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EDITORIAL

Functional ion channels in stem cells

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Abstract

Bioelectrical signals generated by ion channels play crucial roles in excitation genesis and impulse conduction in excitable cells as well as in cell proliferation, migration and apoptosis in proliferative cells. Recent studies have demonstrated that multiple ion channels are heterogeneously present in different stem cells; however, patterns and phenotypes of ion channels are species- and/or origin-dependent. This editorial review focuses on the recent findings related to the expression of functional ion channels and the roles of these channels in regulation of cell proliferation in stem cells. Additional effort is required in the future to clarify the ion channel expression in different types of stem cells; special attention should be paid to the relationship between ion channels and stem cell proliferation, migration and differentiation.

Key words: Stem cells; Ion channels; Proliferation

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STEM CELLS

Stem cells are found in all multi-cellular organisms and are characterized by the ability to self-renew through mitotic cell division and differentiate into a diverse range of specialized cell types. There are two types of original mammalian stem cells: embryonic stem cells and adult stem cells found in adult tissues. In addition, it has recently been found that induced pluripotent stem cells (iPS) can be developed from other types of cells including fibroblasts[1].

Embryonic stem (ES) cells are derived from mammalian embryos in the blastocyst phase of development[2,3]. Adult (or somatic) stem cells were initially isolated from mouse bone marrow[4]; further studies have shown that stem cells are present in different types of tissue including brain, heart, blood vessels, skeletal muscles, skin, liver and fat tissue. Adult stem cells remain in a quiescent or non-dividing state and can be activated by disease or tissue injury. In adults, stem cells/progenitor cells act as a repair system for the body and maintain the normal turnover of regenerative organs such as blood, skin and intestinal tissues[5].

iPS cells are recently developed cells induced from somatic cells such as skin fibroblasts and B lymphocytes[6]. They were generated initially by Takahashi & Yamanaka[1] by reprogramming somatic cells by over-expressing a combination of four transcription factors: octamer 3/4 (Oct4), SRY box-containing gene 2 (Sox2), Kruppel-like factor 4 (Klf4) and c-Myc in murine fibroblasts to induce the cells enter an embryonic-like state[1,7]. The iPS cells are then produced by introducing the four transcription factor–encoding genes into human fibroblasts[7]. Two other groups produced similar iPS cells by introducing slightly different combinations of genes: POU5F1 (OCT4), SOX2, NANOG and LIN28A (LIN28)[8,9]. These iPS cells are similar to ES cells in morphology, growth properties and expression of phenotypic markers. These cells closely resemble ES cells and can differentiate into multiple types of cells *in vitro* and *in vivo*[1,6,7,9]. ES cells, adult tissue mesenchymal stem cells (MSCs) and their progenitors and iPS cells all possess potential therapeutic value in regenerative medicine.

In addition to the three major types of stem cells mentioned above that possess potential benefit for regenerative medicine, another type of stem cells is found within tumors or hematological cancers and has characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. Cancer stem cells are tumorigenic in contrast to other non-tumorigenic cells[9] and may induce tumors through the stem cell processes: self-renewal and differentiation into multiple cell types. Moreover, cancer stem cells are believed to persist in tumors as a distinct population and cause relapse and metastasis by giving rise to new tumors. Therefore, cancer stem cells may be a target for developing specific therapies to improve survival and quality of life of cancer patients, especially sufferers of metastatic disease[10].

Although stem cells are important in regenerative medicine and/or cancer treatment, their cellular physiology and biology are not fully understood. Membrane ion channels are known to play a crucial role in proliferation, apoptosis and migration in a wide range of cells.

ION CHANNELS IN STEM CELLS

Multiple functional ion channel currents have been reported to be heterogeneously present in different types of stem cells. They include the voltage-gated delayed rectifier K^+ current IK_{DR} (encoded by different Kv genes), the Ca^{2+}-activated K^+ current K_{Ca} (including BK_{Ca}, large conductance K_{Ca}; IK_{Ca}, intermediate conductance K_{Ca}; and SK_{Ca}, small conductance K_{Ca}), the transient outward K^+ current I_{to} (or A-type current, I_A), inward rectifier K^+ current (I_{Kir}), hyperpolarization-activated cyclic nucleotide-regulated cation current (I_h), chloride current (I_{Cl}), voltage-gated Na^+ current (I_{Na}), L-type calcium current ($I_{Ca.L}$), transient receptor potential (TRP) nonselective cation currents. These currents have been found to be heterogeneously present in ES cells, mesenchymal stem cells (MSCs) from bone marrow, fat tissue and human umbilical cord vein, neural progenitor cells, cardiac progenitor cells or iPS cells derived from different species.

