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# Role of the calcium toolkit in cancer stem cells

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ABSTRACT

Cancer stem cells are a subpopulation of tumor cells that proliferate, self-renew and produce more differentiated tumoral cells building-up the tumor. Responsible for the sustained growth of malignant tumors, cancer stem cells are proposed to play significant roles in cancer resistance to standard treatment and in tumor recurrence. Among the mechanisms dysregulated in neoplasms, those related to $Ca^{2+}$ play significant roles in various aspects of cancers. $Ca^{2+}$ is a ubiquitous second messenger whose fluctuations of its intracellular concentrations are tightly controlled by channels, pumps, exchangers and $Ca^{2+}$ binding proteins. These components support the genesis of $Ca^{2+}$ signals with specific spatio-temporal characteristics that define the cell response. Being involved in the coupling of extracellular events with intracellular responses, the $Ca^{2+}$ toolkit is often hijacked by cancer cells to promote notably their proliferation and invasion. Growing evidence obtained during the last decade pointed to a role of $Ca^{2+}$ handling and mishandling in cancer stem cells. In this review, after a general overview of the concept of cancer stem cells we analyse and discuss the studies and current knowledge regarding the complex roles of $Ca^{2+}$ toolkit and signaling in these cells. We highlight that numbers of $Ca^{2+}$ signaling actors promote cancer stem cell state and are associated with cell resistance to current cancer treatments and thus may represent promising targets for potential clinical applications.

## 1. Introduction

$Ca^{2+}$ is a versatile signal that relies on specific ion channels, pumps and exchangers to produce complex and diverse $Ca^{2+}$ signals defined by their magnitude as well as their spatial and temporal characteristics. Although existing in virtually every cell, the $Ca^{2+}$ signal is selective and allows to produce specific responses to extracellular signals. Initially described on excitable cells such as those of the heart or the brain, intracellular $Ca^{2+}$ signals were found to exert pleiotropic effects in a wide range of cells including cancer cells.

In neoplasm, a subpopulation of cells endowed with proliferative and self-renewing capacities is considered as the root of the tumor, which led to their name “cancer stem cells”. During the last decade, there has been a deeper understanding of how $Ca^{2+}$ channels and $Ca^{2+}$ signals control several cancer stem cell properties. In this Review, we provide first a general overview of the concept of cancer stem cells for those outside the field and then explore how $Ca^{2+}$ signals affect specific functions and properties of these cells. Finally, we discuss these data of the literature in the context of resistance to treatment, tumour micro-environment and pharmacological developments.

## 2. Cancer stem cells concept and identification

### 2.1. Discovery of cancer stem cells

Histological heterogeneity within tumors is known since the nine-tieth century. In their pioneer experiments exploring tumor complexity, Furth and Kahn uncovered that single leukemic cells when inoculated in mice, were able to induce leukemia and death within fifteen to fifty days in only 5% of mice. Based on these results, they suggested that these hematological malignancies contain a small subpopulation of cells that is able to build a tumor with the expected characteristics when transplanted in a host mouse [1]. A few decades later, Pierce et al identified that only undifferentiated cells can form tumors when grafted

*Abbreviations:* ALDH, aldehyde dehydrogenase; Calmodulin, $Ca^{2+}$MODULated protein; CaMK, $Ca^{2+}$/calmodulin-dependent protein kinase; CRAC, $Ca^{2+}$ release activated $Ca^{2+}$channel; Cs, calcineurin; CSC, cancer stem cell; EMT, epithelial to mesenchymal transition; FACS, fluorescence activated cell sorting; HIF, hypoxia inducible factor; IP3, inositol trisphosphate; IP3R, IP3 receptor; NFAT, nuclear factor activated T-cells; neg, negative; pos, positive; ROC, receptor-operated channel; ROCE, receptor-operated $Ca^{2+}$entry; RYR, ryanodine receptor; SOC, store-operated channel; SOCE, store-operated $Ca^{2+}$entry; STIM, stromal interaction molecule; TRPC, transient receptor potential-canonical; TRPV, transient receptor potential vanilloid

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in a compatible host while differentiated cells of the neoplasm do not [2], supporting the hypothesis that a subset of cancer cells named human tumor stem cells may drive tumorigenesis [3]. The characterization of adult stem cells in normal non-tumoral tissue fostered the discovery of cancer stem cells (CSCs) during the last decades. Using FACS cell sorting based on hematopoietic stem cell-surface-marker expression, the team led by John Dick was the first to isolate, within leukemia, a $CD34^{pos}$ $CD38^{neg}$ subpopulation of cells (positive for CD34 and negative for CD38). When injected into the tail vein of immunodeficient mice, these cells were able to home to- and engraft into the bone marrow wherein they proliferated to generate high levels of leukemia blasts and finally induced establishment of human leukemia in mice [4]. These cells called leukemic stem cells were found to represent about one cell per 250 000–1 000 000 leukemic cells [4,5]. Following evidence in leukemia, CSCs were then also identified in breast cancers where as few as one hundred $CD44^{pos}$ $CD24^{low}$ $Lineage^{neg}$ CSCs were able to form tumors in xenografted mice, while tens of thousands of cells with alternate phenotypes failed to form tumors [6]. Since, most if not all solid tumors including ovarian, prostate, lung, melanomas, pancreas, liver, colon, brain and gastric cancers have been consistently reported to harbor CSCs [7–15].

### 2.2. Cancer stem cell markers

In an attempt to characterize CSCs prospectively, several studies tried to determine the molecular signature of CSCs. Like adult stem cells, CSCs express the transcription factors SOX2, OCT-4 and NANOG that are crucial for maintaining self-renewal capacities as well as the detoxification enzyme aldehyde dehydrogenase (ALDH) [16–19]. Hoechst 33,342 extrusion by ABC transporters, like multidrug resistance transporters, is also often used to isolate a side population with a great potential of initiating tumor in xenografts that may therefore represent CSCs [20].

In addition to these general markers, tumor-specific cell surface markers have also been identified in CSCs, allowing the use of FACS to isolate them. For instance, in leukemia, CSCs were identified as $CD34^{pos}$ $CD38^{neg}$ cells [4]. Although extensive knowledge of marker expression in normal stem/progenitor cells has been fruitful to allow the first isolation of CSCs in leukemia, identification of CSC markers in solid tumors has suffered from the partial characterization of normal adult stem cells in these tissues. Nevertheless, it has been evidenced that CSCs from breast cancers [6] and pancreas cancers [11] can be defined as $CD44^{pos}$ $CD24^{low}$ cells and that CSCs from some glioma [21], prostate cancers [8], pancreatic carcinoma [22] and colorectal tumors [13] display high levels of CD133. However, it should be mentioned that there are some controversies. For example, in glioblastoma, even though $CD133^{pos}$ cells have great tumorigenic abilities, some $CD133^{neg}$ cells can also recapitulate the tumor when engrafted into a host mouse [23]. Yet, keeping in mind these limits, the combinatorial use of CSC markers represents a real asset for the CSC field.

