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Review

New Insights into TRP Ion Channels in Stem Cells

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Abstract: Transient receptor potential (TRP) ion channels are cationic permeable proteins located on the plasma membrane. TRPs are cellular sensors for perceiving diverse physical and/or chemical stimuli; thus, serving various critical physiological functions, including chemo-sensation, hearing, homeostasis, mechano-sensation, pain, taste, thermoregulation, vision, and even carcinogenesis. Dysregulated TRPs are found to be linked to many human hereditary diseases. Recent studies indicate that TRP ion channels are not only involved in sensory functions but are also implicated in regulating the biological characteristics of stem cells. In the present review, we summarize the expressions and functions of TRP ion channels in stem cells, including cancer stem cells. It offers an overview of the current understanding of TRP ion channels in stem cells.

Keywords: TRPs; stemness; self-renewal; proliferation; cell cycle; calcium influx

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1. Introduction

Stem cells possess the capacity to self-renew; they show multilineage differentiation potential and can develop into more mature, specialized cells [1,2]. Stem cells can be classified as embryonic or adult stem cells, depending on their origins. Adult stem cells, such as hematopoietic stem cells, mesenchymal stem/stromal cells, endothelial progenitor cells, neural stem cells, colon stem cells, lung stem cells, epidermal stem cells, hair follicle bulge stem cells, etc., are present in all types of organs and tissues in diverse organisms [3]. Cancer stem cells (CSC) have been found in tumors and leukemia. CSCs are tumorigenic and are capable of producing all types of cells found in tumor tissues [4]. They are responsible for tumor maintenance, tumor metastasis, and tumor recurrence [5–8]. While the significance of stem cells in development, injury repair, and even carcinogenesis, is well-known, how stem cells respond to internal and environmental cues is not fully understood.

Transient receptor potential (TRP) channels are non-selective cation ion channels particularly noticeable for their physiological roles as cellular sensors. TRP channels on the plasma membrane are responsible for receiving signaling from other cells and the ambient environment and, hence, they play critical roles in stem cells. TRP ion channels are presumed tetramers formed of either identical or different subunits. Each TRP channel subunit has six transmembrane segments, with both N-terminal and C-terminal located in the intracellular compartment [9,10]. The mammalian TRP channel family consists of 28 members distributed in six subfamilies, including TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPML (mucolipin), TRPA (ankyrin), and TRPP (polycystin). Intracellular calcium signaling is crucial for modulating stem cell functions. Most TRP channels are Ca^{2+} permeable, which can directly trigger Ca^{2+} influx. Thus, they may be involved in regulating stem cell functions.

TRP ion channels are mainly expressed in neuronal and non-neuronal cells and tissues. As molecular sensors, TRP ion channels exhibit diverse activation mechanisms with physiological and pathophysiological implications [11,12]. TRP ion channels respond to changes in the external environment; they are also involved in regulating the cellular

microenvironment. Given the functional properties of TRP channels and their expressions in stem cells, it is not surprising that they may participate in regulating stem cell physiology and differentiation. Indeed, recent studies have found that TRP ion channels are implicated in stem cells [13–15]. This review summarizes the expression patterns of TRP channels in various stem cells, with particular focus on the potential roles TRP channels play in regulating stem cell physiology and pathophysiology.

2. TRPs in Stem Cells

The *Trp* gene was first cloned from Drosophila in 1989; in the following years, mammalian TRP channels were identified and characterized. The presence of the TRPC complex in the central nervous system (CNS) development sparked the research of TRPs in stem cells [16,17]. To date, TRP channels (TRPCs, TRPMs, TRPVs, TRPA, TRPMLs) are distributed in stem cells, including mesenchymal stem cells (MSC), neural stem cells (NSC), dental pulp stem cells (DPSC), trophoblast stem cells (TSC), embryonic stem cells (ESC), intestinal stem cells (ISC), etc. (Table 1).

2.1. TRPCs

The TRPC subfamily comprises seven members—TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6, and TRPC7.

TRPC1 has been abundantly expressed in C2C12 mouse skeletal myoblasts and upregulated in the differentiation of myoblasts [18,19]. It suggests a crucial role for TRPC1 in myogenesis.

In a study by Fiorio Pla et al., TRPC1, 2, 3, 4, and 6 transcripts were broadly expressed in embryonic rat NSCs. Furthermore, TRPC1 co-expressed with fibroblast growth factor receptor (FGFR)-1 in proliferating NSC-derived progeny in the presence of the basic fibroblast growth factor (bFGF) [16]. In addition, the store-operated channel complexes of TRPC1, Orai1, and STIM1 were co-expressed in mouse NSCs [20].

TRPC1, 2, 3, 4, 5, and 6 mRNAs were observed in MSCs derived from human tissues or the bone marrow of rabbits [21–23]. Only the TRPC1 protein was detected by both immunofluorescence staining and western blot analysis in these cells [23].

Researchers found TRPC1 and TRPC6 expressed in rat bone marrow stromal cells (BMSCs) [24].

TRPC1, 3, 6, and 7 transcripts were detected in $CD34^+$ stem cells isolated from human umbilical cord blood. During stem cell differentiation to megakaryocytes, TRPC6 expression was found significantly increased [25,26].

2.2. TRPMs

The TRPM channel subfamily includes eight members (TRPM1, TRPM2, TRPM3, TRPM4, TRPM5, TRPM6, TRPM7, and TRPM8).

