, silencing of VDAC1 in GSCs results in reduced mitochondrial metabolism and NAD⁺ levels, which in turn downregulates the activity of sirtuin deacetylases SIRT1 and SIRT6-key epigenetic regulators [93,94]. This inhibition leads to hyperacetylation of histone H3 (at Lys9 and Lys27) and histone H4, altering the expression of genes involved in stemness and oncogenic signalling. Notably, this also affects the expression of calcium and potassium ion channels such as CACNA1C (L-type calcium channel) and KCNMA1 (BK channel), both of which are epigenetically regulated and critical for CSC maintenance and invasiveness [94]. These bidirectional interactions between ion channels and epigenetic modifiers represent a complex regulatory axis, critical to CSC maintenance, tumour progression, and therapeutic resistance.

12. Ion Channel-Targeted Therapies in CSCs

Targeting ion channels presents a promising therapeutic approach, especially in cancer, where their dysregulation contributes to tumour growth, invasion, and treatment resistance. By modulating these channels, it is possible to disrupt critical signalling pathways and impair CSC functions, contributing a novel avenue for more effective treatments [95]. CSC ion channel blockers have shown significant potential in cancer therapy, influencing tumour cell proliferation, differentiation, apoptosis, and metastasis [96]. This chapter explores the emerging strategies aimed at modulating ion channel activity to selectively target CSCs, offering novel avenues for more effective and durable cancer treatments (Table 3 and Figure 3).

Table 3. Therapies targeting ion channels in CSCs.

Ion Channel	CSC Type / Cancer	Inhibitor / Drug / Compound	Effect on CSCs	Reference
ASIC1a	Glioblastoma CSCs	PcTx1 (antagonist)	Necroptosis via RIPK1; cell death modulation	[62]
ASIC3	Glioblastoma CSCs	ASIC3 inhibitors	↓ Proliferation, migration, tumour growth	[105]
ASIC1a	Breast, prostate, pancreatic CSCs	—	Promotes ROS, EMT via RhoA; activates AKT/NF- κ B; role in survival	[106]
AQP3	Gastric CSCs	AQP3 inhibition	↓ Self-renewal; blocks Wnt/GSK3 β / β -catenin pathway	[107]
AQP5	Gastric CSCs	AQP5 inhibition	↓ Autophagy, ↓ stemness	[108]
AQP9	Liver CSCs	AQP9 restoration	↑ ROS, ↓ β -catenin activity; interaction with FOXO3a; ↓ stemness	[78]
ENaC, GABA _A , iGluRs	Glioblastoma CSCs	TTX, TEA, 4-AP, CPP, CNQX, ω -Conotoxin MVIIC, CdCl ₂	↓ CSC viability; targets enriched ion channel families	[109]

**Figure 3.** Targeting ion channels in CSCs as a promising therapeutic strategy.

The figure illustrates the pharmacological targeting of ion channels in CSCs impairs stemness and promotes apoptosis. Blockade of voltage-gated Na⁺ channels using temozolomide (TMZ) and tetrodotoxin (TTX) reduces SOX2 and NANOG expression, suppressing glioma stem cell (GSC) self-renewal and shifting cell cycle progression toward the G1 phase [63,127]. L-type Ca²⁺ channel blockers (manidipine, lomerizine HCl, and benidipine HCl) inhibit stemness by suppressing AKT/ERK signalling, triggering apoptosis [98]. Aquaporin-mediated ROS elevation impairs Wnt/ β -catenin signalling, disrupting proliferation and inducing apoptosis, while ROS scavenging via NAC restores stemness [74]. Activation of ASIC3 by 2-Guanidine-4-methylquinazoline (GMQ) selectively depolarizes GBM CSCs, causing cell damage [105,128]. In ovarian CSCs, inhibition of K⁺ channels (VGCC and KCa) by trimebutine maleate (TM) downregulates stemness markers and Wnt/ β -catenin signalling, sensitizing cells to therapy. Chloride channel modulators such as chlorotoxin and bufalin reduce migration and survival by modulating MMP-2 and the PI3K/Akt/mTOR pathway, respectively. TRPM4 inhibition via 9-phenanthrol impairs breast CSC stemness and induces apoptosis [38].