### 2.3. Cancer stem cell hallmarks

The CSC theory states that a subpopulation of cells (the CSCs) hidden within the cancer tissue fuels the tumor, as do adult stem cells for normal tissue. Thus, in this hierarchical model, CSCs are defined as cells that self-renew through either symmetric or asymmetric cell division (Fig. 1A). CSCs generate non-CSC progenies that may proliferate and produce a heterogeneous population of differentiated tumor cells building-up the bulk of the tumor (Fig. 1B). Owing to these properties, CSCs contribute to long-term tumor growth and heterogeneity. Conversely, non-CSCs are capable only of transient proliferation and therefore do not contribute to long-term tumor growth (Fig. 1B).

CSCs can consistently be derived from patient tumors and grown in vitro in a serum-free medium enriched with growth factors, the most commonly used being EGF (Epidermal Growth Factor) and FGF (Fibroblast Growth Factor). This culture medium promotes the formation of colonies developing as spheres [24–26] and in most cases, the cells that form spheres are also the ones that are the most effective for spreading tumors in serial xenotransplantation [14,24,27,28]. Analysis of the structure and composition of glioma tumor spheres showed a concentration of CSCs in the core and an outward differentiation gradient [29]. Because CSCs form colonies, sphere assays along with limit dilution assays, which are both based on the ability of CSC to form colonies, are commonly used to detect CSCs and estimate their amounts.

Confirmation of the CSC nature of a cell is usually performed by using the gold standard method consisting in the analysis of the cell capacity to form tumors when xenografted into non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice over serial passages [30]. This fundamental property has led the scientific community to also use the term tumor initiating cells. Of note, this assay allowed the first identification of CSC in leukemia and later in solid tumors including human breast cancers [6] and brain cancers where as few as 100 cells $CD133^{pos}$ were able to form a tumor that could be serially transplanted while injection of $10^5$ $CD133^{neg}$ cells did not [14]. Originally designed for studies on hematological malignancies, this method presents caveats when applied to solid cancers as these latter not only harbor a higher tumor heterogeneity compared with hematological malignancies but also are formed of cells relying on cell contacts with the matrix and with surrounding cells [30,31]. Indeed, efficiency of melanoma cells to exhibit CSC properties strongly depends on xenograft conditions [32]. To circumvent the variability inherent to the xenotransplantation assay, alternative lineage-tracing approaches have been developed to study CSCs in their native intact microenvironment using genetically engineered mice harboring chemically- or genetically-induced tumors. Such approaches allowed to identify CSCs displaying cardinal stem cell properties in glioblastoma, intestinal adenoma and epidermis papilloma [33–35].

CSCs are thought to be resistant to standard chemotherapy and radiotherapy, a property that explains inevitable recurrence of the tumor after an initial successful treatment. For example, breast CSCs and glioblastoma CSCs survive to conventional chemotherapy and radiotherapy [21,36–38]. Conversely, the genetic ablation of CSCs in mice models with glioblastoma confers to the tumor responsiveness to chemotherapy, stops tumor growth and prolongs mice survival without any apparent regeneration of the cancer [33]. Resistance of CSCs to therapies has been linked to overexpression of drug resistance transporters [39] and a highly efficient DNA damage repair ability [36,40]. Slow cycle kinetics [41] and a quiescent state [42] are also believed to confer to CSC, resistance to treatment. This dormancy would explain the relapse of the tumor after long lag delays although there are examples showing that CSCs are not necessarily quiescent [6].

Whereas numerous studies consistently support an involvement of CSCs in tumor relapse, the roles of CSCs in metastasis remains debated. Metastasis occurs when a cancer cell acquires a mesenchymal program that prompts the cancer cell to leave the primary tumor site, migrate, join the circulation and invade other tissues, where a secondary tumor grows. This process called epithelia mesenchymal transition (EMT) is associated with the expression of a specific set of genes including TWIST1, SNAI1, SNAI2 and ZEB1. Because overexpression of key EMT factors leads to the acquisition of CSC properties [43,44], it has been inferred that EMT promotes stemness. Additionally, clinical studies have reported that cells matching the phenotype criterion of putative cancer stem/progenitor cells are identified in the bone marrow samples of patients with breast cancer, suggesting that breast cancer CSCs disseminate [45]. Furthermore, circulating tumor cells that have CSC hallmarks were found in patients with colorectal cancer, reinforcing the hypothesis of a tight link between CSCs and metastasis [46]. However, the picture might be more complex than initially thought. Studies on pancreatic adenocarcinoma demonstrated that while pancreatic CSCs, identified as $CD133^{pos}$ cells, could induce orthotopic tumor formation

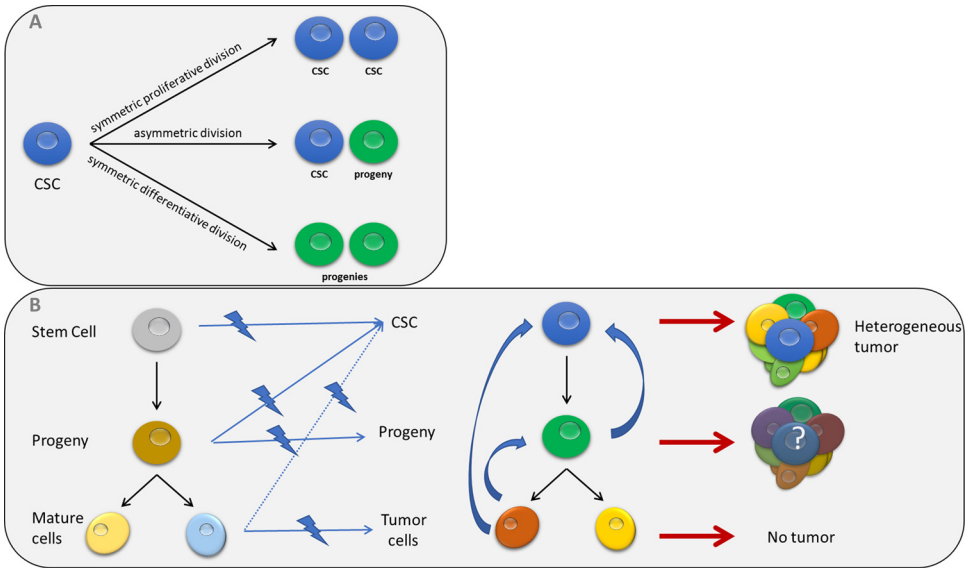


**Fig. 1.** Cancer Stem Cells.
**A.** CSC can divide following three different modes: In the symmetric proliferative division, a CSC (blue) gives rise to two CSCs. This division mode leads to an increase of the pool of CSCs. A CSC can give rise to one CSC and one progeny during an asymmetric division; this division mode maintains the CSC pool and leads to differentiated cells. Finally, the symmetric differentiative division leads to two progenies and depletes the stem cell population. **B.** The CSC hierarchical model. CSCs give rise to progenies (green) which are at the origin of more engaged cells that in turn, generate tumor cells forming the bulk of the tumor. In this model, a single CSC can give birth to a heterogeneous tumor. In addition, several studies consistently described the existence of a tumoral plasticity that endows tumoral progenies or even more differentiated cells with cancer stem cell properties.