ION CHANNELS IN EMBRYONIC STEM CELLS

In ES cells, it has been reported that a tetraethylammonium (TEA)- and 4-aminopyridine (4-AP)-sensitive IK_{DR} is co-present with iberiotoxin-sensitive BK_{Ca} in 52% of mouse ES cells and homogenously present in (100%) human ES cells[11]. However, phenotypes of IK_{DR} differ between mouse and human ES cells. IK_{DR} is encoded by Kv1.1, Kv1.2, Kv1.3 and Kv1.6 genes in mouse ES cells and by Kv7.2 and Kv9.3 in human ES cells. Interestingly, a Cs^+-sensitive hyperpolarization-activated current (I_h, encoded by HCN3) is present in 23% of mouse ES cells but not in human ES cells. In addition, iberiotoxin-sensitive BK_{Ca} is encoded by MaxiK (Slo or KCa1.1) in mouse ES cells[11]. Although human ES cell and mouse ES cells share similar expression of many surface markers and intracellular signal pathways[12,13], significant differences are found in the expression of vimentin, h-III tubulin, alpha-fetoprotein, eomesodermin, HEB, ARNT and FoxD3 as well as in the expression of the LIF receptor complex LIFR/IL6ST (gp130)[12,14]. The different patterns and phenotypes of ion channel expression in human ES cells and mouse ES cells support the notion that some basic information on human ES cells can be derived from mouse ES cells; however, such information does not correspond on a one-to-one basis[14].

ION CHANNELS IN MESENCHYMAL STEM CELLS

A noise-like iberiotoxin-sensitive K_{Ca} and a 4-AP- and TEA-sensitive IK_{DR} are detected in most human bone marrow-derived MSCs[15,16]. The noise-like K_{Ca} is encoded by MaxiK (KCa1.1 or Slo) as demonstrated by several research groups[15-17]. Our study demonstrates that IK_{DR} shares similar characteristics with EAG channels cloned from the brain[18] which is encoded by hEAG1 (Kv10.1) in human MSCs[16]. In addition, a voltage-gated tetrodotoxin (TTX)-sensitive Na^+ current ($I_{Na.TTX}$, encoded by hNE-Na or Nav1.7), a 4-AP-sensitive I_{to} (I_A, encoded by Kv1.4 and Kv4.2)[16] and a nifedipine-sensitive $I_{Ca.L}$ (encoded by CACNA1C or Cav1.2) are present in a small population (29%, 8% and 15% respectively) of human MSCs[16].

IK_{Ca} current (encoded by KCa3.1 or KCNN4), volume-sensitive Cl^- current ($I_{Cl.vol}$, encoded by Clcn3) and I_{Kir} (encoded by Kir2.1) but not IK_{DR}, are present in mouse bone marrow-derived MSCs[19]. The patterns and phenotypes of ion channels in mouse MSCs are different from mouse ES cells, suggesting that ion channel expression is origin-dependent.

In addition to $I_{Na.TTX}$ (encoded by SCN2A), I_{to} (encoded by Kv1.4) and $I_{Ca.L}$ (encoded by CCHL2a) recorded in a small population (16%, 10% and 8% respectively) of rat bone marrow MSCs, 4-AP sensitive IK_{DR} (encoded by Kv1.2 and Kv2.1) is present in 91% of cells. BK_{Ca} (KCa1.1) and IK_{Ca} (KCa3.1) are co-present in 33% of rat MSCs[20]. Interestingly, IK_{DR} (encoded by Kv1.2 and Kv2.1) is present in 78% of rabbit bone marrow MSCs, BK_{Ca} and IK_{Ca} are co-expressed with IK_{DR} in 29% of cells, while I_{Kir} (encoded by Kir1.1) is present in 28% of cells[21]. These results demonstrate the different patterns and phenotypes of ion channels heterogeneously expressed in MSCs from mouse, rat, rabbit and human bone marrow, indicating a species-dependence of ion channel expression in bone marrow MSCs.