TRPM2 has been identified in fetal mouse NSCs [27].

Dental pulp harbors subpopulations of stem cells that are capable of differentiating via several pathways, fulfilling a function in tissue damage. TRPM4 channels are permeable to monovalent cations, and their presence in rat DPSCs introduces voltage dependency and Na^+ conductivity to these cells [28]. Moreover, it has been revealed that voltage-gated TRPM7 is widely expressed in the cell membranes and cytoplasms of human DPSCs [29].

TRPM7 channels are abundantly expressed in mouse TSCs as well as mouse ESCs; in comparison, TRPM4 shows a lower distribution in mouse TSCs [30].

Among mammalian TRP ion channels, both TRPM6 and TRPM7 have a C-terminal kinase, which is combined with Mg^{2+} and Mg^{2+}-ATP to attenuate the activities of TRPM7 with Mg^{2+} or Ca^{2+} permeation [31]. TRPM7 has been found present in both mouse and human bone marrow-derived MSCs, and TRPM7 mRNA (but not TRPM6) is upregulated during osteogenesis [32,33]. It should be noted that TRPM7 is involved in mediating Mg^{2+} permeation in mouse MSCs, yet its mechanical stimulation involves facilitated Ca^{2+} permeation in human MSCs [34–36].

Besides internal Mg^{2+} and Ca^{2+}, cytosolic pH (protons) also mediates the TRPM7 channel activity in mouse BMSCs [37].

2.3. TRPVs

The TRPV subfamily is composed of six members (TRPV1, TRPV2, TRPV3, TRPV4, TRPV5, and TRPV6).

TRPV1 plays a prominent role in sensory neurons, exhibiting functions in inflammation and nociception in the peripheral nervous system and somewhat ambiguous implications in the central nervous system [38,39]. Ramírez-Barrantes et al. detected signals of immune-fluorescent TRPV1 in rat NSCs [40]. Further, TRPV1 has been found expressed in human NSCs and upregulated in differentiated NSCs [41]. In neural crest-like stem cells from a neonatal mouse epidermis, TRPV1 has been detected and is shown to be activated by capsaicin [42]. Moreover, TRPV1 could traffic rapidly from intracellular localizations to the plasma membrane upon stimulation of the nerve growth factor (NGF) in dorsal root ganglia [43]. On the other hand, the vascular endothelial growth factor (VEGF) can downregulate the expression of TRPV1 in rat NSCs [44].

The expression of TRPV1 has been identified during human DPSC differentiation toward neurons, where activation of this channel is suggested to play an important role [45].

In addition, recent studies have identified the presence of TRPV1 in human adipose-derived stem cells and myogenic cells [46,47].

In mouse TSCs, a strong expression of TRPV2 has been observed, while TRPV4 exhibits a lower expression. The expression of TRPV2 increases during TSC differentiation [30].

TRPV4 is permeable to monovalent and divalent cations, but with higher affinities to Ca^{2+} and Mg^{2+} than Na^{+} cations [48,49]. Studies have found that TRPV4 channels are expressed in the murine mesenchymal stem cell line C3H10T1/2 as well as human and mouse MSCs isolated from bone marrow [50–52].

Jin et al. uncovered TRPV4 expression in periodontal stem cells and demonstrated that activation of TRPV4 by mechanical force could induce cell proliferation, with accumulation of inflammatory cytokines of IL-1β, TNF-α, IL-6 and MCP-1 [53].

2.4. TRPA1

The TRPA subfamily only contains one member (TRPA1).

TRPA1 is remarkably localized in the ISCs of drosophila [54].

Recently, it has been found that TRPA1 is expressed in human DPSCs, and intracellular ROS could upregulate TRPA1 distribution in vitro and in vivo [55].

TRPA1 is also expressed in human MSCs and NSCs, and is upregulated in differentiated NSCs [21,41].

2.5. TRPMLs

The TRPML subfamily consists of three members—TRPML1 TRPML2, and TRPML3.

The transcripts of TRPML1 and TRPML2 have been detected in MSCs and NSCs, but their roles in these cells are lacking [15,21].

Table 1. TRPs distributed in stem cells.

TRPs	Stem Cells	Origins	References
TRPC1	MSCs	Rabbit bone marrow	[23]
	MSCs	Human tissue and cells	[21,22]
	BMSCs	Rat bone marrow	[24]
	NSCs	Rat embryos	[16]
	NSCs	Mouse	[20]
	CD34+ stem cells	Human cord blood	[25]
	C2C12 myoblasts	Mouse skeleton	[18,19]
TRPC2	MSCs	Rabbit bone marrow	[23]
	NSCs	Rat embryos	[16]

