Chapter 6

Mesenchymal Stem Cells: A Future Option for Intervening Disease Management

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Abstract

Regeneration, revitalizing and reversal (RRR) are the primordial functions of the stem cells in the field of regenerative medicine. Though there are several cases of successful stem cell transplantation the reversal of metabolic diseases and the acquired secondary complications like chronic renal failure, neuropathy, stroke or vascular diseases are not well studied. The transplanted cells in many cases failed to home or graft in the host with no reason to attribute for such failures. Therefore, it becomes necessary to address these secondary complications with cellular therapy. The oxidative stress of the cells and tissues are attributed to the hostile microenvironment, not suitable for the survival of newly recruited cells. From our few animal studies and published literatures sources elsewhere, we foresee a huge potential for using mesenchymal stem cells (MSCs) to initially combat the secondary cardiovascular and neuronal complications in the management of the metabolic diseases. However, not all the stem cells have been tested in these lines, and further we do not know, whether all the progenitor cells from various sources and origin will behave like MSCs, which needs to be studied extensively.

Keywords: mesenchymal stem cells (MSCs), secondary complications, metabolic diseases, microenvironment

1. Introduction

In the past 4 decades of cell therapy, many hematological diseases, both malignant and non-malignant origin, have been treated with wide success, prominently with hematopoietic stem cells (HSCs) [1]. With the growth of regenerative medicine and stem cell research, various other sources of the progenitor stem cells have been identified at different niches

of the organs, and few of them are well characterized and tested for its ability to be better performing than HSCs in general. Mesenchymal stem cells (MSCs) are one such progenitor population identified and well characterized for their ability to differentiate in a rigid stress environment like oxidative stress or reperfusion injury, which would usually kill the cells or tissues [2]. There has not been enough investigation on the response of stem cells or progenitor cells in general to the stimuli of biological or mechanical origin in-vivo. Some of our experiences and literature evidences [3] have shown $[Ca^{2+}]_i$ playing a major role in the death or survival of the stem cells through oxidative stress observed at the site of pathological manifestations [4, 5]. Recent studies have shown the involvement of the mitochondria by its Ca^{2+}-buffering homeostatic mechanisms to be largely playing a role in cell sustenance toward survival and differentiation [6]. Much was taught on the stem cells regenerative capacity by grafting, homing and repairing by differentiation of the transplanted stem cells. However, for many years, there was no mechanistic definition for the failure of the stem cells other than physiological parameters like viability of the cells or volume of the cells used in the transplantation [7–9]. The microenvironment which largely supports repair by mobilization of the MSCs or in general the progenitor stem cells required experimental evidence on the survival time, dose, frequency and preconditioning of the repair area. In many cases, the stress is characterized by the irregular Ca^{2+} homeostasis resulting in triggering of destructive signals like oxidants and transcription factors responsible for the eventual cell death [10]. Further physiologically normal Ca^{2+} signaling is an essential part of the cell growth and differentiation, and when the homeostasis is challenged, the Ca^{2+} acts as a trigger of self-destruction in the matured cells [11, 12]. The role of Ca^{2+} in the progenitor cells may induce signals of survival as observed in the tumor microenvironment, which might result in the destruction by the host cells. **Table 1** gives Ca^{2+} channels associated with the MSCs. It can be noted that MSCs offer a good threshold to these cellular factors resulting in the sustained survival. However, these Ca^{2+} thresholds are broken when the disturbance of the cellular Ca^{2+} is transferred to mitochondria, resulting in the loss of the mitochondrial membrane potential ($\Delta\psi_m$) and leading cellular ROS (cROS) mediated to mitochondrial ROS (mROS) and thereby apoptotic signals skewing the cells toward death phenotype [3, 5]. Cellular mechanisms like survival, death or differentiation require a clear understanding on the normal calcium homeostasis, thereby equilibrium between $[Ca^{2+}]_c$ and $[Ca^{2+}]_m$ existing within the cells [13]. Cells of different tissue origins and physiological functions differ in their ability to respond to these stress signals while general speculation is that progenitor cells, either resident at the niche or mobilized to the site of damage, usually have higher threshold which makes its activity of regeneration successful [14]. There are studies which indicate the dose dependency of the MSCs for successful regeneration, and we speculate that the ability of the MSCs to tolerate the stress at the pathological site is the mechanism behind the dose dependency [15, 16]. However, another dimension of MSC's potential is in the therapeutic modulation of the given disease conditions or at least in animal models, through release of inducible factors without direct involvement of the MSCs by division or differentiation [17, 18]. In such cases, the tissue revival post MSC treatment shows no trace of the transplanted cells by the common tracking methods like 5(6)-Carboxyfluorescein diacetate N-succinimidyl ester (CFSE) chase or Green Fluorescent Protein (GFP). Additionally, MSCs are known for their immunomodulation capability and stromal character in the regeneration of the organs and