Interestingly, BK_{Ca}, $I_{Na.TTX}$, and I_{to} are present in 92%, 30% and 50% of MSCs from human umbilical cord vein and encoded by KCa1.1, hNE-Na, and Kv1.4 and Kv4.2 respectively[22], and Ba^{2+}-sensitive I_{Kir} (encoded by TWIK and Kir2.1) is present in 5% of cells. However, no typical IK_{DR} is recorded, although Kv1.1 and hEAG1 (Kv10.1) genes are detected in these cells[22]. In MSCs from human fat tissue[23], $I_{Na.TTX}$ (encoded by hNE-Na) and 4-AP sensitive I_{to} are recorded in a small population (8% and 19%) of cells. In addition to 4-AP- and TEA-sensitive IK_{DR} (likely encoded by the multiple genes Kv1.1, Kv1.5, Kv2.1, Kv7.3, Kv11.1 and Kv10.1) recorded in 73% of cells, three types of K_{Ca} currents sensitive to inhibition by the BK_{Ca} blocker iberiotoxin, IK_{Ca} blocker clotrimazole and SK_{Ca} blocker apamin are present and the corresponding channel genes (KCa1.1, KCa3.1 and KCa2.3) are detected in human fat tissue-derived MSCs[23]. These studies suggest that patterns and phenotypes of ion channel expression in MSCs are species- and/or tissue-specific dependent.

ION CHANNELS IN NEURAL STEM/PROGENITOR CELLS

In neural stem/progenitor cells, an earlier study reported that two types of K^+ currents, IK_{DR} (encoded by Kv1.2, Kv1.5 and Kv1.6) and I_A (encoded by Kv1.4), were co-expressed in oligodendrocyte progenitor cells and differentiated cultured oligodendrocytes from neonatal rats[24]. Recent studies demonstrated that both Ba^{2+}-sensitive I_{Kir} (encoded by Kir4.1 and Kir5.1) and TEA-sensitive IK_{DR} (encoded by Kv3.1) are present in mouse neural sphere-derived progenitor cells[25,26].

Cai and colleagues demonstrated that multiple ion channels are heterogeneously expressed in rat embryonic neural stem cells, including I_A and IK_{DR} in > 80% of cells, I_{Na} (both TTX-sensitive and TTX-insensitive) and $I_{Ca.L}$ in a small population (22% and 19%) of neural stem cells[27]. IK_{DR} (encoded by Kv2.1) and I_A (encoded by Kv4.3) are also detected by Smith *et al*[28] in rat embryonic neural progenitor cells. Multiple ion channels, i.e. TTX-sensitive I_{Na}, TEA-insensitive IK_{DR} (likely encoded by Kv1.6, Kv2.1, and Kv2.2) and 4-AP-sensitive I_A (encoded by Kv4.2 and Kv4.3), are co-expressed in progenitor cells from neonatal rat forebrain[29]. However, only IK_{DR} encoded by Kv1.3 and Kv3.1 is present in adult rat neural progenitor cells[30]. Interestingly, 4-AP-sensitive I_A (encoded by Kv4.2) and α-dendrotoxin-sensitive IK_{DR} (likely encoded by Kv1.1, Kv1.6, and Kv3.1) are recently reported in human embryonic neural progenitor cells derived from aborted fetal brain tissue (12 weeks post-fertilization)[31]. Four types of ionic currents, I_A, IK_{DR}, I_{Kir} and $I_{Na.TTX}$, are also described by Lim *et al*[32] in human neural stem cells from aborted fetal cortex. In addition, a recent study reports that nifedipine-sensitive $I_{Ca.L}$ is expressed in neural stem/progenitor cells from the brain cortex of postnatal mice[33]. Moreover, TRPC1 has been found to mediate growth factor receptor-induced Ca^{2+} entry in embryonic rat neural stem cells[34].

ION CHANNELS IN CARDIAC PROGENITOR CELLS AND iPS CELLS

In cardiac progenitor cells, a recent study demonstrated that IK_{DR} (encoded by Kv1.1, Kv1.2 and Kv1.6), $I_{Cl.vol}$ (encoded by Clcn3) and I_{Kir} (encoded by Kir1.1, Kir2.1, and Kir2.2) are present in adult mouse cardiac c-kit$^+$ progenitor cells[35]. Only IK_{DR} (likely encoded by KCNQ2) is expressed in human iPS cells[36]. More information on ion channel expression in cardiac progenitor cells and iPS cells from different species is required.

