

Calcium channels and their role in regenerative medicine

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Abstract

Stem cells hold indefinite self-renewable capability that can be differentiated into all desired cell types. Based on their plasticity potential, they are divided into totipotent (morula stage cells), pluripotent (embryonic stem cells), multipotent (hematopoietic stem cells, multipotent adult progenitor stem cells, and mesenchymal stem cells [MSCs]), and unipotent (progenitor cells that differentiate into a single lineage) cells. Though bone marrow is the primary source of multipotent stem cells in adults, other tissues such as adipose tissues, placenta, amniotic fluid, umbilical cord blood, periodontal ligament, and dental pulp also harbor stem cells that can be used for regenerative therapy. In addition, induced pluripotent stem cells also exhibit fundamental properties of self-renewal and differentiation into specialized cells, and thus could be another source for regenerative medicine. Several diseases including neurodegenerative diseases, cardiovascular diseases, autoimmune diseases, virus infection (also coronavirus disease 2019) have limited success with conventional medicine, and stem cell transplantation is assumed to be the best therapy to treat these disorders. Importantly, MSCs, are by far the best for regenerative medicine due to their limited immune modulation and adequate tissue repair. Moreover, MSCs have the potential to migrate towards the damaged area, which is regulated by various factors and signaling processes. Recent studies have shown that extracellular calcium (Ca^{2+}) promotes the proliferation of MSCs, and thus can assist in transplantation therapy. Ca^{2+} signaling is a highly adaptable intracellular signal that contains several components such as cell-surface receptors, Ca^{2+} channels/pumps/exchangers, Ca^{2+} buffers, and Ca^{2+} sensors, which together are essential for the appropriate functioning of stem cells and thus modulate their proliferative and regenerative capacity, which will be discussed in this review.

Key Words: Ca^{2+} signaling; Ca^{2+} channels; Transient receptor potential channel 1/Orai1 stem cells; Regenerative medicine; Stem cells

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Core Tip: Regenerative medicine has the potential to replace damaged tissues. Stem cells provide new hope for regenerative therapy as they have indefinite self-renewable capability and can differentiate into all cell types. Stem cells can be obtained from both exogenous and endogenous sources. Moreover, stem cells migrate towards the damaged organs; however, signaling molecules/factors that allow them to move to damaged organs and facilitate repair have not been fully identified. Ca²⁺ signaling is critical for appropriate functioning of stem cells. Importantly, Ca²⁺ signaling is highly adaptable, and how it modulates stem cell function and its regenerative capacity is discussed in this article.

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INTRODUCTION

Stem cells are unique, undifferentiated cells that possess two fundamental properties, indefinite self-renewable capability and differentiation capability into all types of cell lineages. These two stem cell traits make them special, and thus, they can be used for organ development or tissue therapy^[1,2]. Self-renewal capability primarily means that cells have the ability to maintain an undifferentiated state, while undergoing multiple cell divisions. Similarly, differentiation capability or plasticity/potency of stem cells means that the cells have the capability to differentiate into different cell lineages. Thus, understanding the factors that make them proliferative as well identifying the niches/signaling events that allow them to develop into unique cell lineages is essential for their use in regenerative therapy. Based on their source, stem cells can be broadly divided into two types: “embryonic stem cells” (ESCs) and “non-embryonic adult/somatic stem cells”^[3]. However, stem cells can also be named according to their origin and plasticity such as embryonic, germinal, and somatic (fetal or adult) stem cells. Furthermore, based on their differentiating potential, stem cells are also classified into totipotent, pluripotent, and multipotent cell types^[4].

ESCs

After fertilization, the zygote divides into multiple cells, which are called the morula stage, and these individual cells are named totipotent cells. Totipotent cells exhibit a very high self-renewal capacity along with a similarly high differentiation potential into multiple lineages. These cells further grow, mature, divide, and develop into a blastocyst. Cells of the blastocyst’s inner cell mass are more specialized cells and thus are referred to as ESCs or pluripotent stem cells. ESCs have a unique property and can differentiate into all three germ layers that develop all potential organs with endless dividing potential, which makes them perfect for regenerative therapy. Although ethical concerns prevent them from being used for regenerative therapy, extraembryonic tissues or placental cells also have self-renewing capacity that maintains an undifferentiated state similar to that observed in ESCs, and thus are also a great source of non-ESCs^[3,5-7]. However, these cells are in limited quantity and are sometimes contaminated with other cells, making them hard to be used for regenerative therapy.

Non-embryonic adult/somatic cells

Pluripotent stem cells can generate into multipotent stem cells, which are more “mature” cells but have restricted ability to differentiate into specialized cells. Multipotent stem cells are already committed to lineage-specific differentiation, and thus have minimal plasticity potential. These can be isolated from a variety of tissue sources^[3,6] as described below and shown in [Figure 1](#).

Bone marrow and bone marrow stem cells: Bone marrow niches are structurally organized in the medullary cavity and are protected within the bones. Importantly, bone cells serve as skeletal support for hematopoietic cells (HPCs) along with serving as calcium (Ca²⁺) reservoirs. The mammalian bone marrow is an organ of the immune