Channel/receptor	Type of MSCs	Species	Differentiation	Functional expression
Voltage-gated Ca^{2+} channels (VGCC)				
VGCC:LT	AMSCs	Human	Undifferentiated	No
VGCC:LT	AMSCs	Human	Undifferentiated neuronal	No
VGCC:LP/QN	AMSCs	Rat	Undifferentiated neuronal	No/yes
VGCC:LT	BMSCs	Human	Undifferentiated	Yes
VGCC:LT	BMSCs	Human	Undifferentiated	Yes
VGCC:LP/QTNR	BMSCs	Human	Undifferentiated	Yes
VGCC:LP/QN	BMSCs	Murine	Neuronal	Yes
VGCC:LT	BMSCs	Rat	Undifferentiated	Yes
VGCC:L	BMSCs	Rat	Osteogenic	Yes
VGCC:LP/QN	BMSCs	Rat	Undifferentiated neuronal	No/yes
Intracellular Ca^{2+} stores				
InsP3 R RyR	AMSCs	Human	Undifferentiated	Yes
InsP3	AMSCs	Human	Adipocyte	Yes
InsP3	AMSCs	Human	Adipocyte	Yes
InsP3 R1-3 RyR 1-3	BMSCs	Murine	Neuronal	Yes
InsP3RyR	BMSCs	Human	Undifferentiated	Yes
InsP3	BMSCs	Human	Adipocytes	Yes
P2 purinergic receptors				
P2X, P2Y1	AMSCs	Human	Adipogenic osteogenic	Yes
P2XP2Y	AMSCs	Rat	Undifferentiated neuronal	Yes
P2Y2	BMSCs	Rat	Undifferentiated	Yes
P2XP2Y	BMSCs	Rat	Undifferentiated neuronal	Yes
P2Y1P2X	BMSCs	Human	Undifferentiated	Yes
P2Y1	BMSCs	Human	Adipogenic	Yes
Oxytocin (OT) and vasopressin (AVP) receptors				
AVP V1a, AVP V1b AVP V2	AMSCs	Human	Adipogenic	Yes
OT R	AMSCs	Mouse	Neuronal	–
OT R AVP-V1a AVP V2	BMSCs	Rat	Undifferentiated	Yes

Channel/receptor	Type of MSCs	Species	Differentiation	Functional expression
OT R AVP-V1	BMSCs	Rat	Undifferentiated neuronal	Yes
OT R	AMSCsBMSCs	Human	Adipogenic osteogenic	Yes

Abbreviations: AMSCs, adipose tissue derived mesenchymal stromal cells; AVP, vasopressin; BMSCs, bone marrow mesenchymal stromal cells; $InsP_3$, inositol 1,4,5-trisphosphate receptor; LVA, low voltage activated Ca^{2+} channels; OT, oxytocin; OT R, oxytocin receptor; and RyR, ryanodine receptor. **Table 1** is modified and reproduced from the original **Table 1** with written permission from Forostyak et al. [27].