The therapeutic potential of targeting various calcium channels in CSCs is increasingly recognized for its ability to disrupt tumour progression and overcome treatment resistance. FDA-approved manidipine and lacidipine inhibit L- and T-type voltage-gated calcium channels, leading to reduced sphere formation, viability, and proliferation of ovarian CSCs [97]. They also induce apoptosis and suppress stemness by inhibiting the AKT and ERK signalling pathways, which are crucial for maintaining CSC properties [97]. Mibefradil inhibits the T-type calcium channel Cav3.2, which is overexpressed in glioblastoma stem-like cells (GSCs) [98]. This inhibition leads to decreased

proliferation, survival, and stemness of GSCs, and sensitizes them to temozolomide chemotherapy. This effect is mediated through suppression of the pro-survival AKT/mTOR pathway and activation of apoptotic regulators such as survivin and BAX [98]. SOCE channels are essential for calcium influx in glioblastoma CSCs [26]. Pharmacological inhibition of SOCE reduces proliferation, impairs self-renewal, and decreases the expression of stem cell markers like SOX2, thereby targeting the CSC population responsible for tumour recurrence [26]. Verapamil, a Ca²⁺ channel blocker, targets MDR-related proteins, reducing proliferation and inducing apoptosis in gemcitabine-resistant pancreatic CSCs [99]. In GBM, combining the KCa3.1 inhibitor TRAM-34 with temozolomide (TMZ) significantly decreases DNA synthesis and CSC survival compared to TMZ alone, also reducing tumour cell infiltration [100,101].

TRPC6 supports breast cancer stem cell traits and chemoresistance by regulating integrin $\alpha 6$ mRNA splicing [102]. It suppresses epithelial splicing regulatory protein 1 (ESRP1), promoting the $\alpha 6B$ splice variant, which activates transcriptional co-activator with pDZ-binding motif (TAZ) and reduces Myc expression. Blocking TRPC6 disrupts this pathway, sensitizing TNBC cells to chemotherapy [102]. Several compounds have been reported to irreversibly suppresses the TRPM7 channels, such as waixenicin A, an organic extract of the soft coral *S. edmondsoni* 14, but they lack specificity and therefore are of limited use [38]. The activation of STAT3 and Notch signalling pathway that leads to the regulation of ALDH1 pathway genes in GSC identify potential therapeutic targets for the treatment of glioma [38].

In hepatocellular carcinoma CSCs, the VGCC subunit CACNG4 is implicated in maintaining stemness, and its inhibition by amlodipine suppresses CSC characteristics [25].

Potassium (K⁺) channel inhibition promotes apoptosis and may reverse multidrug resistance (MDR). Kv1.3 inhibitors like margatoxin (MgTX) and non-selective blockers such as 4-aminopyridine (4-AP) suppress metastasis in prostate cancer and reduce lung cancer cell growth, with MgTX also promoting apoptosis by inducing G1-S phase arrest [103].

Glioblastoma CSCs show strong resistance to BCNU (bis-chloroethylnitrosourea) chemotherapy; however, combining BCNU with the chloride channel inhibitor DIDS (4,4'-diisothiocyanostilbene-2,2'-disulfonic acid) promotes apoptosis and reduces proliferation [104]. CLIC1 contributes to this resistance and may act as a drug efflux channel. Inhibiting CLIC1, either pharmacologically (e.g., with metformin) or via RNA interference, enhances CSC sensitivity to treatment. Similarly, blocking the CLCN3 channel also suppresses CSC proliferation. These findings highlight chloride and calcium channel inhibitors as potential tools to overcome multidrug resistance in cancer therapy [104]. New biguanide compounds Q48 and Q54 block CLIC1 more effectively than metformin, reducing GSC proliferation, invasion, and self-renewal with minimal toxicity, showing promise as targeted glioblastoma therapies [51].