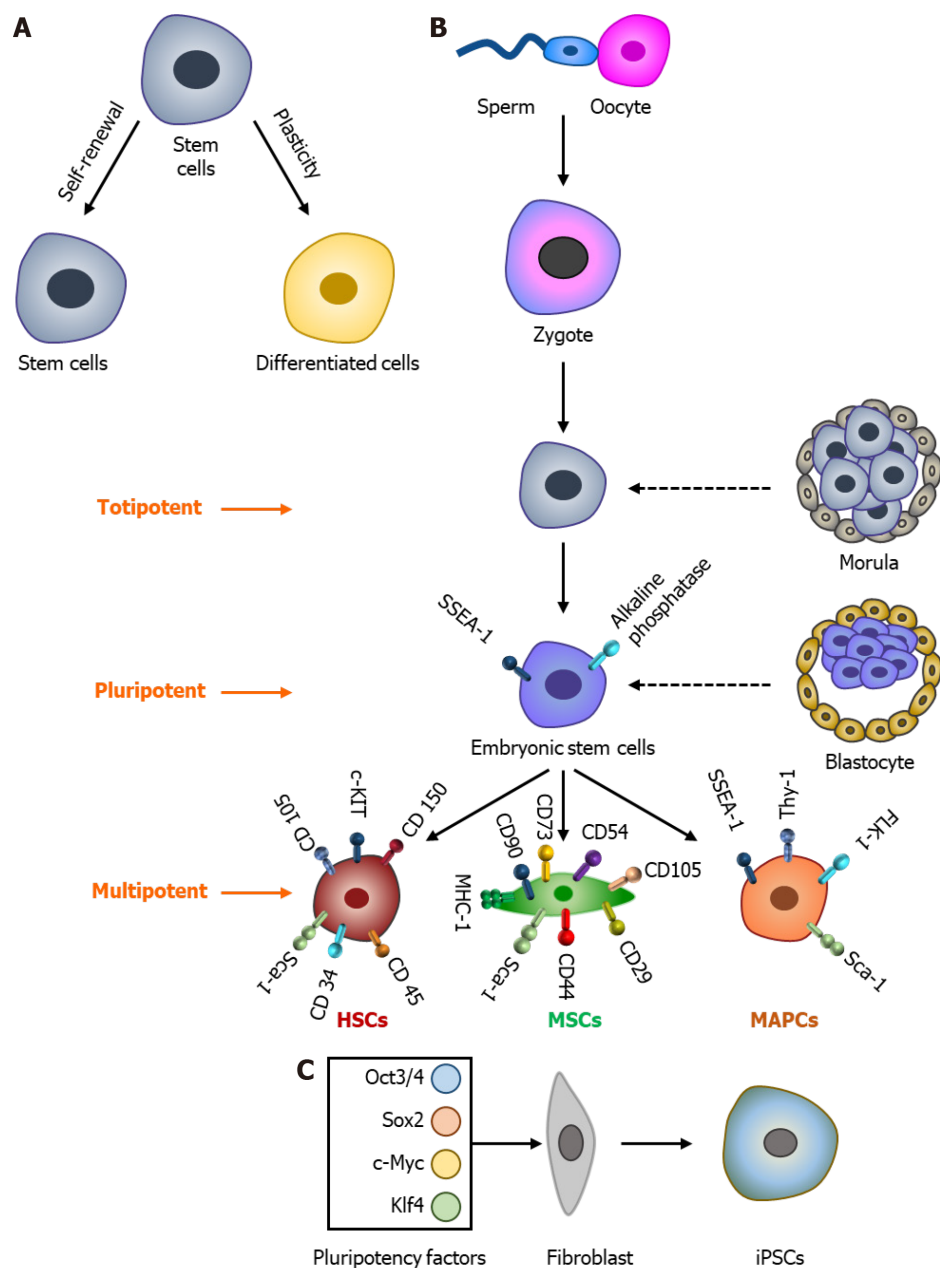


Figure 1 Stem cell properties and their types. A: Stem cells have two unique fundamental properties, self-renewal, and differentiation potential; B: Showing the development of different stem cells such as embryonic stem cells, hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and multipotent adult progenitor stem cells (MAPCs); C: Showing the generation of induced pluripotent stem cells (iPSCs) from mouse fibroblast cells using four factors (octamer-binding transcription factor 3/4, SRY-box transcription factor 2, c-Myc, Kruppel-like factor 4). SSEAs: Stage-specific embryonic antigens.

system, which is the largest semisolid organ of the human body. Bone marrow exists in the medullary cavity and epiphysis of the long bones such as humeri, ribs, femora, tibia, pelvis, and skull. It constitutes a soft gelatinous and dynamic tissue, which varies from person to person in its structure, quantity, and quality^[8-10]. Bone marrow contains both soluble and cellular parts that change within the person over time. The soluble part is made up of cytokines, growth factors, chemokines, hormones, and various ions. The cellular portion comprises different cell types such as adipocyte, macrophage, fibroblast, osteoblast, and stem cells^[11]. Importantly, bone marrow is the largest reservoir of non-ESCs that contains hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), and multipotent adult progenitor stem cells (MAPCs). The hematopoietic region of the bone marrow contains HSCs and HPCs, whereas the vascular component contains non-HPCs such as MSCs and MAPCs^[12]. Stem cells are not distributed randomly within the bone marrow; instead, they are highly organized and constitute the bone marrow microenvironment or niche where cells are protected and work in a synchronized manner^[10,11].

HSCs

HSCs are essential for making different types of blood cells and are present in specialized areas of bone marrow referred to as the “the primary hematopoiesis site”^[13]. Hematopoiesis is a dynamic process that maintains homeostasis between the production and consumption of all terminally differentiated blood cells^[14]. HSCs produce myeloid progenitor cells, which can be differentiated into granulocytes, monocytes, erythrocytes, platelets, and lymphoid progenitor cells, which further differentiate into lymphocytes and plasma cells. HSCs express specific surface markers such as stem cell antigen-1 (Sca-1), c-kit, cluster of differentiation 34 (CD34), Thy-1, CD201, and CD105/endoglin, whereas human HSCs express c-Kit, Sca-1, Thy-1, and CD133. Additional markers for individual cells are indicated in [Table 1](#)^[15].

MAPCs

MAPCs were first isolated from rat bone marrow by Dr. Verfaillie’s group in 2002. Rodent bone marrow-derived MAPCs can differentiate into endothelial cells, adipocytes, chondrocytes, and osteocytes^[16]. Rat MAPCs express c-Kit⁺, CD9⁺, CD13⁺, CD31⁺ but are negative for CD44, major histocompatibility complex class I, CD45, and Thy1 surface markers^[17], while human MAPCs exhibit higher expression of CD44, CD13, CD73, and CD90. MAPCs also have immunomodulatory properties and show higher expression of pluripotency factors such as octamer-binding transcription protein 4 (Oct4), SRY-box transcription factor 7 (Sox7), Sox17, Rex-1, GATA binding protein 4 (GATA4), and GATA6 and thus are used for tissue regeneration ([Table 1](#))^[18].

MSCs

Friedenstein’s group first discovered adult bone marrow-derived MSCs in 1968^[19] but Caplan gave the term ‘mesenchymal stem cell’^[20]. Bone marrow is considered the primary source of MSCs; however, MSCs have extensive localization such as in adipose tissue, placenta, amniotic fluid, umbilical cord blood, umbilical cord, periodontal ligament, and dental pulp^[19,21,22]. MSCs regulate and maintain stemness, proliferation, and differentiation (such as into adipocytes, osteocytes, chondrocytes, and other cells), and are essential for the self-renewal of HSCs and their progenitor cells^[11]. As per the Mesenchymal and Tissue Stem Cell Committee of the International Society of Cellular Therapy guideline, the minimal criteria for MSC characterization include plastic adherent property and spindle-shaped morphology, along with the expression of MSC-positive markers such as CD29 (b1-integrin), CD44, and Sca-1, and negative for markers such as CD11b, CD34, and CD45 ([Table 1](#)). In addition, they should have a tri-lineage differentiation such as adipocytes, osteocytes, and chondrocytes and cells, those satisfy these criteria are thus called “MSCs,” and those that do not, are termed “multipotent mesenchymal stromal cells”^[10,11,23-28]. Human MSCs must also be positive for certain surface markers and must be negative for specific surface markers as indicated in [Table 1](#)^[29].

Very small embryonic-like stem cells

Another type of pluripotent stem cell that is present in multiple tissues, including bone marrow, cord blood, and gonads, are proposed as very small embryonic-like (VSEL) stem cells^[30]. Kucia *et al*^[31] in Ratajczak *et al*^[32] first reported VSEL stem cells in adult mice bone marrow. Later, VSELS were found in various organs such as the human cord and peripheral blood. VSEL stem cells show multiple characteristics of ESCs, including differentiating ability into all three germ layers^[30]. In addition, VSEL stem cells are the most primitive stem cells that migrate to the gonadal ridges during development and further relocate to all developing organs and survive throughout life^[33].

Induced pluripotent stem cells

Although different types of stem cells are used in biomedical and clinical research, one of the challenges that remain is that they are not in sufficient quantity. In addition, they are not from the same individual and are thus considered foreign, thereby having immunological issues^[34]. To overcome these issues, induced pluripotent stem cells (iPSCs) have come to light in recent years that can not only solve the ethical issues related to the use of ESCs but can also be developed from the same individual and thus can be a safer alternative. In 2006, Takahashi and Yamanaka^[35] were able to generate iPSCs directly from mouse fibroblast using four critical factors, Oct3/4, Sox2, c-Myc, and Kruppel-like factor 4 (Klf4)^[35,36]. Similarly, another group showed that four factors that include Oct4, Sox2, Nanog, and Lin28 were also essential to generate iPSCs from human somatic cells. Importantly, generated iPSCs exhibited essential