ION CHANNELS IN CANCER STEM CELLS

Although cancer stem cells have been described in different types of cancers[37,38], information regarding ion channels in cancer stem cells is limited. A recent study reported that hERG (Kv11.1) channels are expressed in CD34$^+$/CD38$^-$/CD123(high) leukemia stem cells but not in normal bone marrow CD34$^+$ cells[39]. A high expression level of BK_{Ca} current has recently been recorded in CD133$^+$ stem cells from SH-SY5Y neuroblastoma[40]. Additional information remains to be collected on ion channel expression in stem cells from different types of cancer.

ROLES OF ION CHANNELS IN REGULATING PROLIFERATION AND/OR DIFFERENTIATION OF STEM CELLS

The effect of voltage-gated K^+ channels on cell mitogenesis was initially reported in human T lymphocytes by DeCoursey *et al*[41]. Great progress has been made in establishing the roles of specific channels in cell proliferation. K^+ channels modulate the cell progression through G0/G1 and K^+ channel expression changes with cell cycle progression.

Ion channels play an important role in controlling cell proliferation[42-44]. Kv channel blockade exhibits a significant anti-proliferative effect in numerous types of proliferative cells including glial cells, lymphocytes, endothelial cells, breast and prostate cancer cells[42,45]. These studies indicate that cell proliferation requires activity of K^+ channels. In addition, inhibition of voltage-gated K^+ channels and Na^+ channels suppresses migration of gastrointestinal epithelial cells[46,47]. It is believed that Kv, K_{Ca}, Na^+ and Cl^- channels mediate cancer cell migration, proliferation, invasion and metastasis[48].

We recently demonstrated that IK_{DR} is upregulated in early G1 phase while IK_{Ca} is increased in progressing G1 phase in rat bone marrow-derived MSCs. Silencing IK_{DR} channels or IK_{Ca} channels with corresponding short interference RNAs (siRNAs) targeting Kv1.2 and Kv2.1 or KCa3.1 inhibits cell proliferation and accumulates cells at G0/G1 phase[49], suggesting that IK_{DR} and IK_{Ca} are required for the regulation of cell proliferation in rat MSCs[49,50]. Blockade of IK_{DR} by 4-AP or TEA remarkably reduces proliferation of mouse and human ES cells[11], human iPS cells[36] and human fat tissue-derived MSCs[23] but not mouse cardiac *c*-kit$^+$ progenitor cells[35]. On the other hand, the inhibition of IK_{DR}, e.g. Kv1.3 by psora-4 or Kv3.1 by TEA, promotes proliferation of adult rat neural progenitor cells[25,26,30]. Also the blockade of IK_{DR}

by α-dendrotoxin is found to increase proliferation of human neural progenitor cells[31].

Blockade of IK_{Ca} with the selective blocker clotrimazole or silencing IK_{Ca} channel expression with KCa3.1 siRNA also reduces cell proliferation in mouse bone marrow-derived MSCs by accumulating cells at G0/G1 phase[51]. However, this is not the case for human fat tissue-derived MSCs in which the IK_{Ca} inhibition by clotrimazole has no inhibitory effect on cell proliferation[23].

The regulatory effect of BK_{Ca} on cell proliferation is dependent on cell type and/or experimental conditions. BK_{Ca} inhibition or KCa1.1 silencing reduces cell proliferation in human preadipocytes[52]. Block of BK_{Ca} by the selective channel blocker iberiotoxin inhibits cell proliferation in human endothelial cells[53,54] and in mouse ES cells[11] but not in human fat tissue-derived MSCs[23]. We recently found (unpublished) that inhibition of BK_{Ca} with paxilline or silencing BK_{Ca} with lentiviral-based short hairpin RNA targeting KCa1.1 reduces cell proliferation in human bone marrow-derived MSCs.

The volume-sensitive Cl^- channel ($I_{Cl.vol}$) has been implicated cell proliferation and apoptosis in a variety of cells[45,55,56]. We have found that $I_{Cl.vol}$ inhibition by the blocker 5-nitro-1-(3-phenylpropylamino) benzoic acid (NPPB) or silencing $I_{Cl.vol}$ channel with Clcn3 siRNA remarkably reduces cell proliferation in mouse MSCs by accumulating cells at G0/G1 phase, and the effect is mediated by suppressing cyclin D and cyclin E[51]. Similarly, block of $I_{Cl.vol}$ channel with NPPB also decreases cell proliferation in mouse cardiac c-kit$^+$ progenitor cells[35].