Recent studies have highlighted the therapeutic potential of targeting ASICs in CSCs, particularly within glioblastoma, where acidic tumour microenvironments activate these channels. ASIC1a has been shown to induce necroptosis in GSCs through a RIPK1-dependent pathway [62]. This cell death mechanism can be inhibited by the ASIC1a antagonist PcTx1, indicating that pharmacological modulation of ASIC1a could be a viable therapeutic strategy [62]. Additionally, ASIC3 has been identified as a contributor to GSC proliferation and migration, with its inhibition leading to reduced tumour growth, suggesting that ASIC3 is another promising target for therapy [105]. Beyond glioblastoma, ASIC1a's role extends to other cancers; for instance, in breast and prostate cancers, its activation leads to reactive oxygen species (ROS) production and activation of survival pathways like AKT and NF- κ B, while in pancreatic cancer, it promotes epithelial-mesenchymal transition via RhoA signalling [106]. These findings describe the significance of ASICs in cancer progression and the potential of ASIC-targeted therapies across various tumour types.

AQP channels also regulate CSC functions, offering novel targets for cancer therapy. In gastric cancer, AQP3 is overexpressed and correlates with the CSC marker CD44. This overexpression enhances stem-like traits in gastric cancer cells by activating the Wnt/GSK-3 β / β -catenin signalling pathway. Experimental manipulation of AQP3 levels directly influences tumorigenic potential and

self-renewal capacities, emphasizing its role in maintaining CSC characteristics. Targeting AQP3 could, therefore, disrupt these pathways and diminish CSC-driven tumour growth [107]. Similarly, AQP5 is upregulated in gastric cancer stem cells and contributes to their self-renewal by modulating autophagy. Inhibiting AQP5 expression has been shown to reduce the stemness of these cells, suggesting that AQP5 is integral to the maintenance of CSC properties and represents a potential therapeutic target [108]. In hepatocellular carcinoma, AQP9 expression is typically reduced in liver CSCs. Restoring AQP9 levels suppresses CSC characteristics by increasing reactive oxygen species (ROS) accumulation, which in turn inhibits β -catenin activity and promotes its interaction with FOXO3a. This mechanism leads to the attenuation of stemness features in liver CSCs, highlighting AQP9 as a promising target for therapeutic intervention [78]. Collectively, these findings emphasize the diverse roles of AQPs in sustaining CSC properties across different cancer types. Therapeutic strategies aimed at modulating AQP function or expression could, therefore, be effective in targeting CSCs and impeding cancer progression.

Many ion channels enriched in GSCs belong to broader families with overlapping functions, making it challenging to target specific channels therapeutically [109]. To address this, Pollak *et al* [109] analysed enrichment patterns at the family level, identifying 12 ion channel families (including epithelial Na⁺ channels, GABA_A receptors, and ionotropic glutamate receptors) with significant GSC-specific expression. Pharmacological blockade of these enriched ion channels, such as with TTX, TEA, 4-AP, CPP, CNQX, ω -Conotoxin MVIIC, and CdCl₂, significantly reduced GSC viability in vitro, confirming their functional relevance and therapeutic potential [109].

Taken together, the expanding landscape of ion channel-targeted therapies offers a promising avenue for eradicating CSCs and overcoming treatment resistance. However, to fully realize their clinical potential, these strategies must be integrated with precise diagnostic tools, molecular profiling, and advanced drug delivery technologies.