Table 1. Expression of the Ca^{2+} channels in the MSCs.

structural elements in the organ or tissue [19]. There are few reports and studies on the scope and wide use of MSCs in cellular therapy either individually or combined with HSCs, creating a microenvironment for better homing, grafting and differentiation for HSCs [20, 21]. From the above observations, it is clear that alterations in the microenvironment are crucial for MSC's behavior toward differentiation or other modulation properties. Not only changes associated with Ca^{2+} but also changes in the oxygen concentration can alter the MSCs behavior drastically. There is no clear-cut explanation on what makes MSCs unique though it has been well studied for its in-vitro and in-vivo differentiation as well as therapeutic ability without integration or differentiation at the site of transplantation [22]. Few observations like loss of differentiation capacity at higher passages can be dubbed to senescence observed in vivo or in many failure models of MSC cell therapy [23]. Thus, the cellular senescence can be attributed as the MSCs respond to prolonged or higher oxidative stress encountered at the affected tissues [24–26]. But still the promising aspect of MSCs is from their anatomical locations like Bone Marrow (BM), where these cells are at a constant interaction with the immune cells. We do not know whether this aspect of the BM MSCs is responsible of enhanced expression for the cytokine receptors or its functional expression of the inducible soluble factors or its immunomodulatory properties.

However, the scope of the current topic is to check how far the MSCs without any subsect difference are useful as a promising allogeneic source for the functional restoration of the organ or tissues. Addressing the issue of higher threshold for the MSCs to counteract the oxidative stress, It is well known that MSC's immunomodulate the host immune responses and secrete factors for therapeutic amelioration of the disease complications. We do have substantial data to directly relate the ability of secretome for the therapeutic activities with controlled release ex-vivo in regulated bioreactors. In all these aspects, the reactivity of the MSCs in the microenvironment toward various signals decides the survival, differentiation, modulation or the reactivity toward the repair signals.

2. Mesenchymal stem cells react differently to stress pathology

Cellular stress is mostly mechanosensitive or chemosensitive in nature. Many studies have shown that intracellular Ca^{2+} signaling is closely interconnected with mechanical properties of a cell. The flow of calcium from the extracellular matrix (ECM) through mechanosensitive

calcium channels like transient receptor potential (TRP) or Stromal Interaction Molecule (STIM), Ca2+ release-activated Ca2+ (CRAC) channels is closely interconnected to the spatiotemporal intracellular Ca^{2+} signaling (**Figure 1**). Adult differentiated cells exhibit varied calcium dynamics depending on their anatomical location, tissue origins and physiological functions [27]. Cells of cardiac and vascular tissues, for example, withstand more stress, and their Ca^{2+} buffering ability is higher than other cells [28, 29]. There are many studies in various matured cells on the patterns of the Ca^{2+} oscillations regulated by signaling proteomes [30].