Table 1. *Cont.*

TRPs	Stem Cells	Origins	References
TRPC3	MSCs	Human tissues	[21]
	NSCs	Rat embryos	[16]
	CD34+ stem cells	Human cord blood	[25]
TRPC4	MSCs	Human tissues	[21]
	MSCs	Rabbit bone marrow	[23]
	NSCs	Rat embryos	[16]
TRPC5	MSCs	Human tissues	[21]
TRPC6	MSCs	Human tissues	[21]
	MSCs	Rabbit bone marrow	[24]
	NSCs	Rat embryos	[16]
TRPC7	$CD34^+$ stem cells	Human cord blood	[25]
TRPM2	NSCs	Mouse embryos	[27]
TRPM4	DPSCs	Rat	[28]
	TSCs	Mouse	[30]
TRPM7	DPSCs	Human	[29]
	TSCs	Mouse	[30]
	ESCs	Mouse	[30]
	MSCs	Mouse bone marrow	[33]
	MSCs	Human bone marrow	[32,34–36]
	BMSCs	Mouse	[37]
TRPV1	NSCs	Rat	[40,44]
	NSCs	Human	[41]
	Neural crest-like stem cells	Mouse	[42]
	DPSCs	Human	[45]
	Adipose-derived stem cells	Human	[47]
	Myogenic cells	Mouse	[46]
TRPV2	TSCs	Mouse	[30]
TRPV4	TSCs	Mouse	[30]
	MSCs	Mouse	[50,52]
	MSCs	Human	[51]
	Periodontal stem cells	Rat	[53]
TRPA1	ISCs	Drosophila	[54]
	DPSCs	Human	[55]
	MSCs	Human	[21]
	NSCs	Human	[41]
TRPML1	MSCs	Human tissues	[21]
TRPML2	NSCs	Human	[15]

3. TRPs in Cancer Stem Cells (CSCs)

CSCs are villains in cancer origination and development. They account for most cancer malignancies and recurrences. So far, members of TRPC, TRPM, TRPV, and TRPA subfamilies have been characterized in CSCs (Table 2).

3.1. TRPCs

Early evidence showed that TRPC1 presented in glioblastoma stem cells (GSC) with store-operated channel proteins of Orai1 and STIM1 [56].

3.2. TRPMs

TRPM7 has been found in GSCs derived from the human glioblastoma cell line A172 [57].

Moreover, increasing TRPM7 mRNA has been observed in tumor spheres derived from human lung cancer cells, accompanied by enhanced expression of the cancer stem cell markers SOX2, CD133, and KLF4 [58].

3.3. TRPVs

TRPV1 has been observed in GSCs and is upregulated in differentiated GSCs of proneural-like and mesenchymal-like cells in an ERK-dependent manner [41]. Nabissi et al. have demonstrated that glioblastoma and GSCs selectively express the TRPV1 5′ untranslated region variant 3 (TRPV1V3), where one of four variants is produced by selective splicing of the first exon. In addition, increased expression of TRPV1V3 was found by inducing differentiation of GSCs [59], suggesting that the TRPV1 variant 3 can be a potential prognostic marker for glioma.

TRPV2 is present in glioma and GSCs isolated from adult patients. Differentiation of GSCs facilitates the incremental accumulation of TRPV2 expression [60,61].

Hepatocellular stem cells are partially accountable for the highest mortality rate in liver cancer. Hu et al. reported the elevated expression of TRPV2 in established hepatocellular carcinoma cell lines. There is a positive correlation between stemness and TRPV2 expression levels [62].

3.4. TRPA1

Research indicates that TRPA1 is expressed in human GSCs and its expression increases during the differentiation of GSCs [41].

TRPA1 has been observed to be overexpressed in the MSCs of human lung cancer tissues, which might be related to the poor prognosis of non-small cell lung cancer [63]. The finding indicates that TRPA1 may serve as a potential prognosis marker and facilitate the search for the target drug to inhibit the progression of non-small cell lung cancer.

Table 2. TRPs expressed in cancer stem cells.

TRPs	Cancer Stem Cells	Origins	References
TRPC1	GSCs	Human tumor tissues	[56]
TRPM7	GSCs	Human glioblastoma cells	[57]
	Tumor spheres	Human lung cancer cells	[58]
TRPV1	GSCs	Human tumor tissues	[41]
TRPV2	GSCs	Human Adult patients	[60,61]
	Stem-like cells	Human liver cancer cells	[62]
TRPA1	GSCs	Human	[41]
	MSCs	Human lung cancer tissues	[63]

4. TRPs in Progenitor Cells

TRP channels are mainly cell sensors prominently distributed in the nervous system. In neural progenitor cells (NPC), almost all TRP channel subfamilies have been detected. Moreover, TRPs distribute in endothelia progenitors, hematopoietic progenitors, myeloid precursors, and osteoclast precursors (Table 3).

4.1. TRPCs

NPCs are precursor cells presenting in the process of differentiation of NSCs toward neurons. To date, TRP ion channels are observed in NPCs with relatively high permeability to calcium. Studies have found that mRNAs for TRPC1, 3, 4, 5, and 6 are present in both A2B5$^+$ (neural cell surface antigen) NPCs and differentiated neuronal cells. In A2B5$^+$ NPCs isolated from SD rats, there were upregulations of TRPC1 and TRPC4 gene expressions compared to the differentiated cells, while TRPC3, TRPC5, and TRPC6 a down-regulated compared to differentiated cells [64]. Louhivuori et al. performed research on embryonic mouse NPCs and found that corresponding to the motor patterns of NPCs,

TRPC1 and TRPC3 genes were expressed during cell proliferation [65]. Another study elucidated that TRPC1 was detected, along with Orai1 and STIM1, in NPCs isolated from the hippocampal tissue of an adult male mouse [66]. In human NPCs derived from fetal midbrain tissue, TRPC1, 3, 4, 5, and 6 were found expressed during NPC proliferation and differentiation [67].

As the precursors of vascular endothelial cells, endothelial progenitor cells (EPC) could be recruited to repair blood vessels in vascular injury. With the distribution of TRPC1 on the plasma membranes of EPCs, this channel appears to be involved in regulating cell migration and angiogenesis via the signaling pathway of Calmodulin/eNOS [68,69].