in athymic mice, only the fraction of $CD133^{pos}$ cells that also express CXCR4 was able to migrate and metastasize while $CD133^{pos}$ $CXCR4^{neg}$ could not. Elimination of this $CD133^{pos}$ $CXCR4^{pos}$ CSC subpopulation abrogated the metastatic activity of pancreatic cancer cells [22]. The fact that only a subset of long-lived CSCs can drive metastasis following transplantation has also been reported for human colon cancers [47], indicating that even though CSCs are involved in metastasis, only part of them are endowed with this dissemination capacities.

### 2.4. Origin of cancer stem cells

Given that CSCs sustain malignant growth and propagate the tumor and thus represent potential targets for cancer therapies, numerous studies were designed to disclose the identity of the population of cells that may give birth to CSCs.

The CSC model postulates that a minority of cells residing in the tumor is endowed with the potential to drive cancer progression, holding most if not all of a tumor-initiating potential, while the majority of neoplastic cells, the non-CSCs, lack these features. To ensure tumor genesis, CSCs self-renew and are capable of reiterating tumor hierarchy [48]. Because of their inherent self-renewing and proliferating properties, adult stem cells and progenitors have been considered as possible candidates for cell of origin for tumors and for CSCs. Consistent with this notion, stem cells and/or progenitors have been implicated as cellular targets in both hematopoietic malignancies and solid tumors. For instance, in chronic myeloid leukemia that is driven by the oncogene BCR-ABL, Daley and collaborators established that murine hematopoietic stem cells forced to express BCR-ABL develop in irradiated syngeneic recipients a transplantable leukemia whose characteristics are reminiscent of the human pathology [49]. Conversely, in mice where hematopoietic stem cells are deficient in long-term growth and maintenance, the ability of mice to develop BCR-ABL-induced chronic myeloid leukemia (CML) is profoundly reduced, while progression of acute lymphocytic leukemia (ALL) still occurs [50]. These studies show that leukemia can arise from stem cells or from progenitors [51] and that the identity of the cell of origin harboring the mutation plays a critical role in defining the type of cancer. Similar results have been observed in glioblastoma where oncogenic hits in either stem cells or in progenitors could drive in mice, the emergence of diffuse and infiltrating gliomas whose characteristics and sensitivity to treatment were dependent on the cell of origin [52–55]. Recently, deep sequencing of human tissue acquired during tumor resection along with genetic engineering of neural stem cells in mice by using the CRISPR-Cas9 strategy identified neural stem cells as the cell of origin that contains the driver mutations of human glioblastoma [56]. These studies, along with the tracing of genetic lineage combined with the expression of oncogenes or deletion of oncogenic repressors, collectively support that mutated stem or progenitor cells are responsible for the emergence of tumor initiating cells. Some scarce studies, however, suggest that tumor initiating cells may also derive from mature cells (Fig. 1) [57].

On the other hand, a body of experimental evidence pinpoints that non-CSCs may dedifferentiate, revert into multipotent cells and gain a CSC tumorigenic phenotype in response to appropriate stimuli [58,59]. This notion has been exemplified in breast cancers and in melanoma where cancer stem-like cells have been found to arise *de novo* from non-stem-like cells [58,60–62]. At odds with the CSC hierarchical model, the acquisition of CSC properties in non-CSCs has also been reported following exposure to an inflammatory environment or in response to ablation of CSCs in breast, colon and intestinal cancers [63–66]. Furthermore, when analyzing the mechanisms responsible for CSC plasticity, the group of Weinberg determined that non-CSCs in human basal breast cancers carry a ZEB1 promoter that can readily switch from a poised to active state, resulting in the efficient induction of ZEB1 and consecutive acquisition of a CSC phenotype [58]. This proclivity of non-CSCs to generate CSCs implies not only that non-CSCs are plastic cell populations, but also that non-CSCs are highly adaptable to signals from the microenvironment. Among the mechanisms involved in CSC maintenance or plasticity, aberrant activation of Wnt, Hedgehog or Notch signaling has been implicated in the regulation of a plethora of CSC types including breast, colorectal, hematologic and lung cancers [67,68]. Conversely, small molecules that inhibit these pathways disrupt stemness and induce differentiation of CSC, which is highly desirable for cancer treatment. Interestingly, it has been shown in colorectal cancers that cells from the CSC niche secrete hepatocyte growth factor that elevates Wnt signaling and subsequently confers self-renewal and tumorigenic potential to non-CSC, indicating that signals from the microenvironment govern CSC stemness [69]. At the opposite, the fact that genetic ablation of the CSCs impaired glioblastoma growth and relapse suggests a more restricted plasticity in this neoplasm [33]. The existence of CSC plasticity represents a major challenge for cancer biology and points to the necessity to address in-depth the extent to which the different tumor types are prone to reversion as well as to determine the intrinsic and extrinsic mechanisms that govern the CSC phenotype.