Largely, current understanding of mitochondrial Ca^{2+} homeostasis and regulation by the mitochondrial uniporter (MCU), a Ca^{2+} transmembrane protein identified in recent years, have made it more easier in understanding the cell reactivity to the external stress [5, 13]. When the threshold of the cells to withstand the Ca^{2+} oscillations is exceeding the buffering limits, the cells are skewed to death phenotype by oxidative mechanisms [31]. The threshold of the progenitor cells like MSCs makes it unique in understanding the Ca^{2+} homeostasis, for example, human MSCs (hMSCs) exhibit spontaneous Ca^{2+} oscillations, a phenomenon not routine in other matured cells and progenitors with a few exceptions [32] though like other cell types in MSCs Ca^{2+} oscillations are triggered by influx of extracellular Ca^{2+} and release from endoplasmic reticulum (ER) via inositol 1,4,5-trisphosphate receptors (IP3Rs) and ryanodine receptors by calcium-induced calcium release [27]. There are studies that suggest mesenchymal stem cells respond to the extracellular Ca^{2+} levels sensed by calcium sensing receptor (CaSR) in the cell membrane for its proliferation and differentiation [33]. Though low Ca^{2+} levels are favorable for all cells in general, higher Ca^{2+} levels beyond the threshold are detrimental to MSCs. In general, the physiological role of the Ca^{2+} homeostasis largely regulates differentiation, proliferation and cell survival at the site of repair [30]. Studies have revealed the Ca^{2+} handling properties of the precursors are similar to the adult differentiated cells as observed in the neuronal precursors compared with differentiated neuronal cells. There are reports of enhanced Ca^{2+} accumulation in the precursors or embryonic cell types; however, the success of the differentiation largely depends on the microenvironment of the tissue where the progenitors are deployed [34–37]. Further the intracellular compartmentalization and capacity of the various organelles response to heavy $[Ca^{2+}]_i$ is another factor, which might be a factor for sustained survival of the transplanted MSCs. The apparent Ca^{2+} threshold of cells $[Ca^{2+}]_i$ per say basal or resting is ~50–100 nM. These physiological levels of the $[Ca^{2+}]_i$ can rapidly rise to ~1–10 μM on stimulation with mechano or chemosensitive factors [5]. The regulation and balance of Ca^{2+} homeostasis do not stop here when these signals can activate the ER to release the stored intracellular Ca^{2+} which thereby promotes the stress inside cell. The role of the mitochondria and its ability to buffer $[Ca^{2+}]_i$ are several folds higher than the cytoplasmic threshold, and thereby the role of mitochondria cannot be undermined in the survival of the progenitor cells, especially stromal origin cells like MSCs [38]. Hence, the pathological fate of the transplanted or mobilized MSCs does not only depend on the homeostasis of $[Ca^{2+}]_i$ but also on the $[Ca^{2+}]_m$ in evading the stress phenotype for better differentiation and repair [39, 40]. Many studies on the isolated mitochondria suggest that the Ca^{2+} buffering capacity of mitochondria is 100-fold higher than the basal or resting $[Ca^{2+}]_i$ or intracellular release on the stimulation of Ca^{2+} release in the cytoplasm [41–43]. This phenomenon is observed during the physiological stress arising due to ischemia or reperfusion and can be experimentally induced with a known Ca^{2+} agonist like histamine or thapsigargin.