Table 1 Stem cells and their phenotypic markers and transcription factors

Embryonic stem cells (expression of SM/TF)		
Human	Positive SM	SSEA-3, SSEA-4, TRA-1-60, TRA-1-81, alkaline phosphatase (ALP), CD9, Thy1, HLA-I CD133, and CD326 ^[92-94]
	Negative SM	SSEA-1 ^[92-94]
	TF	Oct 3/4, Sox2, Nanog, activin/nodal, FGF, Esrrb, and Tfcg2l1, Klf4, Klf2, Tbx3, and Gbx2 ^[92,94,95]
Mouse	Positive SM	SSEA-1 and alkaline phosphatase ^[92,94]
	Negative SM	SSEA-3, SSEA-4, TRA-1-60, and TRA-1-81 ^[92,94]
	TF	Oct-3/4, Sox2, Nanog, LIF, BMP, genesis, germ cell nuclear factor, GDF-3, FGF-4, UTF1, Fbx15, and Sall4 ^[92,94,96]
Hematopoietic stem cells (expression of SM/TF)		
Human	Positive SM	CD34, CD90, CD49R, and CD133 ^[7,97,98]
	Negative SM	Lin, CD38, and CD45RA ^[7,97,98]
	TF	AHR, BMI1, GF11, HES1, HLF, Runx-1, Scl/tal-1, Lmo-2, MII, Tel, and GATA-2 ^[97,99]
Mouse	Positive SM	Sca-1, c-kit, CD49b, CD150, (endoglin), and Slamf1 ^[7,97,100]
	Negative SM	Lin, FLT3, CD34, CD41, Flk2, and CD48 ^[7,97,100]
	TF	Runx-1, Scl/tal-1, Lmo-2, MII, Tel, Bmi-1, Gfi-1, and GATA-2 ^[99,101]
Multipotent stem cells (expression of SM/TF)		
Human	Positive SM	CD146, CD44, CD13, CD73, CD90, CD105, and MHC class I ^[18,102]
	Negative SM	CD34, CD45, c-kit, KDR, CD56, CD271, CD140a, CD140b, and ALP ^[18,102]
	TF	Oct-4 Rex-1, Nanog, and Bmi-1 ^[102,103]
Mouse	Positive SM	c-Kit, CD9, CD13, CD31, SSEA-1, and Sca-1 ^[17,104]
	Negative SM	CD3, CD19, CD34, CD44, CD45, c-Kit Thy1, Flk-1MHC-I, MHC class II, Gr-1, and Mac-1 ^[17,104]
	TF	Oct-4, Rex-1, and Nanog ^[16,102]
Mesenchymal stem cells (expression of SM/TF)		
Human	Positive SM	CD10, CD13, CD29, CD44, CD49e (a5-integrin), CD54 (intercellular adhesion molecule [ICAM]-1), CD58, CD71, CD73, CD90, CD105, CD140a, CD140b, CD146, CD166 (activated leukocyte cell adhesion molecule), CD271, Sca-1, ALP MHC class I, vimentin, cyokeratin (CK) 8, CK-18, and nestin ^[18,27-29]
	Negative SM	CD4, CD8, CD11a, CD11b, CD14, CD15, CD16, CD19, CD25, CD31, CD33, CD34, CD45, CD49b, CD49d, CD49f, CD50, CD56, CD62E, CD62L, CD62P, CD79a, CD80, CD86, CD106 (vascular cell adhesion molecule [VCAM]-1), CD117, CD271, c-kit, KDR, HLA-DR, cadherin V, and glycoporin A ^[18,27-29]
	TF	Oct-4, Rex-1, and Sox-2 ^[105]
Mouse	Positive SM	CD29, CD44, CD73, CD90, CD105, and Sca-1, Thy1.2, and CD135 ^[10,23,24,26,28]
	Negative SM	CD11b, CD14, CD31, CD34, CD45, and CD86, CD135, c-Kit, and VCAM-1 ^[10,23,24,26,28]
	TF	HOX, stage-specific embryonic antigen 1 (SSEA-1), Nanog, Oct-4, Rex-1, and GATA-4 ^[25]

SM: Surface marker; TF: Transcription factor.

characteristics like ESCs such as normal karyotypes, telomerase activity, cell surface markers, and maintaining the developmental potential that also has differentiation potential^[36,37]. Importantly, as a proof of concept, iPSCs are used to treat sickle cell anemia using mouse models that show its importance for therapeutic usage. However,

more research is needed to understand the key signaling changes due to overexpression of these transcription factors as they can lead to uncontrolled growth. Cost as well as time to develop these stem cells are also issues and moreover, as several factors and animal products are used to grow these cells, they hinder its use for regenerative medicine.

Stem cells and issues for using them for regenerative medicine: Stem cells are critical for the repair, replacement, and regeneration of damaged tissues that are able to restore organ function. Stem cells can act as regenerative medicine as they are valuable sources of new cells to treat various degenerative/aging, autoimmune and genetic disorders^[38]. The rapid expansion of stem cell research and stem cell product commercialization has also created numerous ethical issues. The killing of embryos to obtain stem cells or create human ESC lines is considered the primary cause of controversy^[39-41]. iPSCs provide an essential tool for stem cell therapy, but they are not ideal. Although the destruction of embryos is not required to generate iPSCs as they are obtained from somatic cells' reprogramming, they come with their own issues. Insertion of multiple copies of the retroviral vectors is needed to generate iPSCs from skin fibroblast cells, which can easily cause mutations and thus could be harmful. In addition, one of the four genes, c-Myc, is a proto-oncogene and can be oncogenic based on certain conditions and can induce tumors. Also, studies have revealed that 1 in 5000-10000 transfected cells became iPSCs, *i.e.* only specific cells have the potential to be reprogrammed into iPSCs. Thus, iPSCs may not be the ultimate candidate for transplantation therapy^[42]. Also, other ethical concerns remain if human iPSCs could be used in the generation of the embryo, germ cells, human clones^[43]. Thus, in spite of the recent development, additional research is needed to overcome some of these issues. Although various factors and signaling mechanisms are required for self-renewal and differentiation of stem cells, explaining all of them is beyond this review. Therefore, in this review, we will focus on essential and significantly less noticed factors, such as Ca²⁺ and other divalent cations Ca²⁺ signaling, and Ca²⁺ channels in stem cell functions and regulation.

Ca²⁺ AND INTRACELLULAR Ca²⁺ STORAGE

Ca²⁺ is the most crucial element in cells as it is an important intracellular secondary messenger. Evolution has utilized Ca²⁺ to bind to various biological macromolecules, which makes it unique that is able to effectively regulate the concentration of free Ca²⁺^[44]. Ca²⁺ modulates a diversity of cellular functions such as transcription, apoptosis, cytoskeletal rearrangement, immune response, growth, proliferation and differentiation, maintenance of pluripotency, and self-renewal of stem cells^[45]. Ca²⁺ is a highly adaptable intracellular signal, and depending on the source, a Ca²⁺ signal may lead to opposing functions such as proliferation and cell death. Another important aspect of Ca²⁺ signaling is that it can trigger the response in microseconds (exocytosis at synaptic endings), to milliseconds (as observed in muscle contraction), and in minutes to hours (gene transcription and cell proliferation)^[46]. One way it can control such diverse function is by modulating the spatial and temporal Ca²⁺ signals, which could be highly localized or widespread. Cells store intracellular Ca²⁺ in various organelles such as the Golgi apparatus, mitochondria, nucleus, lysosomes, and endoplasmic reticulum (ER). These individual Ca²⁺ stores are essential in modulating different functions, mechanism(s), and for the exchange of ions with other Ca²⁺ pools. For example, Ca²⁺ in the sarcoplasmic reticulum act as a rapidly mobilizable reservoir, mitochondrial Ca²⁺ is a crucial dynamic regulator of metabolism, and trans-Golgi network Ca²⁺ store is involved in the formation of secretory granules^[47]. Furthermore, different intracellular organelles release sequestered Ca²⁺ using various Ca²⁺ mobilizing messengers and receptors such as ER use inositol 1,4,5-trisphosphate (IP₃)-IP₃ receptor and cADPR-ryanodine receptors (RyRs) while acidic endosomes and lysosomes use nicotinic acid adenine dinucleotide phosphate (NAADP) and two-pore channels (TPCs) channels^[48] that modulate various cellular functions (Table 2).