Ong and co-workers found TRPC1 expressed in hematopoietic progenitors, myeloid precursors, and osteoclasts precursors, and regulated osteoclastogenesis via store-operated Ca^{2+} entry [70].

4.2. TRPVs

Notably, TRPV1, TRPV2, and TRPV3 trigger Ca^{2+} influx in human NPCs. During cell differentiation, the expressions of TRPV2 and TRPV3 have been remarkably downregulated [71].

Further, NSCs and NPCs induced by somatic mutations are considered to be the sources of high-grade astrocytoma. Stock et al. demonstrated that TRPV1 was overexpressed in high-grade astrocytomas, and activation of TRPV1 could induce tumor cell death. NPCs in proximity are the main sources of releasing the endogenous TRPV1 agonist [72], so TRPV1 may be a potential target for therapy in high-grade astrocytomas.

In addition, TRPV4, 5, and 6 are functionally expressed in human NPCs [67].

Moreover, TRPV4 has been observed in EPCs [73].

4.3. TRPMs and Other TRPs

TRPM2, 3, 4, and 7 have been identified as distributed in mouse and human NPCs; in particular, activation of TRPM3 could induce calcium influx [27,67].

In addition, TRPML1, TRPML2, and TRPP2 are expressed in human NPCs derived from fetal midbrain tissues [15,67].

Table 3. TRPs distributed in progenitor cells.

TRPs	Progenitor Cells	Origins	References
TRPC1	Hematopoietic progenitors	Mouse bone marrow	[70]
	Myeloid precursors	Mouse bone marrow	[70]
	Osteoclasts precursors	Mouse bone marrow	[70]
	NPCs	Rat	[64]
	NPCs	Mouse	[65]
	NPCs	Human	[67]
	EPCs	Rat	[68]
	EPCs	Mouse	[69]
TRPC3	NPCs	Rat	[64]
	NPCs	Mouse	[65]
	NPCs	Human	[67]
TRPC4	NPCs	Rat	[64]
	NPCs	Human	[67]
TRPC5	NPCs	Rat	[64]
	NPCs	Human	[67]
TRPC6	NPCs	Rat	[64]
	NPCs	Human	[67]
TRPV1	NPCs	Human	[71]
TRPV2	NPCs	Human	[71]
TRPV3	NPCs	Human	[71]

Table 3. *Cont.*

TRPs	Progenitor Cells	Origins	References
TRPV4	NPCs	Human	[67]
	EPCs	Human	[73]
TRPV5	NPCs	Human	[67]
TRPV6	NPCs	Human	[67]
TRPM2	NPCs	Human	[67]
	NPCs	Mouse	[27]
TRPM3	NPCs	Human	[67]
TRPM4	NPCs	Human	[67]
TRPM7	NPCs	Human	[67]
TRPML1	NPCs	Human	[67]
TRPML2	NPCs	Human	[15]
TRPP2	NPCs	Human	[67]

5. TRP Roles in Stem Cells

TRP channels mediate Ca^{2+} entry from extracellular compartments or they release from internal stores to stimulate numerous Ca^{2+} signaling and control diverse cellular processes. Based on their distributions in stem cells and cancer stem cells, TRPs are involved in modulating cell cycles, cell proliferation and differentiation, cell migration, and self-renewal of these cells.

5.1. TRPCs

TRPC channels are mainly characterized as receptor-operated channels that can be activated by either intracellular messengers or by depletion of internal Ca^{2+} stores. Studies have identified that TRPCs can interact with STIM1 and Orai1 components to constitute store-operated Ca^{2+} entry. Regarding the complex of TRPC1 with STIM1 and Orai1 in NSCs, NPCs and GSCs may contribute to store-dependent Ca^{2+} signaling [20,56,66].

In rat BMSCs, the resting membrane potential shows cycle-dependent changes, with the highest depolarization in the G1 phase and hyperpolarization in the S phase. Such cycle-dependent changes of resting membrane potential are fully matched with the upregulation of TRPC6 in the G1 phase and downregulation of TRPC6 in the S phase. Knockdown of TRPC6 reduces the resting membrane potential, which promotes the progression of the cell cycle. Therefore, TRPC6 may act as store-operated channels to regulate the cell cycles of BMSCs by changing the membrane potential via modulating the Ca^{2+} entry [24].

In NSCs, Ca^{2+} signaling modified by TRPCs promotes cell proliferation and differentiation. Specifically, TRPC1 potentiates bFGF/FGFR-1-induced Ca^{2+} influx in rat embryonic NSCs, which in turn promotes the proliferation of embryonic NSCs [16]. In addition, the thyroid hormone can induce significant Ca^{2+} influx through TRPC1 in ventral midbrain NSCs, thereby regulating the differentiation of NSCs [74]. The expression of TRPC5 increases with elevated store-operated Ca^{2+} entry during the differentiation of $A2B5^{+}$ NPCs, promoting neuronal differentiation [64].

Insights from Hao et al. found that TRPC3 is expressed in mouse ESCs. Activation of TRPC3 could promote the Ca^{2+} influx in mitochondria, maintain the integrity of mitochondrial membrane proteins of ESCs and, therefore, stabilize the differentiation process of ESCs to NSCs. Knockout of TRPC3 destroys mitochondrial membrane proteins and induces apoptosis in undifferentiated ESCs [75] (Figure 1).