In proliferative cells, membrane hyperpolarization is implicated in silencing proliferation[54,55]. Membrane depolarization by the inhibition of I_{Kir} with Ba^{2+} or increase of extracellular K^+ concentration has been demonstrated to promote cell proliferation in adult neural progenitor cells[25]. This is consistent with the observation in astrocytes in which transient membrane depolarization with a reduction of Kir channel activity is observed during cell cycle progression from G1/S checkpoint to S phase[42]. However, this mechanism does not seem to be applicable for rat oligodendrocyte precursor cells. K_{ATP} openers diazoxide and pinacidil stimulate proliferation of rat oligodendrocyte precursor cells which is believed to be related to membrane hyperpolarization induced by K_{ATP}[57].

Limited information is available in literature regarding the physiological role of I_{to} (or I_A) in proliferative cells. We have recently found that inhibition of I_{to} by 4-AP or silencing Kv4.2 channel reduces cell proliferation in human preadipocytes[52]. Consistent with this observation, activation of I_A (Kv4.2) is found to be a prerequisite for cell proliferation in human embryonic neural progenitor cells[31].

Cytosolic Ca^{2+} activity is crucial for stem/progenitor cell cycle progression and growth[58,59]. Ca^{2+} entry through L-type Ca^{2+} channel is found to strongly correlate with differentiation of neural progenitor cells derived from mouse brain cortex; since nifedipine reduces while Bay K 8644 enhances neural differentiation[33]. In addition, TRPC1-mediated Ca^{2+} entry promotes differentiation of rat embryonic neural stem cells[34]. Silencing TRPC5 but not TRPC6 with corresponding siRNA decreases differentiation in rat neural progenitor cells[60]. These results suggest that cytosolic Ca^{2+} regulation by L-type Ca^{2+} channel, TRPC1 or TRPC5 channel plays an important role as a switch between proliferation and neuronal differentiation in different types of neural progenitor cells. It is interesting to note that a recent study demonstrated that TRPM7 channel is critical for the survival of mouse bone marrow derived mesenchymal stem cells[61].

While it is well recognized that voltage-gated TTX-sensitive (I_{NaTTX}) and TTX-resistant (I_{NaTTXR}, Nav1.5) Na^+ channels play a crucial role in generating action potential and conducting excitation impulse in excitable cells, the physiological function of I_{Na} is not fully understood in non-excitable and proliferative cells[16,27,62]. I_{Na} has been reported to regulate cell proliferation and migration in rat gastric epithelial cells[46,47] and human cancer cells[63,64]; however, blockade of I_{Na} by TTX does not affect cell proliferation in fat tissue-derived MSCs[23]. The effects of I_{Na} on proliferation, migration and/or differentiation remain to be studied in different types of stem cells.

CONCLUSION

Although multiple ion channels have been found to be heterogeneously present in different types of stem cells, it is not clear whether the heterogeneous expression of ion channels is due to different subpopulations of cells and/or different cell cycle phases. An effort has been made to study the relationship between ion channel expression and cell proliferation in different types of stem cells. It is generally believed that IK_{Ca} (KCa3.1) and $I_{Cl.vol}$ (Clcn3) are required for stem cell proliferation. Inhibition of IK_{DR} (encoded by Kv1.2, Kv1.3, Kv1.5, Kv1.6, Kv2.1, Kv3.1 or Kv10.1) reduces proliferation in ES cells and MSCs; however, blockade of some specific Kv channels, *e.g.* Kv1.3 by psora-4 or Kv3.1 by TEA in adult rat neural progenitor cells[30], Kv1.1, Kv1.6 and Kv3.1 by α-dendrotoxin in human neural progenitor cells[31], promotes cell proliferation. No effect on proliferation is observed with TEA or 4-AP inhibition of IK_{DR} (Kv1.1, Kv1.2 and Kv1.6) in mouse cardiac c-kit$^+$ progenitor cells[35]. Thus, the role of IK_{DR} in the regulation of proliferation is cell origin- and/or phenotype-dependent. Ion channels are believed to provide the basis for generating bioelectric signals that control migration, proliferation and differentiation in a variety of types of cells[55,65]. The studies summarized in this editorial indicate that patterns and phenotypes of ion channel expression in stem cells are species-, origin- and/or tissue-specific dependent. How these differences affect the cellular functions needs a detailed investigation in different type of stem cells. Further study should be focused on the effects of ion channels on migration and differentiation of different stem cells to determine which type of ion channel is involved in regulating cell migration and/or differentiation. This information is important for the study of regenerative medicine. Additional effort is required to investigate ion channels in cancer stem cells to locate potential therapeutic targets.

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