Ca²⁺ signaling and Ca²⁺ channel in stem cells/MSCs

Ca²⁺ signaling is associated with several components. In a typical Ca²⁺ signaling process, changes in the intracellular Ca²⁺ stores start several counteracting processes, which may be "on" or "off", which depends on if the intracellular Ca²⁺ concentration is increasing or decreasing. At physiological or "resting" state, cytosolic Ca²⁺ concentration is maintained between 100 and 300 nmol/L range, which favors the "off" processes. However, when the cells are stimulated by different stimuli such as hormonal and mechanical forces, cytoplasmic Ca²⁺ concentration is increased to 50-100 μmol/L that represents the "on" processes^[49]. Binding of the agonist activates the cell

Table 2 Calcium signaling toolkit

Component of toolkit	Name of calcium signaling toolkit components
Cell-surface receptors	G protein-coupled receptors and protein tyrosine kinase receptors such as muscarinic, bradykinin B2, cholecystokinin, α , β -adrenergic, P ₂ X and P ₂ Y, angiotensin II, Ca ²⁺ -sensing receptor, chemokine, metabotropic glutamate, serotonin, oxytocin, epidermal growth factor receptor, and platelet-derived growth factor ^[46,106,107]
Calcium channels	Voltage-gated channels (Cav1.1 to 1.4 [L-type], Cav2.1 to 2.3 [N-, P/Q- and R-type] and Cav3.1 to 3.3 [T-type]) and two-pore channels (TPCs) ^[46] , voltage-gated K ⁺ channel, Ca ²⁺ -activated K ⁺ channel, ATP-sensitive K ⁺ channels, TRPC1-7 ORAI1-3, IP3R, and RyR2 ^[108-110]
Calcium pumps and exchangers	Na ⁺ /Ca ²⁺ exchangers, Na ⁺ /Ca ²⁺ -K ⁺ exchangers, plasma membrane Ca ²⁺ -ATPase (PMCA) and sarcoplasmic/endoplasmic reticulum Ca ²⁺ -ATPase (SERCA) pumps ^[46,111]
Calcium buffers (Ca ²⁺ -binding proteins)	Cytoplasmic buffers (PV [parvalbumin], CB [calbindin D-28k], and calretinin) ^[112] and buffers in lumen of the endoplasmic reticulum (ER) (calsequestrin, calreticulin, glucose-regulated protein [GRP] 78 and GRP94), ERp72, and mitochondrial calcium uniporter (MCU), Golgi buffers (Cab45, CALNUC P54/NEFA ^[46,113] , troponin C, myosin, calmodulin, and sarcolemma (cellular buffers in myocytes) ^[114]
Calcium sensors	EF-hand (CaM, TnC, calpains, miro1-2, S100A1-14, S100B, S100C, S100P, NCS-1, hippocalcin, neurocalcin, recoverin, VILIP1-3, GCAP1-3, MICU1 <i>etc.</i>) or C2 Ca ²⁺ -binding domains (annexin 1-13, otoferin, protein kinase C, RASAL <i>etc.</i>) ^[46] , ER Ca ²⁺ sensors STIM1 and STIM2 ^[115]

surface receptor that generates downstream signals to activate the phospholipase C (PLC)-IP₃ signal transduction cascade, which begins by the opening of intracellular receptors, IP₃ receptors (IP₃Rs) for the cytoplasmic influx of Ca²⁺. Increased intracellular Ca²⁺ binds to different cytoplasmic proteins such as calmodulin, protein kinase C (PKC), 4,5-bisphosphate (PIP₂), calcineurin, and others that participate in Ca²⁺ signaling pathways. At the cellular level, cells use two crucial Ca²⁺ sources for generating intracellular downstream signals. First is the internal reservoir, where Ca²⁺ is released and second is the external sources, that includes the entry of extracellular Ca²⁺ into the cells through various plasma membrane channels (Table 2 and Figure 2A)^[50,51].

In stem cells, extracellular Ca²⁺ influx into the cytoplasm is mediated mainly by store-operated Ca²⁺ channels (SOCCs) rather than the voltage-gated Ca²⁺ channels (VGCCs) or by the Na⁺/Ca²⁺ exchangers. Also, ER Ca²⁺ release is mediated by IP₃Rs rather than the RyRs and Ca²⁺ is moved back by sarco-ER Ca²⁺ ATPase, which is located on the ER membrane in mouse pluripotent stem cells^[52]. Like embryonic stems, human MSCs also showed that discharge of Ca²⁺ was mediated by IP₃Rs, and extracellular Ca²⁺ entry through the plasma membrane was mainly mediated by the SOCCs. This study showed that store-operated Ca²⁺ entry (SOCE) is the leading player in stem cell proliferation instead of VGCCs^[53]; however, the molecular identity of the SOCE channel is still not clear. Stimuli activated cells use different Ca²⁺ channels such as VGCCs, SOCE *via* the transient receptor potential (TRP) channels (TRPCs)/Orai's, and purinergic receptors that are essential for Ca²⁺ diffusion. Several studies showed an essential role for VGCCs in tissue development, such as cartilage development and inactivation or inhibition of VGCCs in stem cells resulted in imperfect chondrogenesis, suggesting that VGCC might have a critical role in differentiation. Moreover, Members of the TRP channel superfamily also showed their involvement in chondrogenic differentiation of MSCs by activating the Sox9 pathway^[51].