5.2. TRPMs

TRPM channels encode nonselective cation channels involved in many biological roles, including thermosensation, taste, cell migration, Mg^{2+} homeostasis, and reabsorption. So

far, TRPMs are found distributed in MSCs, NSCs, NPCs, DPSCs, GSCs, and lung cancer stem-like cells and, hence, are implicated in these cells.

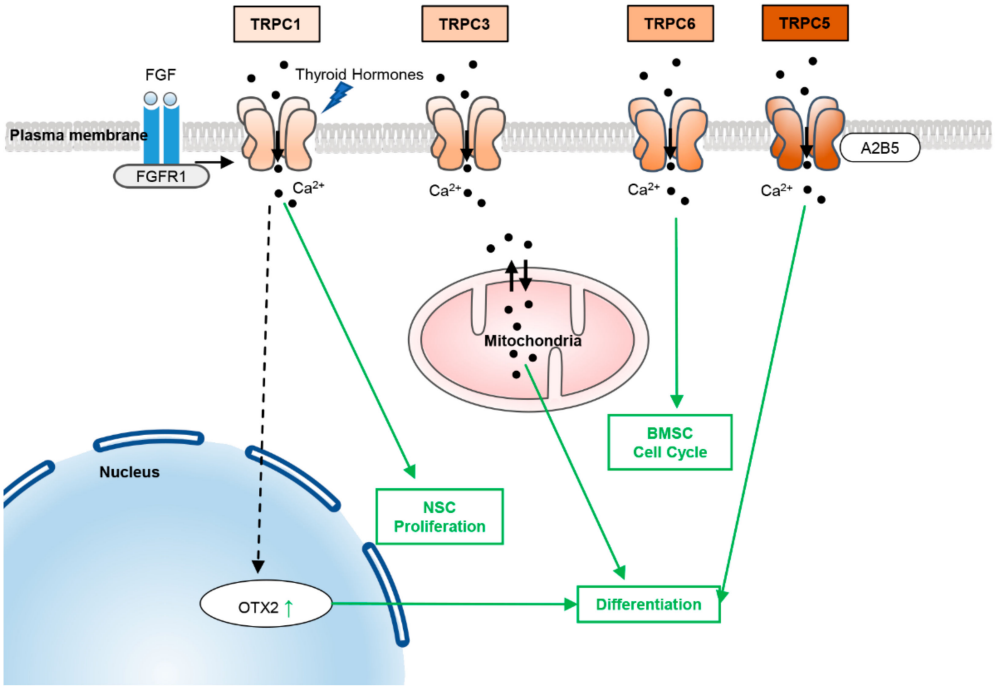

Figure 1. TRPCs function in stem cells. TRPC1-induced Ca^{2+} influx activates the FGF/FGFR1 signaling pathway or OTX2 to promote proliferation or differentiation of NSCs. TRPC3 triggers Ca^{2+} influx in mitochondria, which promotes the stabilization of differentiation processes of ESCs to NSCs. High expression of TRPC5 in $A2B5^{+}$ NPCs with increased store-operated Ca^{2+} entry promotes cell differentiation. Further, the dynamic distribution of TRPC6 can control the magnitude of store-operated Ca^{2+} entry via changes in membrane potential to regulate the cell cycle of BMSCs.

Studies indicate that TRPMs mediated stem cell differentiation and other biological roles via different signaling pathways with Ca^{2+} involvement. The Ca^{2+} influx induced by TRPMs can activate different cellular processes or adjust gene transcription.

Cheng et al. found that TRPM7 upregulated in differentiated MSCs [33]. During this differentiation process, the Ca^{2+} influx mediated via TRPM7 induces the activation of the phospholipase C (PLC) signaling pathway, promotes Ca^{2+} release into the cytoplasm from the endoplasmic reticulum (ER), then the nuclear factor of activated T cells c1 (NFATc1) translocates to the nucleus, promoting osteogenesis in human bone marrow MSCs [36]. Moreover, TRPM7 regulates SMAD1 activity by phosphorylating PLC [32]. Activation of PLC leads to recruitment of PKC and calmodulin (CaM) with stimulation of CaM kinase II, which then phosphorylates SMAD1 and induces its translocation to the nucleus, thereby activating osteogenic genes Runx2, Osterix, and OCN to promote osteogenesis [76].

In human bone marrow MSCs, TRPM8 shows specific expression in the ER, suggesting that its main function may be related to the release of intracellular Ca^{2+}. In addition, activation of TRPM8 promotes osteogenic differentiation of human MSCs [14]. In rat dental follicle stem cells, functional expression of TRPM4 facilitates adipogenesis via Ca^{2+} signaling [77]. The expression of TRPM2 channels is increased during heat stress in NSCs. In hyperthermia, knockout of TRPM2 reduces NPC proliferation and accelerates premature neuronal differentiation. TRPM2 regulates the self-renewal of NPCs by targeting the transcription factor of specificity protein 5 (SP5). Briefly, increased Ca^{2+} influx through TRPM2 by heat stimuli inhibits the phosphorylation of β-catenin, accumulating β-catenin, then binds to the SP5 promoter and activates the gene transcription process to ultimately

promote NPC proliferation [27]. In contrast, activation of TRPM3 and TRPV4 via agonism shows no effects on the proliferation and survival of cultured human NPCs [67].