## 3. Emerging roles of $Ca^{2+}$ in cancer stem cell population maintenance and stemness

The maintenance or the emergence of a population of CSCs is governed by both intrinsic factors and extrinsic signals like those from the microenvironment stimulating a various set of receptors. Numerous extracellular signals are converted in transitory rises of intracellular concentration of free $Ca^{2+}$ that are either restricted to cell micro-domains or propagated throughout the whole cell and that display different durations. Because of the wide repertoire of spatio-temporal fluctuations in its intracellular concentrations, the $Ca^{2+}$ signal is exquisitely poised to link extracellular mechanisms with intracellular modifications that in turn, determine specific cell states [70]. $Ca^{2+}$ signal diversity relies on a $Ca^{2+}$ toolkit, which ensures the transitory elevation of free cytosolic $Ca^{2+}$ concentration through a $Ca^{2+}$ entry from the extracellular compartment and/or by a $Ca^{2+}$ release of intracellular stocks mainly contained in the endoplasmic reticulum (ER) and mitochondria. $Ca^{2+}$ entry from the extracellular compartment occurs through plasma membrane channels and liberation of intracellular stores follows activation of $Ca^{2+}$ release receptor-channels of the ER membrane or exchangers located in mitochondria. To insure a transitory cytosolic $Ca^{2+}$ rise, pumps and exchangers release $Ca^{2+}$ in the extracellular space and reuptake $Ca^{2+}$ ions into cell reservoirs (Fig. 2). This so-called $Ca^{2+}$ toolkit is often either hijacked or modified by cancer cells and many cancers harbor a remodeling of plasma membrane channels as well as alteration of $Ca^{2+}$ exchanges and intracellular $Ca^{2+}$ signals, which then contribute to the neoplastic phenotype [71–74]. Changes in activity and/or expression of these specialized proteins are involved in promoting an enhanced migratory activity, or a sustained and uncontrolled cell proliferation, or a resistance to apoptotic signals. The discovery of enrichment in $Ca^{2+}$ signaling genes in glioma CSCs, that is correlated with a high $Ca^{2+}$ drug sensitivity in these immature cells, set a cornerstone for studies aimed at deciphering the roles of the $Ca^{2+}$ toolkit in CSCs [75]. The fact that $Ca^{2+}$ signaling is the first pathway to be modified by epigenetic regulators in CSCs further reinforces the hypothesis of a crucial role of $Ca^{2+}$ in CSCs [76]. For purpose of clarity, we organized the following sections according to the $Ca^{2+}$ toolkit: plasma membrane channels, intracellular $Ca^{2+}$ handling and $Ca^{2+}$ signaling pathways.

### 3.1. Plasma membrane channels

Located at the interface of the intracellular and extracellular medium, the ionic carriers and transporters of the biomembranes contribute significantly to transmission and integration of extracellular signals that originate, for example, from tumor or stem cell microenvironment wherein CSCs are implanted. Among these trans-membrane proteins, $Ca^{2+}$ channels mediate $Ca^{2+}$ entry from extracellular compartment in response to a diversity of stimuli such as membrane depolarization, extracellular agonists, intracellular messengers, stretch, or depletion of $Ca^{2+}$ stores [70].

#### 3.1.1. Voltage-operated channels (VOC)

Voltage-operated channels (VOC) or Ca$\nu$ family comprise 6 types of channels: L-, N-, P-, Q-, R-, and T-type [77], which require a transient depolarization of the plasma membrane for activation of the intrinsic voltage sensor and subsequent pore opening. These channels, firstly characterized and identified in “excitable cells” such as neurons and muscles, are also found in cancer cells where they regulate proliferation and migration [72]. $Ca^{2+}$ permeable VOC have been scrutinized by several studies, although it was not clear if CSCs display membrane potentials allowing the activation of $Ca^{2+}$ permeable VOC. In this respect, CSCs from hepatocellular carcinoma were shown to display a more depolarized resting membrane potential (−7 mV) relative to normal stem cells (−23. mV) that was related to a differential expression of GABAergic receptor subunit [78]. Interestingly, the voltage-gated $Ca^{2+}$ channel α2δ1 subunit encoded by the gene *CACNA2D1* was nicely identified as a marker of CSCs in hepatocellular carcinoma [79]. Beginning with the search of biomarker for tumor initiating cells in these liver cancers, a subtractive immunization approach using cells with high tumorigenic potential versus cells with no tumor-initiating capacities allowed the generation of an antibody named 1B50-1. This antibody was then proven to recognize a subset of cells expressing stem cell markers including CD133, ALDH and SOX2 and able to self-renew and to recapitulate the tumor when grafted in immunodeficient mice. Identification of the antigen targeted by the 1B50-1 antibody revealed

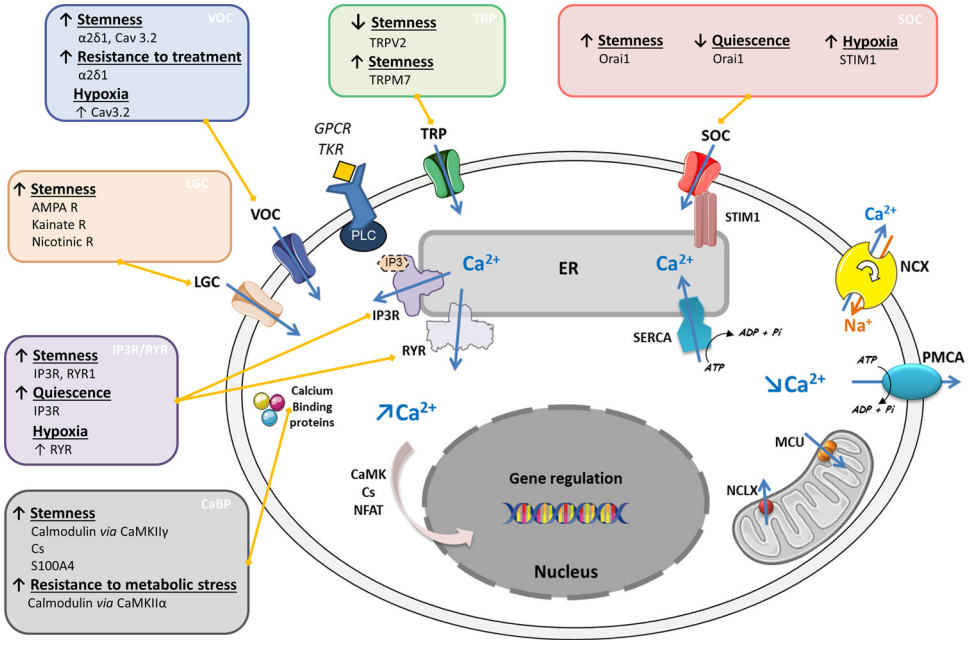


**Fig. 2.** The $Ca^{2+}$ toolkit in cancer stem cells. Transient rise of intracellular $Ca^{2+}$ leads to regulation of various cellular functions including proliferation and migration. Accordingly, the cells possess a complex toolkit to control intracellular $Ca^{2+}$ fluctuations. Increase of intracellular $Ca^{2+}$ concentrations follows $Ca^{2+}$ entry from the extracellular environment and/or $Ca^{2+}$ release from intracellular reservoirs. Different plasma channels (LGC, VOC, TRPs, and SOC) can induce an entry of extracellular $Ca^{2+}$ into the cell. Endoplasmic reticulum (ER) and mitochondria, the main reservoirs of $Ca^{2+}$ of the cell can release their $Ca^{2+}$ stock following IP3R or RYR activation for ER and MCU for mitochondria. To ensure a transient rise of $Ca^{2+}$, exchangers and pumps are present at the plasma membrane, NCX and PMCA respectively. SERCA allows replenishing of ER reservoir, and NCLX replenishing of mitochondrion reservoir. Different actors of the $Ca^{2+}$ toolkit regulate CSCs. Plasma membrane channels type LGC (ligand gated channels), VOC (voltage operated channels, TRP (transient receptor potential) channels, SOC (store operated channels), but also intracellular receptor from the ER IP3R (inositol trisphosphate receptor) and RYR (ryanodine receptor) control various properties of CSCs. Moreover, $Ca^{2+}$ binding proteins regulate stemness and resistance of CSC in different type of cancer.