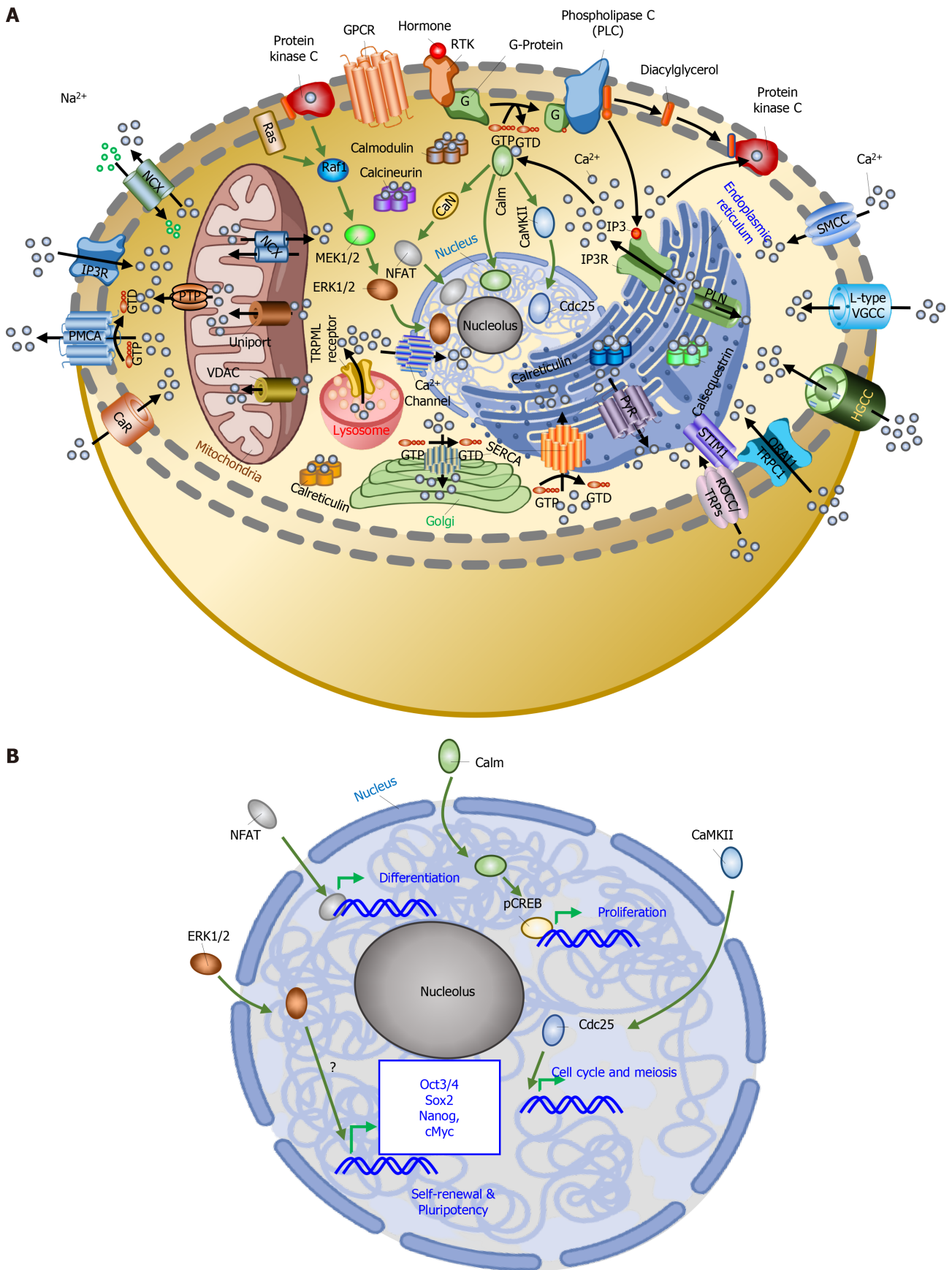


Figure 2 Calcium toolkit and calcium signaling. A: Calcium (Ca²⁺) signaling toolkit components include cell-surface receptors (G protein-coupled receptors (GPCRs) and protein tyrosine kinase receptors), Ca²⁺ channels (voltage-gated channels and two-pore channels, voltage-gated K⁺ channel, Ca²⁺-activated K⁺ channel, ATP-sensitive K⁺ channels, TRPC1-7 ORAI1-3, IP3R, RyR2), Ca²⁺ pumps and exchangers (Na⁺/Ca²⁺ exchangers (NCX), Na⁺/Ca²⁺-K⁺ exchangers, plasma membrane Ca²⁺ ATPase (PMCA) and sarco-endoplasmic reticulum (ER) Ca²⁺ ATPase, Ca²⁺ buffers (parvalbumin, calbindin, and calretinin [cytoplasmic buffers] and Ca²⁺ buffers

of the ER lumen, calsequestrin, calreticulin, glucose-regulated protein [GRP] 78 and GRP94), Ca²⁺ sensors (EF-hand [CaM, TnC, calpains, NCS-1, hippocalcin, neurocalcin, recoverin, MICU1, *etc.*] or C2 Ca²⁺-binding domains [annexin 1-13, otoferin, protein kinase C, RASAL, *etc.*], ER Ca²⁺ sensors STIM1 and STIM2), and Ca²⁺-sensitive cellular process. In a typical Ca²⁺-sensitive cellular process, the hormone binds to a specific receptor. This binding causes GDP-GTP exchange on the G protein. G protein (GTP-bound) activates phospholipase C (PLC). Activated PLC breaks phosphatidylinositol 4,5-bisphosphate (PIP₂) to inositol trisphosphate (IP₃) and diacylglycerol. IP₃ moves to a specific receptor on the ER, binds with the receptor, and triggers the release of sequestered Ca²⁺. Released Ca²⁺ and diacylglycerol activate protein kinase C enzyme. Activated protein kinase C phosphorylates cellular proteins and activates downstream proteins (Raf1 and other proteins). Activated Raf1 binds and activates MEK1/2 and MEK1/2, which phosphorylate extracellular signal-regulated kinase (ERK) 1/2. ERK1/2 enters the nucleus and on/off the genes against the hormone response. The released Ca²⁺ decreases ER calcium level. Low Ca²⁺ of ER sense by ER Ca²⁺ sensor (STIM) and activate it. An activated Ca²⁺ sensor binds the Ca²⁺ channel protein (ORAI) on the plasma membrane, opens the Ca²⁺ channel, and allows the Ca²⁺ entry into the cytoplasm from extracellular space. This process is called store-operated Ca²⁺ entry; B: Activated transcription factors and other proteins bind to DNA and increase the gene expression for self-renewal, proliferation, and differentiation processes in the stem cells. CaR: Ca²⁺ receptor; CREB: cAMP response element-binding protein; IP₃R: Inositol trisphosphate receptor; NFAT: Nuclear factor of activated T-cells; VDAC: Voltage-dependent anion channel; VGCC: Voltage-gated Ca²⁺ channel.

MSCs do express the L-type VGCCs and decreases in Cav1.1 expression are able to lower the immune response^[54]. Blocking VGCCs by dihydropyridines (DHPs) can suppress the proliferation of immune cells and both DHPs and cyclosporine are frequently used in transplantation patients. Another investigation confirmed that L-type VGCCs of skin-derived MSCs are involved in autocrine interleukin (IL)-6-mediated cell migration. Importantly, patch-clamp experiments showed that 15% of human undifferentiated bone marrow stem cells (BMSCs) express functional L-type VGCCs. Moreover, blockade of L-type VGCCs by nifedipine suppressed the proliferation of rat BMSCs by downregulating bone morphogenetic protein (BMP)-2 expression, which is an essential inducer of osteoblast differentiation^[55]. Furthermore, Ca²⁺ also plays an essential role in osteoclast formation. HSCs lineage-generated osteoclasts possess different types of Ca²⁺ channels and receptors. Osteoclast precursors express IP₃R2, while mature osteoclasts express the IP₃R1 isoform and cytokine stimulation promotes osteoclast differentiation. Accumulated activities of these receptors initiate intracellular Ca²⁺ signals and modulate bone turnover^[56]. Thus, Ca²⁺ channels are involved in the differentiation of osteoblasts and osteoclasts. Differentiated osteoblasts and osteoclasts are involved in the modeling and remodeling process resulting in new bone tissue regeneration or bone formation^[13]. Moreover, considering the potential role of Ca²⁺ channels in stem cell function, it offers the hope of tissue engineering and tissue regeneration in the future. However, one of the main caveats that remains is that these stem cells are not excitable and thus it is not clear how these VGCCs are activated; therefore, more research is needed to fully establish their role.

ROLE OF CA²⁺ AND CA²⁺ CHANNELS IN THE VARIOUS CELLULAR PROCESS OF STEM CELLS/MSCS

Proliferation and self-renewal of stem cells

Studies have shown that Ca²⁺ mobilization plays a crucial role in the self-renewal and proliferation of stem cells by activating or inhibiting different Ca²⁺ channels. Previous studies on the cell cycle of progenitor and undifferentiated cells have shown that transient Ca²⁺ oscillation, maintained by Ca²⁺ stores, increases the levels of cell cycle regulators such as cyclins A and E and plays a crucial role during the G1 to S transition. IP₃Rs and L-type channels (in differentiated cells) and ryanodine-sensitive stores (in neural progenitor cells) maintain the Ca²⁺ oscillations. This study suggests that Ca²⁺ oscillation is involved in cell cycle progression and proliferation^[57]. Also, mouse ESC (mESC) proliferation is stimulated by epidermal growth factor *via* the phosphorylation of connexin 43 (involved in the influx of Ca²⁺ and translocation of PKC) and downstream activation of p44/42, p38 mitogen-activated protein kinase (MAPK) pathway (Figure 2B). Moreover, gamma-aminobutyric acid A receptors can modulate the proliferation of mESCs by regulating intracellular Ca²⁺. Furthermore, the expansion of ESCs is also regulated by ligands such as ATP (adenosine triphosphate) and lysophosphatidic acid, which activate the PLC/PKC/IP₃ pathway by triggering a release of Ca²⁺^[52].