In CSCs, TRPM7 activates STAT3, which in turn binds to acetaldehyde dehydrogenase (ALDH)-1 promoter to upregulate the expression of ALDH1, a marker of GSCs, thus facilitating the self-renewal and differentiation of GSCs. Furthermore, TRPM7 activates Notch signaling pathways and promotes the expression of CD133 and ALDH1, enhancing glioma stemness [57,78]. Similarly, upregulated TRPM7 enhances the lung cancer stem cell-like phenotype and promotes lung cancer metastasis via the Hsp90α/uPA/MMP2 signaling pathway [58]. TRPM7 also maintains the stem cell features of neuroblastoma by regulating the expression of the Snail family transcriptional repressor 2 (SNAI2) transcription factor, which is involved in epithelial–mesenchymal transitions and has antiapoptotic activity [79,80]. Further studies need to determine the molecular mechanisms of TRPM7-driven SNAI2 to control stem cell features.

Mg^{2+} and microRNA have been found implicated in TRP modulation in stem cell functions. Specifically, TRPM7 regulates cell proliferation in human DPSCs via intracellular Mg^{2+} signaling. In the absence of TRPM7, cell proliferation is significantly subdued; as a result, the cells are mainly arrested in the G0/G1 phase. Moreover, inhibition of TRPM7 suppresses cell migration, and downregulation of TRPM7 in human DPSCs inhibits osteogenic differentiation. These suggest that TRPM7 may play a role in the dental pulp repair process [29]. MiR-204 is an intron miRNA located between exons 7 and 8 of the *TRPM3* gene. The reduction of miR-204 due to the high methylation of its host gene *TRPM3* in gliomas can promote cell migration and enhance cell stemness [81]. It has been demonstrated that TRPM3 could interact with STAT3, with activation of STAT3 suppressing miR-204 expression. Furthermore, downregulation of miR-204 leads to the activation of the Src-STAT3-NFAT signaling pathway in pulmonary artery smooth muscle cells [82]. STAT3 also directly facilitates NFAT expression. Hence, the silence of miR-204 may promote GSC migration via the Ca^{2+}-sensitive STAT3-NFAT pathway (Figure 2).

5.3. TRPVs

TRPVs are the main pathways of Ca^{2+} entry in stem cells and have been involved in mediating cell differentiation and proliferation [71]. TRPV1 can be activated by light in the blue (415 nm) and green (540 nm) wavelength range, inhibiting cell proliferation in adipose-derived stem cells [47]. TRPV2 is upregulated in the differentiation of mouse TSCs. It suggests that TRPV2 may be involved in placental development [30]. It has been found that far-infrared radiation inhibits the adipogenic differentiation of tonsil-derived MSCs by inducing intracellular Ca^{2+} mobilization [83]. Further studies have shown that the TRPV2 ion channel acts as a receptor of far-infrared radiation and mediates the inhibition process in the adipogenic differentiation of MSCs [84]. Hu et al. reported that flow shear stress activates TRPV4 in MSCs, follows Ca^{2+} influx, and induces early osteogenic differentiation [50,85]. In addition, TRPV4-mediated Ca^{2+} signaling is crucial for the formation of collagen in bone marrow MSCs [51]. Furthermore, Ca^{2+}/calcineurin/NFAT signaling involves bone development and regeneration [86,87]. One study has revealed that TRPV1 deletion in BMSCs can downregulate the expression and nuclear translocation of NFATc1, and, thus, impair osteoclastogenesis and osteogenesis [88]. TRPV4, in vitro or in vivo, promotes the proliferation of mature endothelial cells by activating a series of calcium-dependent transcription factors, reshaping the vascular network of injured tissues [89,90].

In cancer stem cells, TRPV2 inhibits GSC proliferation both in vitro and in vivo. Activation of TRPV2 by cannabidiol could trigger GSC differentiation and activate the autophagic process. During GSC differentiation, the upregulated splicing variant of acute myeloid leukemia 1a (AML-1a) directly affects the expression of TRPV2 via binding to the gene promoter of *TRPV2*, establishing a positive feedback circuit to promote cell differentiation [60]. In adult glioma patients, TRPV2 expression increases during GSC differentiation. Indeed, silencing or inhibiting TRPV2 can affect the differentiation of GSCs [61].