*This figure was created using modified Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License.*

that it corresponds to the α2δ1 isoform 5 subunit of VOC. Functional assays showed that the VOC α2δ1 subunit supports $Ca^{2+}$ influx into liver CSCs through L- and N-type voltage-gated $Ca^{2+}$ channels and that its blockade dramatically reduces the population of CSCs [79]. Subsequently, analysis of $Ca^{2+}$ channel α2δ1 subunit expression performed in cohorts of patients substantiated the relevance of α2δ1 as biomarker for diagnosis of hepatocellular carcinoma [80]. The biomarker property of the VOC α2δ1 subunit was then extended to CSCs of two other neoplasms, namely small cell- and non-small cell lung cancers [81,82]. Moreover, these studies provided evidences that expression of this VOC alpha-subunit could be tightly linked to CSC resistance to radio- and chemotherapies. Indeed, it was shown that cells expressing the VOC α2δ1 subunit in small-cell lung cancer or in non-small-cell lung cancer resist to chemotherapy or radiotherapy respectively [82]. Conversely, blocking α2δ1 with a monoclonal antibody sensitized the cells to treatment, suggesting that this antibody may be used to improve the treatment outcome [81].

Other types of VOC have been found in CSCs and correlated with poor prognosis. For instance, the T-type $Ca^{2+}$ channel Caν3.2 that is more expressed in CSCs of glioblastoma ($CD133^{pos}$) than in either non-CSC-tumor cells or normal tissue represents a main regulator of the CSC population. Pharmacological inhibition of this channel with mibefradil (currently used to treat hypertension) or its shRNA-mediated knockdown was sufficient to reduce the CSC population by promoting CSC differentiation. Noteworthy, mibefradil not only proved as efficient as temozolomide (the current chemotherapy used to treat glioblastoma) in reducing tumor growth in xenografts but exerted an additive effect when combined with temozolomide, resulting in a prolonged survival of mice [83]. Moreover, this study also reported that hypoxia, which favors resistance to anticancer therapies, also leads to increased expression of the VOC Caν3.2 in glioblastoma [83]. CSC resistance to radio- and chemotherapies being a major hurdle in current oncology, these studies suggest that additive treatment targeting VOC could improve current therapies by preventing a resistant population of CSCs to rebuild a tumor despite a successful initial therapy.

#### 3.1.2. Receptor operated channels (ROC) and store-operated channels (SOC)

$Ca^{2+}$ entry occurring after ligand fixation to a transmembrane receptor was originally called Receptor Operated $Ca^{2+}$ Entry (ROCE) and was supposed to be mainly carried by Receptor Operated Channels (ROC). ROCE recorded subsequent to activation of PLC (phospholipase C) are due to activation of tetrameric TRPC (Transient receptor potential canonical) channels, which support a cationic current ($Na^+$ and $Ca^{2+}$). Unless directly activated by DAG (diacylglycerol) or its homolog OAG (1-oleoyl-2-acetyl-sn-glycerol), ROCE recordings by intracellular $Ca^{2+}$ fluorescent probes can be difficult to distinguish from Store-Operated $Ca^{2+}$ Entry (SOCE) that also secondarily occurs after PLC activation promoting IP3 (inositol 1,4,5-trisphosphate)-dependent $Ca^{2+}$ release from ER.

Store-operated channels (SOC), largely distributed in both excitable and non-excitable cells, are activated after a partial depletion of ER $Ca^{2+}$ stores, which is sensed by the ER transmembrane protein Stromal Interaction Molecule 1 (STIM1) through an EF hand motif and leads to the opening of SOC at the plasma membrane [84]. The core component of SOCs is constituted of Orai1 homopolymers supporting $Ca^{2+}$ selective currents ($I_{CRAC}$) firstly identified as CRAC ($Ca^{2+}$ Release-Activated Channels) in T cells [85] and mast cells [86,87] for instance. Depending on the cell type and also on the STIM1 /TRPC channel ratio [88], SOCE and $I_{SOCE}$ can be supported by TRPC tetrameric channels, constituted in particular of TRPC1 and TRPC4 that can interact directly with STIM1 [89,90], cooperate with Orai1 and support a sustained SOCE [91,92]. SOCE is a major mechanism in non-excitable cells that, upon stimulation, finely refills ER $Ca^{2+}$ stores, modulates intracellular $Ca^{2+}$ signals and downstream stimulates $Ca^{2+}$-dependent intracellular signaling cascades. In normal stem cells of various organs including brain, bone marrow or heart, SOC control cell proliferation and differentiation [93–97]. Our own studies also strongly suggested that $Ca^{2+}$ entries through SOC control the expansion of the stem cell population by tuning the proportions of symmetric and asymmetric divisions of stem cells [94]. Because stemness and differentiation are essential to sustain malignant growth and propagate the tumor, SOCs have been considered as interesting candidates in CSC stemness. For instance, Lee and collaborators [98] disclosed that Orai1 promotes stemness in oral/oropharyngeal squamous cell carcinoma. Specifically, they found that the $ALDH^{high}$ CSC population was indeed enriched in Orai1 proteins when compared to the rest of the bulk. When these tumor cells were transduced with a dominant negative mutant of Orai1, sphere formation and tumor initiation in xenografts were substantially reduced. On the contrary, ectopic expression of Orai1 in non-tumorigenic immortalized oral epithelial cells resulted in increased proliferation, self-renewal and tumor-initiating capacities [98]. Overall, this study performed on oral/oropharyngeal squamous cell carcinoma suggested that Orai1 and SOCE through activation of NFAT (Nuclear Factor Activated T-cells) signaling pathway might underpin a stemness state in this neoplasm.

Promotion of stemness as well as CSC resistance to anticancer therapies are also known to be favored by the hypoxic conditions present in the CSCs microenvironment. Interestingly, in hepatocarcinoma cells, the hypoxia-inducible factor-1 alpha (HIF-1) was found to directly control STIM1 transcription and to contribute to SOCE. The STIM1-mediated SOCE, in turn, induced $Ca^{2+}$ signaling pathways that triggered HIF-1 accumulation in hypoxic cells, suggesting a mutual dependency between SOCE and hypoxia [99]. These features suggest that hypoxia and STIM1/Orai1-dependent SOCE could work together in promoting stem cell-like phenotype within the tumor. In support of a role of SOC in CSCs, analysis of the expression of 260 genes involved in $Ca^{2+}$ signaling in brain tumor samples allowed to disclose a set of 6 genes involved in $Ca^{2+}$ entry, including ORAI1, which are highly expressed in glioblastoma tissues or in glioma stem cells but not in normal brain tissues [100]. This suggests that in these highly aggressive brain tumors, Orai1 and SOC, in addition to supporting invasion abilities [101], may play major roles in maintaining or expanding the stem cell population. In line with these observations, a recent study reported that inhibition of SOC channels with SKF-96365 significantly decreased cell proliferation of glioblastoma stem cells, which was associated with a quiescent transcriptomic signature [102]. Of note, greater SOCE amplitude correlated with Orai1, TRPC1 and STIM1 overexpression were also found in endothelial progenitor cells isolated from peripheral blood of patients affected by renal cellular carcinoma, suggesting that SOCE is deregulated in both the tumoral CSCs and the tumoral progenitor cells that participate to the formation of primitive tumor endothelium [103].