Previous research has shown that SOCCs are important for Ca²⁺ influx in mESCs. SOCCs blockers (*e.g.*, 2-aminoethoxydiphenyl borate [2-APB] and SKF-96365) reduce mESC proliferation, suggesting that SOCE is essential for ESC proliferation^[58]. Similarly, SKF-96365 and 2-APB (SOCE inhibitors) treatment decreases the expansion of murine bone marrow-HSCs, human bone marrow, and umbilical cord blood

mononuclear cells^[59]. Moreover, 2-APB downregulates pluripotent markers (Sox-2, Klf-4, and Nanog), which suggests that SOCE is associated with the self-renewal property of mESCs (Figure 2B). Furthermore, estrogen enhances the proliferation of stem cells *via* enhancing SOCE; however, the molecular identity of the channel has not yet been identified. The nuclear factor of activated T-cells (NFAT) is involved in estrogen-stimulated proliferation, indicating that NFAT is the downstream target of estrogen-induced SOCE. This study showed how estrogen (a female sex hormone) affects ESC proliferation^[58] (Figure 3). Another study showed that extracellular Ca²⁺ promotes the proliferation and migration of MSCs^[60]. Our unpublished research on MSCs also shows that extracellular Ca²⁺ promotes proliferation and SOCE blockers (*e.g.*, 2-APB and SKF-96365) reduce MSC proliferation, suggesting that SOCE is essential for MSC proliferation.

Differentiation: Stem cells can generate any tissue cells by modulating the differentiation process. Previous research has shown that Ca²⁺ directly upregulates the catalytic activity of protein arginine methyltransferase 1 and enhances methylation. Increased methylation stimulates differentiation suggesting that Ca²⁺ plays a crucial role during erythroid differentiation^[61]. Ca²⁺ provokes a signaling cascade in human bone marrow-derived mesenchymal stromal cells and promotes MSC osteogenic differentiation^[62]. Also, physical stimuli activates the Ca²⁺ channel that results in increased intracellular Ca²⁺ concentration, leading to the chondrogenic differentiation of MSCs^[51]. Ca²⁺-activated potassium channels also play a crucial role in MSC differentiation^[63]. Similarly, Na⁺/Ca²⁺ exchanger in mESCs plays a crucial role during ESC differentiation into cardiomyocytes^[64]. Studies have shown that L-VGCCs play an essential role in maintaining intracellular Ca²⁺ homeostasis in differentiating cells^[65]. Ca²⁺ also plays a significant role in the neuronal differentiation process. A previous study suggested that the TPCs and NAADP-regulated Ca²⁺ channels play an essential role in the neural differentiation of mESCs. mESCs showed decreased expression of TPC2 during differentiation into neural progenitors at an early stage while gradually increasing again during the late stages of neural differentiation. TPC2 knockdown disrupts Ca²⁺ signaling and inhibits differentiation^[48,66]. Another study suggested that TPCs and NAADP-regulated Ca²⁺ channels play essential roles in myogenesis differentiation. Ca²⁺ is critical in regulating the transcription factors that promote differentiation. For instance, Ca²⁺ signal transducer such as Ca²⁺/calmodulin-dependent protein kinase and calcineurin regulate transcription factors, such as cAMP response element binding protein and NFAT, which activate the transcription of myogenin, a key regulator of muscle cell differentiation. Impairment of intracellular Ca²⁺ signaling inhibits muscle differentiation. These studies suggest the critical role of Ca²⁺ signaling and Ca²⁺ channels in cellular differentiation. Furthermore, the HPC and osteoclast differentiation process involves ADP-ribosyl cyclase CD38, which is associated with the generation of NAADP and cADPR. Thus, these studies suggest the critical role of Ca²⁺ signaling and Ca²⁺ channels in cellular differentiation^[48].

The differentiation process is regulated by several biological and chemical factors, including steroid hormones, BMPs, BMP-2, BMP-4, BMP-7, (crucial for chondrogenesis differentiation and synthesis of aggrecan, collagen type 2, and other extracellular matrices proteins) and tumor growth factors- β (TGF- β), TGF- β 1, and TGF- β 3^[67]. In many of these processes, Ca²⁺ plays a crucial role, *e.g.*, the higher intracellular Ca²⁺ influx through Ca²⁺ channels and modulates the cell differentiation process. Several studies have shown that the inhibition of Ca²⁺ channels, VGCCs in stem cells, inhibits chondrogenesis. Therefore, activation of these Ca²⁺ channels in the stem cells opens a new research area, leading to innovative approaches to improve MSC self-renewal and differentiation potentials such as chondrogenic differentiation and cartilage repair of MSCs^[51].

Adhesion, migration, and homing: Cytosolic Ca²⁺, a primary second messenger, regulates various cellular functions including cell migration. Temporal cytosolic Ca²⁺ is mediated by receptors such as G protein-coupled P2Y receptors and ligand-gated ion channel P2X receptors. P2X receptors mediate extracellular Ca²⁺ influx while P2Y receptors trigger the release of intracellular Ca²⁺ from the ER and reduce the ER Ca²⁺ level, which activates SOCE. These receptors perform an essential role in the migration process *via* ATP-induced regulation^[68]. MSCs are found in the connective tissue that surrounds other tissues and organs. During injury and damage, MSCs migrate or homing to the damaged tissues or lesions, differentiation into desired cell types, and play a crucial role in normal tissue morphogenesis, homeostasis, and repair. The homing process begins with the interactions between MSCs and the vascular endothelium at the target tissue^[25]. Adhesive MSCs migrate in the mesenchymal mode

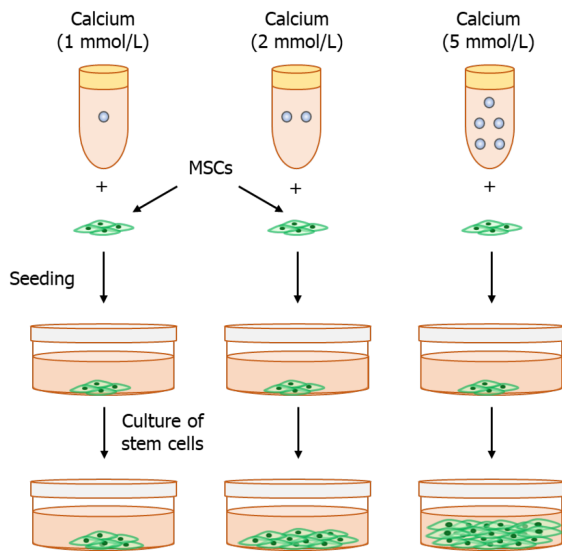


Figure 3 Calcium-dependent stem cell proliferation. Stem cells cultured in 1, 2, and 5 mmol/L calcium. Our results (not published) reveal that higher calcium-treated stem cells show a high proliferation rate. MSCs: Mesenchymal stem cells.

from the healthy tissue area to the damaged area. MSC migration, a complex and highly coordinated process, has several steps (*e.g.*, rear-to-front polarization, protrusion, adhesion formation, and rear retraction) managed by various proteins as integrin, tensin, paxillin, actin, and myosin. Furthermore, these proteins are controlled by multiple signaling molecules, such as Rho GTPase, Rho kinase, focal adhesion kinase (FAK), c-Jun N-terminal kinase (JNK), PKC, MAPK, and extracellular signal-regulated kinase (ERK)^[68]. A previous study showed that electromagnetic fields exposure increases intracellular Ca²⁺, which in turn initiates migratory signaling (FAK/Rho GTPase). Increasing MSC migration towards injury or diseases might be a novel way to improve the efficiency of MSC engraftment in clinical applications^[69].