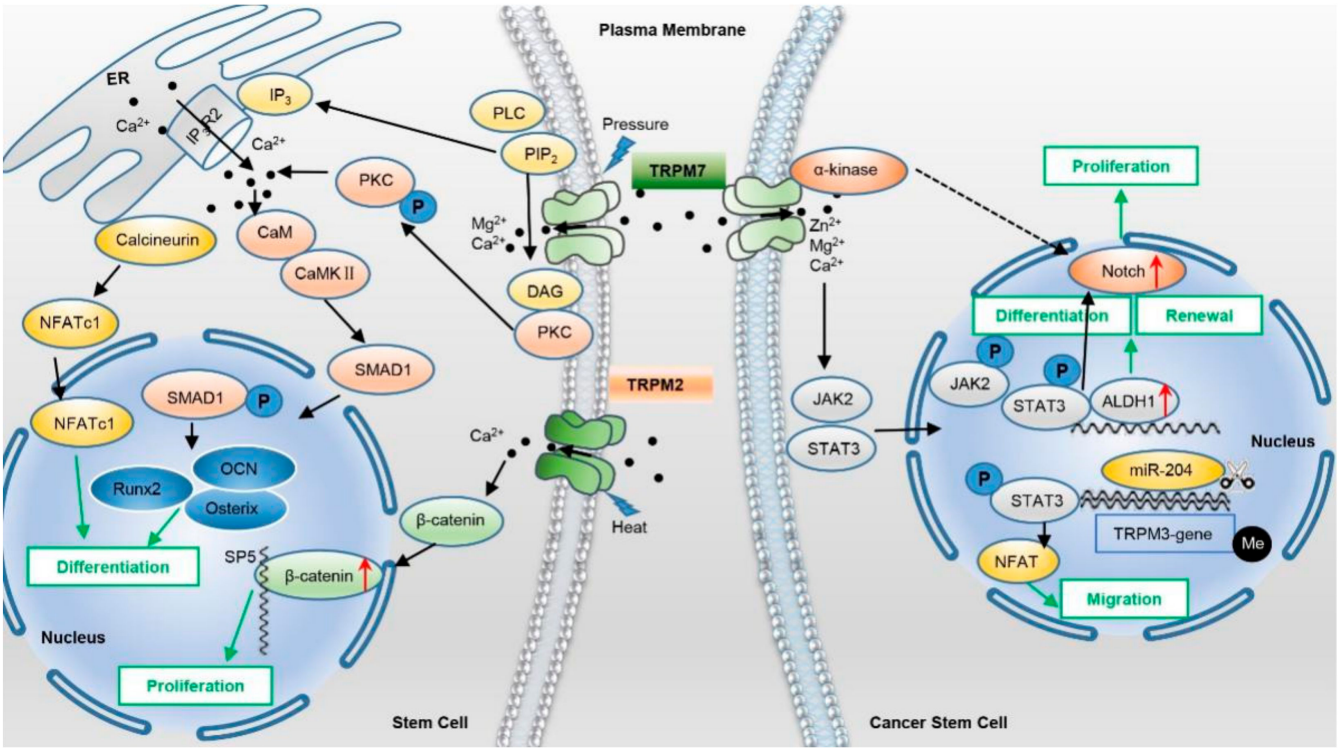

Figure 2. TRPMs function in stem cells and cancer stem cells via different signaling pathways. In MSCs, the Ca^{2+} influx via TRPM7 triggers the activation of the PLC signaling pathway, subsequently releases Ca^{2+} from ER, and induces nuclear translocation of NFATc1, promoting differentiation in human bone marrow MSCs. Moreover, activation of PLC leads to phosphorylation of PKC and its intracellular translocation, recruitment of CaM, and stimulation of CaMKII, which then phosphorylates SMAD1 and induces its translocation to the nucleus, thereby activating osteogenic genes Runx2, Osterix, and OCN to promote MSC differentiation and osteogenesis. Activation of TRPM2 by heat stress elevates intracellular calcium influx, which inhibits the phosphorylation of β-catenin and results in the augment of β-catenin on the SP5 promoter, promoting NPC proliferation. In GSCs, activation of TRPM7 activates the JAK2-STAT3 signaling pathway, which phosphorylates JAK2 and STAT3 and induces the translocation of JAK2 and STAT3 to the nucleus; STAT3 then activates ALDH1 via binding to its promoter and/or activates Notch signaling, enhancing GSC differentiation, renewal, and proliferation. Downregulation of miR-204 via methylation of the promoter of its host gene TRPM3 could activate the STAT3-NFAT pathway, promoting GSC invasion and stem cell-like phenotype.

Over-expression of TRPV2 can attenuate the stemness of hepatoma SMMC-7721 cells. In contrast, knockout of TRPV2 can significantly increase cancer stem cell markers (CD133, CD44, and ALDH1) and enhance spheroid and colony formation in human hepatoma HepG2 cells [62]. However, the precise signaling mechanisms remain largely elusive.

5.4. TRPA1

TRPA1 is a well-known cytoplasmic Ca^{2+} regulator. It could upregulate cytosolic Ca^{2+} in ISCs to amplify and activate EGFR-Ras/MAPK signaling, which in turn drives ISC proliferation to maintain tissue homeostasis in the mid-gut of adult drosophila [54,91,92] (Figure 3).