#### 3.1.3. Cation channels from the TRP family

Little is known concerning the functions of TRPC channels in CSCs although these channels, when mobilized by activation of PLC pathway, can support SOCE and ROCE.

Among the TRP family, TRPM7 (transient receptor potential melastatin 7) is a ubiquitous $Ca^{2+}$ and $Mg^{2+}$ permeable ion channel that acts both as a ion channel and as a serine/threonine receptor [104]. Of interest a study of Liu et *al* demonstrated that activation of TRPM7 in glioma cells upregulates the CSC markers ALDH1 and CD133, and promotes proliferation, migration and invasion [105].

A member of the TRPV (transient receptor potential vanilloid) subfamily, TRPV2 channel that is activated by various stimuli, has been evidenced as impairing stemness in CSCs. In accordance, TRPV2 was found to hinder glioblastoma stem cell proliferation and favor their differentiation both in vitro and in vivo [106]. Indeed, glioblastoma stem cell lines displayed a reduced proliferation and a more mature glial phenotype after TRPV2 overexpression. Moreover, tumor xenografts derived from TRPV2-overexpressing glioblastoma CSCs showed a significant reduction in diameter and mitotic index, associated with a differentiated morphology [106]. After this initial demonstration of an

inhibitory role of TRPV2 in brain CSCs, similar results were obtained in liver neoplasms [107]. Hence, human hepatocellular carcinoma tissue displayed an inverse correlation of TRPV2 expression with those of CD133 and CD44. Accordingly, TRPV2 knockdown in human hepatoma HepG2 cell line enhanced colony formation and expression levels of CSC markers whereas TRPV2 expression rescue in TRPV2 knocked-down HepG2 cells restored low levels of CSC markers and abrogated the effect on colony formation. Similarly, overexpression of TRPV2 in the hepatocarcinoma cell line SMMC-7721, that display low levels of the protein, decreased CSC markers and colony formation. In line with these data, TRPV2 pharmacological agonist probenecid was found to diminish tumor growth in xenografted immunocompromised mice [107].

Whereas it is easy to conceive that agonists of the CSC microenvironment can activate receptors coupled to PLC and favor the stem cell population through the activation of Orai and TRPC channels, the extracellular factors that induce the activation of TRPV2 and impair stemness in CSCs remains challenging. The TRPV subfamily comprises channels critically involved in nociception and thermosensing, and functional studies have evidenced that TRPV2 is stimulated by noxious heat, with an activation threshold greater than 52 °C, and by several exogenous chemical ligands [108,109]. Yet, very little is known about its activation mechanism or concerning possible candidates acting as specific or endogenous activators. Some extracellular factors were suggested to have direct effects on TRPV2 gating [110,111], however these mechanisms are not well understood. On the other hand, TRPV2 was proposed to be a growth-factor-regulated channel. In line with this notion, it was described that IGF-1 (insulin like growth factor 1) or platelet-derived growth factor (PDGF), or chemokines induce a dynamic translocation of TRPV2 from intracellular compartments to the plasma membrane through a (phosphoinositide 3-kinase) PI3K-dependent pathway [112,113]. Thus, TRPV2 activity seems to be dependent on regulated plasma membrane targeting of constitutively active channel, which contribute to a steady-state TRPV2-mediated $Ca^{2+}$ entry in response to some extracellular factors found in serum or to focal mechanical stimulation [114]. One can thus envision that these channels could be recruited/activated by factors present in the microenvironment of CSCs or by physical characteristics such as stretch forces and changes in stiffness of the tumor microenvironment, which will counteract stemness on the contrary of SOCE and ROCE activation.

#### 3.1.4. Ligand-gated channels

Ligand-gated channels among which $Ca^{2+}$-permeable glutamate receptors and nicotinic receptors of acetylcholine have also been associated with CSC stemness. In that respect, high concentrations of functional AMPA (α-amino-3-hydroxy-5-méthylisoazol-4-propionate) glutamate receptors or kainate receptors were detected in CSCs respectively from glioblastoma or urothelial cancer, as compared to the differentiated tumor cultures consisting of non-stem cells [75,115,116]. Their genetical knockdown resulted in a decreased sphere-forming ability [115]. Besides glutamate receptors, much attention has been focused on nicotinic receptors because incidence of several cancers is highly correlated with cigarette smoking whose addictive product is nicotine. In several neoplasms including non-small cell lung cancer, pancreatic cancers or breast cancers, nicotine through activation of nicotinic acetylcholine receptors (nAChRs), specifically the α7 subunit, fostered stemness gene expression and favored the emergence of a CSC phenotype [117–119]. This effect involved downstream effectors that were cancer tissue-specific. Namely, stimulation of nicotinic receptors in non-small cell lung cancer recruited Yes Associated Protein 1 (Yap1), a transcriptional co-activator and effector of the Hippo signaling pathway, that binds to SOX2 promoter [119] and thereby triggered stemness. In pancreatic cancer cells, cholinergic nicotinic receptors elicited signaling to mitogen-activated protein kinase (MAPK) and FOSL1 [118] whereas they were coupled to PKC (protein kinase C)-Notch pathway in breast cancer cells [117]. A potential role of other types of nicotinic receptors has also been suggested in glioma CSCs [120].

#### 3.1.5. Plasma membrane pumps and exchangers

Among the $Ca^{2+}$ toolkit, pumps and exchangers play a crucial role by extruding $Ca^{2+}$ thereby ensuring a transient intracellular $Ca^{2+}$ rise. NCX ($Na^{+}/Ca^{2+}$ exchanger) and PMCA (plasma membrane $Ca^{2+}$ ATPase) role in cancer have already been studied [121,122] but currently, there is only little information about their potential role in CSC. To our knowledge, only a transcriptomic study showed an overexpression of NCX3 in glioblastoma CSCs [100], pointing to the need for further studies on the potential role of these $Ca^{2+}$ toolkit actors in CSC.