Ca²⁺ AND Ca²⁺ CHANNEL-ASSOCIATED DISEASES

Spatial and temporal Ca²⁺ concentrations are necessary for various Ca²⁺ signaling systems for the specific cellular functions of different cell types. The ER releases Ca²⁺ through IP3Rs, which activate various Ca²⁺ signaling systems. Ca²⁺ signaling systems are highly controlled and regulated for normal function. Dysregulation of Ca²⁺ signaling is linked to significant human diseases such as bipolar disorder, cardiac disease, and Parkinson's disease, Alzheimer's disease (AD) and amyotrophic lateral sclerosis, Mucopolidosis type IV, Niemann-Pick disease, and bone disease^[46,70-72]. Ca²⁺ influx from the extracellular space, maintained by Ca²⁺ release-activated channels (CRAC), also participates in various cellular functions. CRAC channels are composed of two components: ORAI1 proteins (ion-conducting pore-forming component) located in the plasma membrane, and stromal interaction molecule (STIM) 1 and 2 (Ca²⁺ + sensor and activator of ORAI1 channels) located in the ER. Alteration of ORAI1 and STIM1 function abolish CRAC channel function and SOCE, resulting in several diseases such as severe combined immunodeficiency-like disease, autoimmunity, muscular hypotonia, and ectodermal dysplasia. In addition, deformity in dental enamel formation and tooth development have been observed^[73].

Ca²⁺ channels are the main signaling elements in neurons and interact with other modulatory proteins, resulting in modulation of Ca²⁺-sensing. Ca²⁺ channels regulate the release of bioactive molecules such as proteins, hormones, and neurotransmitters. Such Ca²⁺-sensing is required for many biophysical and pharmacological properties in neurons. Deformed Ca²⁺ channel activity contributes to disease progression^[74]. Studies have shown that Ca²⁺ channels such as voltage-gated Ca²⁺ channels and glutamate receptor channels are mainly responsible for Ca²⁺ influx into the neuron. SOCE, a Ca²⁺ flow into cells mediated by depleted ER Ca²⁺ stores, with the help of STIM protein such as STIM1 and STIM2. Dysregulation of neuronal SOCE and glutamate receptors promotes acute neurodegenerative diseases such as traumatic brain injury and cerebral ischemia, and chronic neurodegenerative disorders such as AD and

Huntington's disease^[75,76].

STEM CELLS IN DISEASE CONDITIONS

Preclinical studies have shown the great potential of stem cells for tissue engineering and considerable promise to rebuild damaged tissue such as bone, cartilage, marrow stroma, muscle, fat, and other connective tissues, which mark them an attractive option in tissue engineering, disease, cell therapy, and regenerative medicine^[77,78]. Autologous and allogeneic transplantations of stem cells have shown promise for the treatment of various diseases such as Crohn's disease, graft *vs* host disease, refractory systemic lupus erythematosus, multiple sclerosis, and systemic sclerosis, *etc.* (Table 3)^[79].

Stem cells and their progeny cells secrete soluble factors including cytokines, growth factors, hormones, Ca²⁺, and chemokines. These factors are required for the proper functioning of bone marrow. For instance, MSCs and other cells such as osteoblasts and CAR cells secrete stromal cell-derived factor-1 (SDF-1), a critical chemokine necessary for the supporting and homing of HSCs in the HSC niche^[81]. Moreover, stem cells generate growth factors, recruit MSCs for lineage-specific differentiation, ensure proper modeling and remodeling, and promote bone tissue regeneration^[80]. MSCs also produce other important secretory trophic factors such as angiopoietin-1, brain-derived neurotrophic factor, erythropoietin, fibroblast growth factor (FGF-1/2/4/7/9), glial cell-derived neurotrophic factor, granulocyte/macrophage-colony stimulating factor (G/M-CSF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF-1/2), leukemia inhibitory factor, nerve growth factor, platelet-derived growth factor, SDF-1, secreted frizzled-related protein 2, stanniocalcin 1, TGF- β 1/2/3, and vascular endothelial growth factor. These factors support engraftment and modulate tissue development, maintenance, repair of diseased tissues, and self-healing and exert regenerative effects. Interestingly, studies showed that MSCs secrete different trophic factors that modulate their function^[81].

The fundamental immunomodulatory mechanisms of MSCs and how MSCs modulate the immune response remains to be fully investigated. However, some research has noted that the immunomodulatory capacity of MSCs is of two types: first, cell-to-cell contact-dependent, and second is an independent mechanism that does not involve contact. In cell-to-cell contact-dependent mechanisms, MSCs directly suppress and modulate the generation of various pro-inflammatory immune cells such as inhibition of natural killer (NK) cells, activated B cell, and dendritic cells and strongly suppress CD4⁺ T helper cells and cytotoxic CD8⁺ T cells. On the other hand, MSCs promote the production of immune-suppressive regulatory cells such as dendritic regulatory cells, B regulatory cells, CD4⁺ regulatory cells (Tregs), and NK regulatory cells. These regulatory cells actively suppress the immune response in the repair area and build a favorable and tolerogenic microenvironment for tissue repair and regeneration^[11,28]. Importantly, Ca²⁺ especially Orai1/STIM1 plays a critical role in modulating the immune response and although it is not clear if they also contribute towards the immunomodulatory mechanism of stem cells, more research is needed to fully establish this.

Independent mechanisms on the other hand involve MSCs secretome. MSCs secrete both the soluble anti-inflammatory factors and pro-inflammatory factors^[19]. Anti-inflammatory factors including chemokines, cytokines, and hormones such as M-CSF, monocyte chemoattractant protein 1, ILs (IL1, IL2, IL6, IL10, and IL13), HGF, intracellular adhesion molecule 1, indoleamine 2,3-dioxygenase, human leukocyte antigen, prostaglandin E2, and TGF- β ^[11,19,25,82] are secreted from MSCs. Although pro-inflammatory cytokines such as IL1 β , IL6, IL8, and IL9 are also secreted by MSCs, the balance between these anti- and pro-inflammatory cytokines are essential for regeneration of the damaged tissue area^[19]. MSCs differentiate themselves to provide the comprehensive types of the body cells such as cardiomyocytes, hepatocytes, fibroblasts, and neural cells, chondroblasts, chondrocytes, osteoblasts, and osteocytes and have shown their potential in bone regeneration and other tissue regeneration^[78,83]. Although bone has the unique capacity to regenerate and repair itself, bone regeneration is improved when stem cells are used. Although osteoblasts and multipotent cells are available as sources of bone regeneration, exogenous stem cells secrete bioactive molecules that regulate the behavior of osteoblasts and resident MSCs. Importantly, for large and significant skeletal defects, stem cell/MSCs are cultured or seeded on a suitable scaffold/carrier that modulate bone growth. Thus, bone tissue engineering is significant for bone regeneration, especially with trauma or

Table 3 Stem cell transplantation therapy in disease

SCT	SCT therapy in preclinical condition
BMCs	Myelofibrosis ^[116]
HSCs	Fanconi anemia ^[117] , chronic granulomatous disease ^[118] , and Friedreich's ataxia ^[119]
MAPCs	Myocardial infarction ^[120] , and neonatal hypoxic-ischemic injury ^[121]
MSCs	Musculoskeletal disease ^[122] , spinal cord injury ^[123] , liver fibrosis ^[124] , idiopathic pneumonia syndrome ^[125] , Alzheimer's disease ^[126] , and Parkinson's disease ^[127]
	SCT therapy in clinical condition
BMCs	Post-myocardial infarction ^[128] , and sickle cell diseases ^[129]
HSCs	Sickle cell disease ^[130] , human cytomegalovirus infection ^[131] , childhood acute t-lymphoblastic leukemia ^[132] , ankylosing spondylitis autoimmune disease ^[133] , Crohn's disease ^[134] , SARS-CoV-2 ^[135] , refractory lupus nephritis ^[136] , Pemphigus disease ^[137] , Richter syndrome ^[138]
MAPCs	Parkinson's disease ^[139]
MSCs	Graft vs host disease ^[140] , diabetes mellitus type 2 ^[86] , spinal cord injury ^[141] , SARS-CoV-2 ^[142] , multiple sclerosis ^[143] , systemic lupus erythematosus ^[144]