13. Challenges and Strategies in Ion Channel Research for CSCs

Ion channels are key regulators of CSC functions, but despite their therapeutic potential, significant challenges persist in the research and development of ion channel-targeted drugs for CSCs [95,110]. One of the primary obstacles is the remarkable heterogeneity and plasticity of CSCs [95,111–113]. CSCs display remarkable intra- and inter-tumoral heterogeneity. Their phenotypic plasticity allows them to shift dynamically between stem-like and differentiated states, which is often accompanied by changes in ion channel expression and function [95,111–113]. This variability complicates the development of universal ion channel-targeted strategies [95,111–113]. Ion channels in CSCs often exhibit functional redundancy. Upregulated expression of several voltage-gated potassium (Kv) channels, including KCNB1, KCNC1, and KCND1 have been reported in pancreatic CSCs (PK59 CSCs) [114]. Inhibition of KCNB1 with 4-aminopyridine (4-AP) reduced CSC proliferation, suggesting that while multiple Kv channels are overexpressed, targeting specific ones like KCNB1 can impact CSC viability. This indicates potential redundancy among Kv channels in supporting CSC functions [114]. Many ion channels involved in CSC maintenance are also expressed in normal stem cells or vital organs such as the heart and brain. This raises safety concerns and necessitates the development of CSC-specific delivery systems or modulators with high selectivity [95]. Conventional cancer models poorly mimic the CSC niche and ion channel expression patterns [115]. Sphere-forming assays and xenografts are useful but have limitations in throughput and physiological relevance. Additionally, ion channel function is difficult to assess in rare and non-adherent CSCs using traditional electrophysiological tools. High-throughput, label-free technologies suitable for CSCs are still in development [116]. The CSC microenvironment, which are characterized by hypoxia, acidosis, and stromal interaction, profoundly influences ion channel activity [95,117]. Hypoxic conditions can modulate the expression and gating properties of specific ion channels, thereby altering drug sensitivity. Ion channel-targeted therapies must therefore be evaluated in microenvironmentally relevant models to ensure clinical translatability. Identifying CSCs remains challenging, relying on surface markers, functional assays, and gene expression [95]. In cancers like

AML and colorectal cancer, CSCs resemble normal stem cells from their tissue of origin. Markers like CD47 have emerged as promising therapeutic targets, with anti-CD47 antibodies showing success in reducing CSCs in AML. Advances also highlight roles for microRNAs in CSC differentiation and metastasis, offering new avenues for treatment [95].

Overcoming the challenges in targeting ion channels in CSCs must prioritize a multidisciplinary and precision medicine approach. To begin with, the development of CSC-specific ion channel biomarkers using single-cell transcriptomics and spatial proteomics can help distinguish tumour-specific isoforms from those expressed in normal tissues, thus minimizing off-target effects [110,118,119]. Integration of functional electrophysiological profiling with gene expression data will also be crucial to confirm ion channel activity in situ and during different CSC states, including quiescence and EMT [120]. Next-generation screening platforms using organotypic 3D tumour models and patient-derived organoids will be essential for assessing the efficacy and toxicity of ion channel modulators in a physiologically relevant context [121]. Moreover, structure-based drug design using cryo-EM and computational modelling of ion channels can lead to highly selective inhibitors that distinguish CSC-related channel conformations [122]. Targeting ion channel-regulated signalling pathways, such as Ca^{2+} -dependent Wnt/ β -catenin, Notch, or NFAT pathways, in combination with conventional therapies, may suppress CSC resistance and plasticity [18]. The application of nanoparticle-based delivery systems to selectively transport ion channel inhibitors to CSC niches holds promise for enhancing bioavailability while reducing systemic toxicity [12]. Personalized medicine frameworks that incorporate ion channel mutation profiles, CSC surface markers, and drug response phenotypes could guide individualized therapy regimens. These strategic directions, coupled with robust translational pipelines and regulatory support, could unlock the full therapeutic potential of ion channels in combating cancer at its root-through the eradication of CSCs.