### 3.2. Intracellular $Ca^{2+}$ reservoirs and transporters

Evidence has brought to light a possible involvement of the intracellular $Ca^{2+}$ reservoirs and transporters in CSC stemness control. One of the major pathways leading to a $Ca^{2+}$ signal is $Ca^{2+}$ release from the endoplasmic reticulum (ER) to the cytoplasm, through two related $Ca^{2+}$ release channels incorporated into the ER membrane, namely the ryanodine receptors (RYR) and inositol 1,4,5-trisphosphate receptors (IP3R). IP3Rs and RYRs form $Ca^{2+}$–release channels composed of 4 subunits with very large regulatory cytoplasmic domain. IP3Rs and RYRs have been described as implicated in numerous diseases (for review [123,124]). Rapid $Ca^{2+}$ release through these channels is regulated by multiple factors that include free $Ca^{2+}$ ion, which can lead to $Ca^{2+}$-induced $Ca^{2+}$ release. Three different isoforms of RYRs (RYR1, RYR2, RYR3), each encoded by a different gene, have been firstly identified in mammal's skeletal, cardiac and smooth muscles and in brain but recent studies have shown that these receptors are much more widely expressed.

A major role of RYR1 has been disclosed in breast cancer CSCs. In these cells, chemotherapy using carboplatin induced HIF-1 dependent glutathione S-transferase omega 1 (GSTO1) expression, which was shown to interact with the ryanodine receptor RYR1 and promote $Ca^{2+}$ release [125]. As a consequence, increased cytosolic $Ca^{2+}$ levels activated the intracellular signaling cascade PYK2 (pyruvate kinase 2)/ SRC / STAT3 (Signal transducer and activator of transcription 3), leading to an enhanced expression of pluripotency factors and to an enrichment in the CSC population [125]. Moreover, the knockdown of RYR1 decreased the percentage of $ALDH^{pos}$ CSCs, diminished carboplatin-induced pluripotency factor expression as well as tumor initiation after injection in female SCID mice [125].

A similar role for the $Ca^{2+}$ release channels IP3R has also been suggested in CSC stemness control. IP3R are more widely expressed than RYR, with almost all animal cells expressing at least one of the three IP3R subtypes. Their activation is linked to receptors in the plasma membrane that stimulate PLC, leading to IP3 production. The binding of IP3 to IP3R primes IP3Rs to bind $Ca^{2+}$, which in turn leads to channel opening. This regulation by $Ca^{2+}$ when IP3 binds to IP3R allows $Ca^{2+}$ release through IP3Rs as well as the propagation of the $Ca^{2+}$ signal by $Ca^{2+}$-induced $Ca^{2+}$ release in most of the cells. The $Ca^{2+}$ release through IP3R was shown to play an important role in melanoma CSCs. Indeed, impairment of IP3R function in melanoma cells by knock-down of selenoprotein k (SELENOK), a protein that is required for IP3R maturation, reduced $Ca^{2+}$ release and led to a diminution of the CSC population identified by CD133 expression [126]. To confirm these effects in vivo, a transgenic mouse strain that develops spontaneous metastatic melanoma was crossed with SELENOK knockout mice. The littermates that were SELENOK-deficient displayed reduced primary tumor growth on tails and ears, suggesting that $Ca^{2+}$ release through IP3R is required for melanoma stemness and tumor initiation [126]. Thus, $Ca^{2+}$ release from intracellular stores may be crucial for CSC stemness, and this may also involve interplay with channels of the plasma membrane such as SOC, since these channels

can be activated following IP3-dependent $Ca^{2+}$ release and partial depletion of ER $Ca^{2+}$ stores. $Ca^{2+}$ release and IP3R also seems to be involved in acquisition of a quiescent phenotype, which is known to allow CSCs escaping from current anti-cancer therapies. In accordance, Zeniou and collaborators identified a selective cytotoxic agent of quiescent glioblastoma CSCs named bisacodyl while seeking for drugs capable of eradicating CSCs through a screening of the chemical Prestwick library [127]. Consecutive studies of the group disclosed that this drug inhibits $Ca^{2+}$ release through IP3R [128], suggesting that management of $Ca^{2+}$ flux is crucial for maintaining quiescence in CSCs that allows them to resist to chemotherapies.

Another major intracellular organelle involved in $Ca^{2+}$ handling is mitochondria. While a formal demonstration of the role of mitochondrial $Ca^{2+}$ in CSC stemness is still awaiting, it should be underlined that transcriptomic analysis of the $Ca^{2+}$ toolbox highlighted an up-regulated expression of the mitochondrial $Ca^{2+}$ transporter MCU in glioblastoma CSCs [100]. In these cells, it was observed that intracellular $Ca^{2+}$ signals, following activation of SOC, displayed different kinetics with more sustained $Ca^{2+}$ signals in proliferating cells than in quiescent ones [102]. The difference was proposed to be mostly due to difference in $Ca^{2+}$ influx reuptake by mitochondria and mitochondria morphology remodeling.

As for plasma membrane pumps and exchangers, little is known about the involvement of the sarco/endoplasmic reticulum $Ca^{2+}$-ATPase (SERCA) [129] and the mitochondrial sodium calcium exchanger (NCLX) [130] in CSC regulation. A recent study by Park et al. described a role of SERCA in CSC resistance to metabolic stress that is further described in the next paragraph as it was related to a major role of $Ca^{2+}$/calmodulin-dependent protein kinase [131].