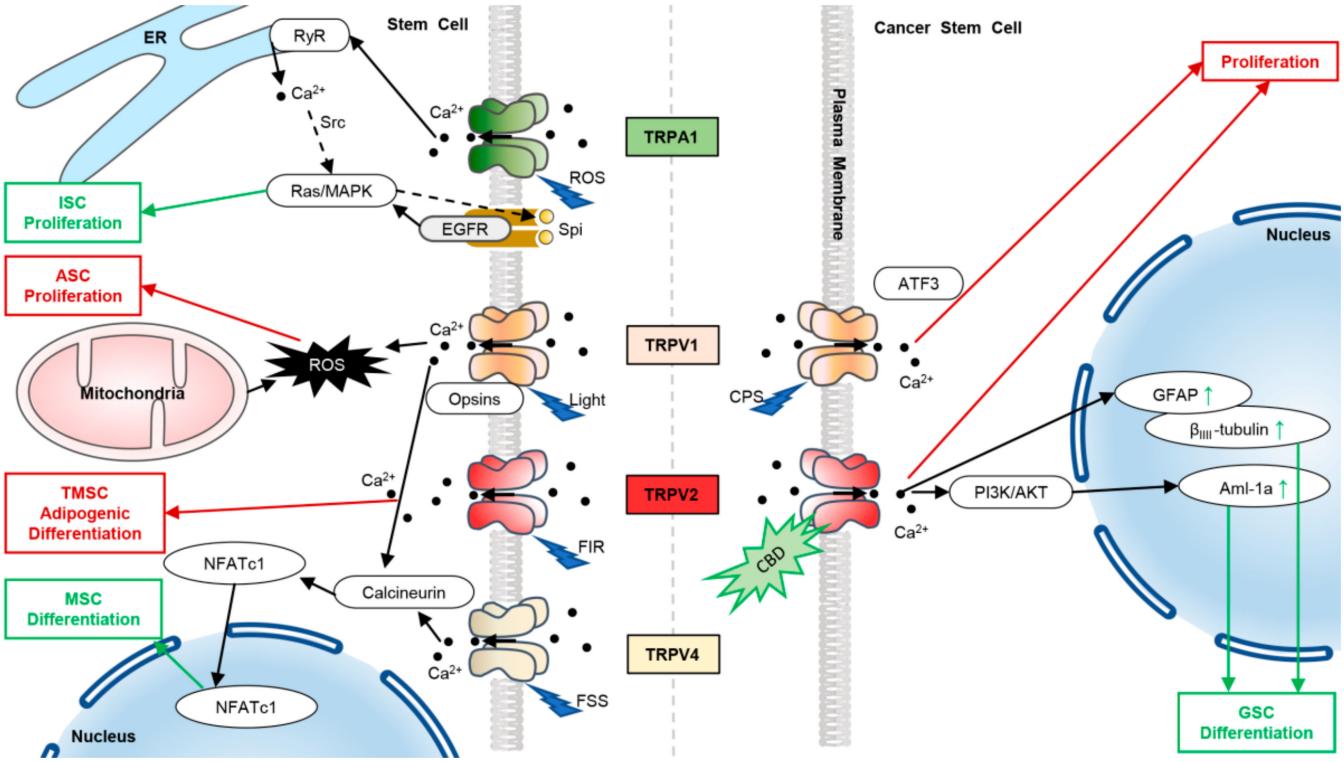

Figure 3. TRPVs and TRPA1 involved in modulating cell proliferation and differentiation in stem cells and cancer stem cells. In stem cells, activation of TRPA1 by ROS induces Ca^{2+} influx, which activates the RyR channel to release Ca^{2+} from ER to cytosol in ISC. The increased Ca^{2+} activates Ras/MAPK signaling via Src, and further amplifies Ras/MAPK signaling by autocrine Spi-EGFR signaling. The activated EGFR-Ras/MAPK signaling then induces the proliferation of ISCs. Blue (415 nm) and green (540 nm) wavelengths of light could activate TRPV1 and increase Ca^{2+} and ROS, thereby inhibiting cell proliferation in adipose-derived stem cells (ASC). Knockout of TRPV1 suppresses the expression and activities of NFATc1, leading to decreased osteoclast and osteoblast differentiation. Upon stimuli of far-infrared radiation (FIR), TRPV2 induces intracellular Ca^{2+} increase and inhibits tonsil-derived MSC (TMSC) differentiation. Flow shear stress (FSS) activates TRPV4 and induces Ca^{2+} influx, which mediates NFATc1 nuclear translocation, thereby promoting the osteogenic differentiation of MSCs. In cancer stem cells, TRPV1 with stimulation of capsaicin (CPS) inhibits the proliferation of NSCs and NPC-derived high-grade astrocytoma in an activating transcription factor 3 (ATF3)-dependent manner. Upon cannabidiol (CBD) application, AKT activity in GSCs has been inhibited by decreasing pAKT levels, leading to autophagy in GSCs. Meanwhile, the expressions of TRPV2 and Aml-1a, which bind to TRPV2 promoters, are both upregulated, and increased TRPV2 enriches the expression of glial fibrillary acidic protein (GFAP) and β_{III}-tubulin, enhancing the differentiation of GSCs via the CBD-mediated autophagic process. Moreover, the activated TRPV2 inhibits GSC proliferation. Green arrows represent enhancement, red arrows represent inhibition.

6. Perspectives and Outlook

TRP ion channels in stem cells have been explored in almost five subfamilies but TRPPs. TRPPs contain three members (TRPP2, TRPP3, and TRPP5). TRPP2 has been demonstrated as an active coordinator in TRP channel heteromerization. Specifically, TRPP2 physically interacting with polycystin-1 (PKD1) has been identified [93]. A study reported that PKD1 was present in stem cells of variable origins. In addition, over-expression of PKD1 enhanced cell mobility and differentiation in umbilical cord blood-derived stem cells [94]. Wide-spread interaction and assembly in TRPs enhance the novel channel maturation and intracellular translocation [95]. It appears that many functional TRPs are distributed in

stem cells. However, knowledge about the co-assembly of TRPs in stem cells is lacking. Further research regarding the heteromerization of TRPs in stem cells should be considered.

Although certain aspects of TRP ion channels in stem cells have been deciphered through independent studies in the past decade, the roles of TRP ion channels and their implications in stem cells need further investigation. With the application of single-cell sequencing and high-throughput screening, the expression patterns of TRP channels in stem cells will be better understood. In addition, the usage of reporter genes and animal models will provide the precise mechanisms of TRP channels involved in stem cells.

TRP channels are expressed/function in stem cells, including cancer stem cells, which may lead to new features of TRPs and stimulate further explorations, ranging from molecular biology to clinical research and even cosmetics. TRPs, as multimode cellular sensors, have been modulated by a wealth of natural compounds, which can be used as potential pharmacological targets for fundamental research and drug discovery.

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