14. Conclusions and Future Perspectives

Although substantial advancements in cancer therapies have extended patient survival, drug resistance-largely driven by CSCs-remains a significant clinical hurdle. A growing body of evidence highlights the pivotal role of ion channels in CSC biology, including their contributions to tumour initiation, progression, and resistance to therapy, hence earning the designation of “oncogenic channels” [113]. Aberrant expression and dysregulation of these channels enable CSCs to evade conventional treatments through diverse mechanisms. Targeting ion channels in CSCs approaches a promising strategy to overcome therapeutic resistance. Ideal ion channel targets should exhibit minimal expression in normal tissues, high expression in tumour tissues, selective ligand binding, and low toxicity profiles [18,113]. However, few candidates have progressed into early-phase clinical trials, indicating the pressing need for focused translational research. Existing ion channel inhibitors-already approved for cardiac or neurological disorders-are now being repurposed in oncology, showing encouraging preclinical and early clinical results [17]. Emerging findings emphasize that CSC-specific ion channels, such as Na^+ , K^+ , Ca^{2+} , and Cl^- channels, modulate key processes including proliferation, invasion, and apoptosis. For instance, inhibition of IKCa and BKCa channels has shown therapeutic promise in glioblastoma models [113], where glioma stem cells exhibit high malignancy and resistance. These results emphasize the translational value of targeting CSC-associated ion channels, particularly in highly aggressive and heterogeneous cancers such as glioblastoma, where standard therapy still relies on maximal resection, radiotherapy, and chemotherapy [123]. Therefore, understanding of ion channel expression and regulation in CSCs is crucial. Herein, we explore the diverse range of ion channels present in CSCs, highlighting recent insights into their roles in regulating CSC behaviour, functional characteristics, and cellular dynamics. Particular attention is given to ASICs and AQP, as their crucial involvement in controlling CSC behaviour and dynamics has remained underexplored in prior reviews. ASIC1 and ASIC3 promote CSC survival and invasiveness under acidic tumour microenvironments by activating PI3K/Akt and ERK/MAPK pathways [124]. Inhibiting these channels has reduced tumour growth in preclinical models, making

them compelling pH-responsive therapeutic targets. Similarly, overexpression of AQP1, AQP3, AQP4, AQP5, and AQP8 has been reported in CSC-enriched tumours, where they regulate cell motility, redox signalling, and chemoresistance [65–73]. Among them, AQP3 is particularly implicated in promoting EMT [66]. Small molecule inhibitors and siRNAs targeting AQPs have demonstrated success in sensitizing tumours to standard therapies [17]. Moreover, advances in drug delivery and natural product pharmacology have shown promise. Natural compound-based modulators like limonin and silibinin, which inhibit TMEM16A, exhibit anticancer potential in lung and prostate cancers [113]. Additionally, existing ion channel blockers such as verapamil, mibefradil, and riluzole have shown clinical benefit when repurposed for cancers like metastatic breast cancer, glioblastoma, and melanoma brain metastases, respectively [113,118]. Despite these advances, a major bottleneck remains: the absence of robust biomarkers to predict therapeutic response to ion channel modulators. Therefore, future studies should emphasize the discovery and validation of such biomarkers through genomics, proteomics, and metabolomics. Progress in biomarker development, rational drug design, and precision delivery systems will be crucial to realizing the full potential of ion channel-targeted therapies [113,125].

Intracellular ion channels such as VDAC in the outer mitochondrial membrane and MCU in the inner mitochondrial membrane have emerged as key regulators of CSC maintenance. However, their potential as therapeutic targets remain largely unexplored. Similarly, ER-resident Ca²⁺ channels like the ryanodine receptor (RyR) and IP₃ receptor play crucial roles in cancer stemness, yet their modulation for CSC-targeted therapy has not been extensively investigated. Future research focusing on these ion channels may reveal novel strategies for cancer treatment. Exploring these underexplored areas holds promise for advancing targeted therapies against CSCs [3,93].

While CSCs have been identified across various cancer types, data on ion channel expression in these cells remain incomplete. However, more research is needed to map ion channel profiles across different CSC types. Moreover, future research must explore how ion channels interact with epigenetic and metabolic pathways that drive CSC plasticity and therapeutic evasion. Understanding these interactions will help refine combination therapies that integrate ion channel inhibitors with chemotherapy, immunotherapy, or radiotherapy. These combinations should ideally be guided by biomarker-based patient stratification to maximize efficacy while minimizing off-target effects.

In summary, targeting ion channels in CSCs offers a novel and promising strategy to overcome drug resistance and enhance cancer therapy. While challenges remain, particularly in achieving CSC specificity and minimizing side effects, the integration of ion channel modulators into combination therapies-guided by biomarker-based patient stratification-holds great promise. We hope future research will advance these strategies toward clinical application, ultimately offering more durable and personalized treatment options for cancer patients.

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