BMCs: Bone marrow cells; HSCs: Hematopoietic stem cells; MAPCs: Multipotent adult progenitor stem cells; MSCs: Mesenchymal stem cells; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SCT: Stem cell transplantation.

tumor resection defect^[84]. Implants (stem cell/scaffold) used in bone tissue engineering have shown good implant integration results, no late fractures, and long-term durability. Successful tissue engineering depends on several important factors including biocompatibility, scaffold chemistry/ surface properties, porosity, pore size, scaffold surface architecture, osteoinductivity of scaffold and cell number, passage of cells, physiological and developmental "state" of seeded MSCs^[85]. Osteoblasts are already committed to bone lineage with a limited number of divisions and differentiate into osteocytes that maintain structural bone integrity. Importantly, osteoclasts can also be generated from monocytes and macrophage lineage of HSCs^[43]. Osteoblasts communicate with HSCs through various signaling, including Notch signaling, Bmp-1/Bmp-1 receptor signaling, parathyroid/parathyroid receptor signaling, and Wnt-catenin signaling that has Ca²⁺ signaling as the few determinants. Osteoblasts secrete various factors, including G-CSF, angiopoietin, and osteopontin. These factors involve regulating HSC activity and expansion and maintenance of the microenvironment for specific functioning of stem cells. HSC and osteoblast cell populations constitute the osteohematopoietic niche, also known as the osteoblastic niche or endosteal niche, which maintains the proliferation, migration, quiescence, and specific functioning of HSCs^[41]. MSC characteristics, comprising self-renewal, multipotency, differentiation properties, availability, immunomodulatory properties, and little ethical concern make them a potential candidate for regenerative medicine^[21,78,86].

CONCLUSION

Future aspect (MSCs and coronavirus disease 2019)

Coronavirus disease 2019 (COVID-19) is a new global public health concern. This disease is caused by the novel coronavirus or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)^[87]. Coronavirus, a positive-stranded RNA virus, uses surface spike protein (has two important subunit S1 and S2) for binding to the angiotensin-converting enzyme 2 (ACE2) receptors on the host cell surface and mediate its entry into the host cells. S1 subunit mediates the attachment, and the S2 subunit is responsible for membrane fusion and internalization of the virus. Lungs, having alveolar epithelial cells, are most affected by the SARS-CoV-2 infection because these cells have a high propensity of ACE2 receptors. The SARS-CoV-2 disease generates pro-inflammatory cytokines and chemokines storm, which cause severe inflammation. Inflammation is the driving power that leads to coronavirus infections such as severe shock, and multiple organ failure results in acute respiratory distress syndrome^[88,89]. Another study showed that COVID-19 patients (mild to severe) showed low serum Ca²⁺. Low serum Ca²⁺ indicates that Ca²⁺-balance is the primary target of

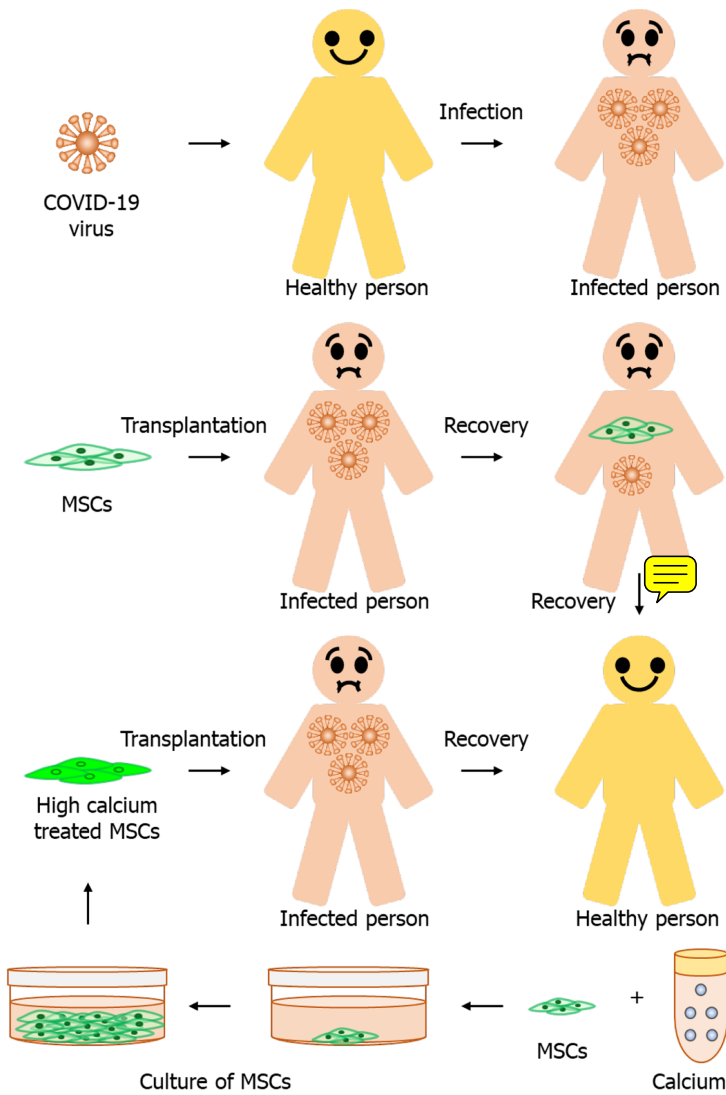


Figure 4 Treatment of coronavirus disease 2019 patient. We hypothesize that calcium-treated mesenchymal stem cells (MSCs) are a better option to counter the coronavirus's inflammatory storm response, treat the coronavirus disease 2019 (COVID-19) patient, and other deadly diseases.

COVID-19. Ca²⁺ balance, a biomarker of clinical severity, is associated with virus-associated multiple organ injuries, and an increase in inflammatory cytokines^[90]. Ca²⁺ channel blockers, also called antihypertensive drugs such as ACE inhibitors and angiotensin II receptor blockers, inhibited the post-entry replication events of SARS-CoV-2 in vitro. In clinics, antihypertensive medications (along with chloroquine) are widely used to treat the Coronavirus disease. This study showed that Ca²⁺ is very crucial for the Coronavirus infection^[87].

MSCs could be a solution for COVID-19 because MSCs transplantation generates tissue regenerative favorable microenvironment and inhibits the immune response activated by virus infection by modulating immune cells and the production of regulatory cells. MSCs also express several interferon-stimulated genes, ISGs (interferon induced transmembrane family), SAT1, IFI6, PMAIP1, ISG15, CCL2, p21/CDKN1) against viral infection. Apart from immunomodulatory properties, MSCs can be isolated from various sources, stored for future use, and have a less ethical concern. Since MSCs did not show any adverse side effects on the patient. Thus, MSCs could be a regenerative medicine for life-threatening diseases. Transplantation of MSCs into COVID-19 patients was studied in China that showed some promise in the treatment of COVID-19, but it is not recommended in other countries. Moreover, to date, MSCs used in 17 clinical studies and 70 trials have shown positive results in treating respiratory disorders. Since MSCs did not show any adverse side effects on the patient. Thus, MSCs could be a regenerative medicine for life-threatening diseases^[88,91] (Figure 4).

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