### 3.3. $Ca^{2+}$-dependent signaling pathways

$Ca^{2+}$ entry and/or $Ca^{2+}$ release through the various $Ca^{2+}$ channels described above result in the increase of intracellular free $Ca^{2+}$ concentration and to the pattern of tightly spatially and temporally regulated intracellular $Ca^{2+}$ signals, which are crucial to differentially activate specific signaling pathways. These latter depend on various $Ca^{2+}$ Binding Proteins (CaBP) that are present in the cytosol, such as calmodulin, calcineurin, PKC, S100 proteins, parvalbumin [132]. Although some of them, like parvalbumin, participate in $Ca^{2+}$ homeostasis by capturing free $Ca^{2+}$, most of CaBP are part of intracellular signaling cascades and are critical for $Ca^{2+}$ signal transduction [133]. Upon binding to $Ca^{2+}$, calmodulin ($Ca^{2+}$ MODULated proteIN) modifies its interaction with many effectors, including kinases or phosphatases, that in turn, trigger various signaling pathways. Specifically, calmodulin regulates $Ca^{2+}$ channels like IP3R and RYR from the ER [134,135] and stimulates calcineurin that subsequently activates MEK/ERK, NFAT or $Ca^{2+}$/calmodulin-dependent protein kinase (CaMK) pathways [136]. Among CaMK, the CaMKII that comprises 4 homologs, α, β, γ and δ, has been involved in leukemia [137]. Studies performed on hematological malignancies revealed that CaMKIIγ is highly activated in CSC from chronic myeloid leukemia but not in their normal counterpart. Inhibition of CaMKIIγ activity by berbamine, a product isolated from traditional Chinese herbal medicine that acts as an ATP-competitive inhibitor of CaMKIIγ, eradicated leukemic stem cells [138]. Moreover, CaMKIIγ aberrant expression accelerated blast crisis that corresponds to the final deadly phase of chronic myeloid leukemia, indicating that this enzyme is crucial for the progression of this hematological pathology [139]. A few years later, CaMKIIγ was also identified in CSCs of liver and lung cancers [140,141]. In these latter, knock-down of CaMKIIγ led to diminution of pluripotency transcription factors, sphere formation and tumorigenicity [141]. Whereas CaMKIIγ seems involved in the maintenance of a stem cell state, CaMK1D amplification has been implicated in EMT of breast cancer. Indeed, forced overexpression of this protein in non-tumorigenic breast epithelial cells led to phenotypic alterations indicative of EMT, including loss of cell-cell adhesions and increased cell migration and invasion [142]. Furthermore, the isoform CaMKIIα has been found to help CSCs to cope with metabolic stress. Indeed, while analyzing genome-wide transcriptional profiles of human breast cancer cells subjected to glucose deprivation, Park and collaborators unveiled that the $Ca^{2+}$ signaling was one of the most significantly over-represented pathways [143]. These changes in $Ca^{2+}$ toolkit gene expression were accompanied by a decrease in resting cytosolic $Ca^{2+}$ concentration and were associated with increased SERCA2 levels in CSCs as compared to parental cells following glucose deprivation. Dissection of the mechanisms involved showed that glucose deprivation substantially increased phosphorylation of CaMKIIα in CSCs. Conversely, knockdown of the gene encoding CaMKIIα in CSCs led to reduced levels of SERCA2 (sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2) with failure to restore basal intracellular $Ca^{2+}$ levels and in turn, and increased apoptosis of CSCs [131]. Accordingly, these studies suggest that CaMK may control several facets of CSC functions.

Calmodulin can also activate calcineurin, a $Ca^{2+}$-activated protein phosphatase whose substrates include most members of the NFAT family of transcription factors. In colorectal cancers, calcineurin supported the survival and proliferation of CSCs in a NFAT-dependent manner and promoted the development of intestinal tumors in mice [144]. The fact that calcineurin/NFAT signaling is required during the early phases of reprogramming reinforces the possible role of this pathway in stemness maintenance [145].

In addition to $Ca^{2+}$ signaling pathways, the $Ca^{2+}$ binding protein can also control the CSC population. This has been exemplified in glioblastoma where cells with high levels of S100A4 expression were enriched in tumor initiating cells [146]. In addition, selective ablation of $S100A4^{pos}$ cells in genetically engineered mice was sufficient to block tumor growth. Moreover S100A4 knockdown significantly reduced proliferation and self-renewal. [146].

## 4. Conclusion

The above-mentioned studies point to an emerging role of $Ca^{2+}$ signals in CSC, a specific population of cells that is considered as the root of the tumor. Activity and expression of numbers of $Ca^{2+}$ actors including plasma membrane channels, ER channels and $Ca^{2+}$ binding proteins are positively correlated with CSC stemness in a wide range of tumors. Interestingly, only TRPV2 expression is inversely associated with CSC in glioblastoma, liver neoplasm and hepatocellular carcinoma. In addition to promoting CSC state, most of these channels confer to the cells resistance to current cancer treatments including radiotherapies and large chemotherapies, which target highly proliferative cells. Table 1 and Fig. 2 summarize the major points that we mentioned in this review.

It should however be underlined that the picture may be more complex as the $Ca^{2+}$ toolkit is also remodeled in non-CSC cells from the microenvironment, as for example endothelial progenitors, that in turn, control CSC biological capacities [103,147]. Thus, studies considering the CSCs within their stem cell niche are awaited to consolidate the understanding of fundamental roles supported by the $Ca^{2+}$ toolkit in the tumor. The strategy consisting in using molecules against $Ca^{2+}$ signaling targets to eradicate CSCs still needs some experimental support before efficient clinical use. Yet, it should be mentioned that promising results were obtained with the non-selective small molecule carboxyamidotriazole, which binds to and inhibits non-voltage-operated $Ca^{2+}$ channels, blocking both $Ca^{2+}$ influx into cells and $Ca^{2+}$ release from intracellular stores, and disrupts $Ca^{2+}$ -mediated signal transduction. A recent multicenter phase IB trial assessed the clinical potential of a combination of the orally bioavailable carboxyamidotriazole orotate (CTO), with temozolomide against brain cancers. The fact that promising signals of CTO activity in this difficult-to-treat population has been found encourages to keep on studying the roles of $Ca^{2+}$ channels in CSCs [148].

**Table 1**
$Ca^{2+}$ toolkit actors and their role in CSC stemness and resistance to treatment. (+ : stimulates ; - : inhibits ; ↗ : increases).

| CSC characteristic | | Family | Protein | Impact | Type of Cancer |
|---|---|---|---|---|---|
| Stemness | Stemness | VOC | α2δ1 subunit | + | lung cancer [81,82] hepatocarcinoma [79] |
| | | | Cav 3.2 | + | glioblastoma [83] |
| | | SOC | Orai1 | + | glioblastoma [100] oral/oropharyngial squamous cell carcinoma [98] |
| | | TRP | TRPV2 | – | glioblastoma [106] liver cancer [107] |
| | | | TRPM7 | + | glioblastoma [105] |
| | | LGC | AMPA R | + | glioblastoma [116] |
| | | | Kainate R | + | urothelial cancer [115] |
| | | | Nicotinic R | + | lung cancer [119] pancreatic cancer [118] breast cancer [117] glioblastoma [120] |
| | | IP3R/RYR | IP3R | + | melanoma [126] |
| | | | RYR1 | + | breast cancer [125] |
| | | CaBP | CaMKIIγ | + | chronic myeloid leukemia [138] liver cancer [140] lung cancer [141] |
| | | | Cs | + | intestinal tumors [144] |
| | | | S100A4 | + | glioblastoma [146] |
| Resistance to treatment | Resistance radio/ chemotherapies | VOC | α2δ1 subunit | + | lung cancer [81,82] |
| | Quiescence | SOC | Orai1 | – | glioblastoma [102] |
| | | IP3R/RYR | IP3R | + | glioblastoma [128] |
| | Hypoxia | VOC | Cav 3.2 | ↗ expression | glioblastoma [83] |
| | | SOC | STIM1 | mutual dependence with HIF1 | hepatocarcinoma [99] |
| | | IP3R/RYR | RYR1 | ↗ activity | breast cancer [125] |
| | Resistance stress metabolic | CaBP | CaMKIIα | + | breast cancer [143] |

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