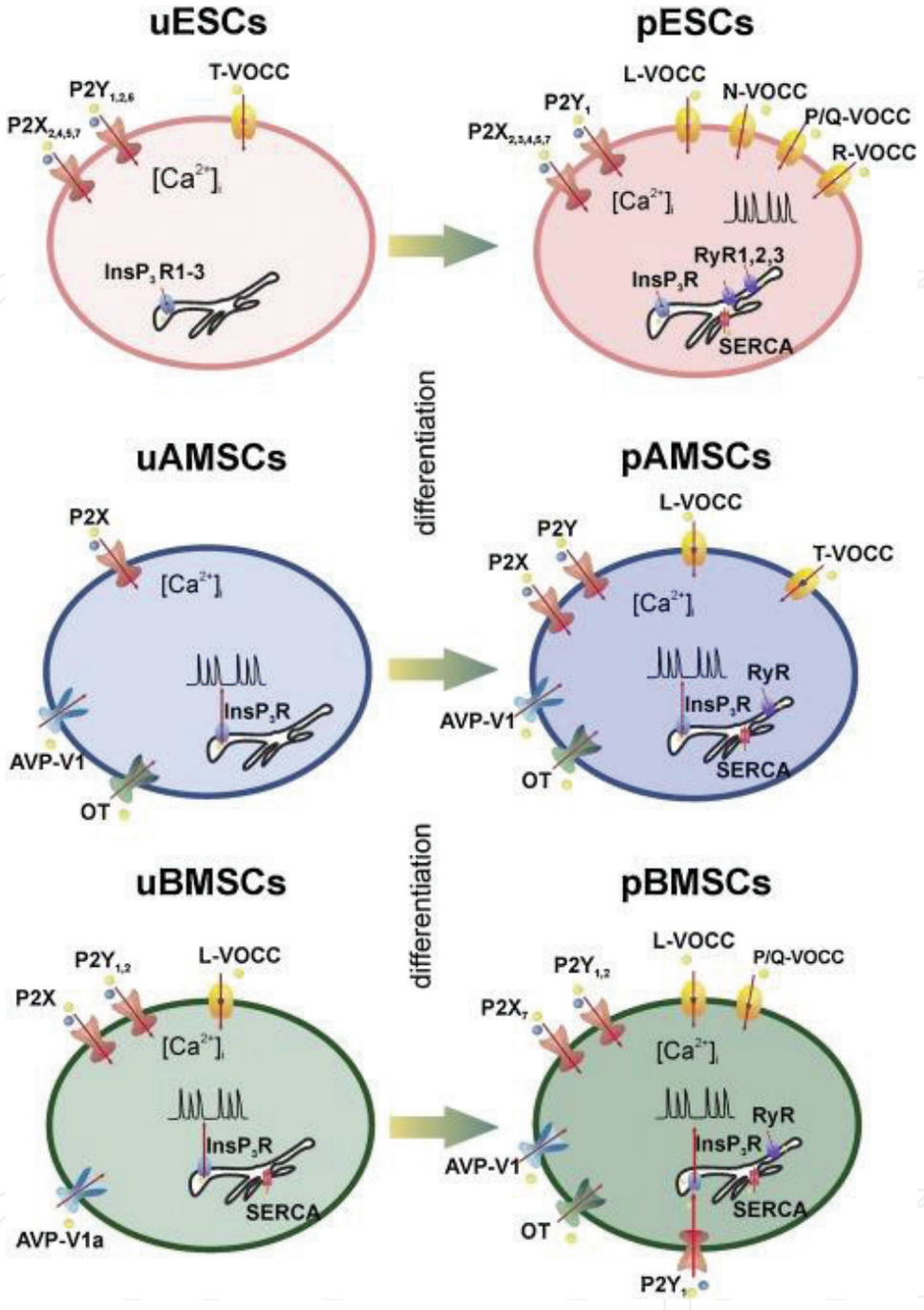

Figure 1. A schematic drawing showing the functional expression of Ca^{2+}-sensitive channels and receptors in ESCs, AMSCs and BMSCs. In particular, VGCC, InsP3, inositol trisphosphate receptors (InsP3R), RyR, P2 purinergic, vasopressin and oxytocin receptors, as well as spontaneous Ca^{2+} oscillations and sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA pump), are shown. Reproduced with written permission from Forostyak et al. [27].

3. Mechanism behind the mesenchymal stem cell repair

Traditional understanding on therapeutic properties of the MSCs or any type of progenitor stem cells is by direct homing, differentiation and repopulation with the normal phenotype tissues at the site of pathology [1]. However, in some cases, the transplantation is not successful and does not have a clear-cut reason for such failure in spite of all favorable

pre- and pro-clinical parameters [44]. The current understanding on the mechanism of the MSC therapy, when supplied exogenously, is homing at the sites of injury and differentiates into adult cell type. In few cases, though we do not know the fate of the MSCs post transplantation or do not follow the traditional understanding, however, the lesions are healed. These phenomena opened a new area of insightful research on what actually the MSCs do at the niche apart from proliferation and differentiation at the site of tissue damage. The term microenvironment simply implies on suitable or favorable conditions promoted by recruited progenitor MSCs at the site of pathology [45, 46]. Transplanted MSCs release soluble factors like cytokines, chemokines, interleukins, secondary messenger molecules and insoluble or physical factors like biomechanical forces, ions and so on for the cell survival. The released factors not only modulate cell death but also induce pro-survival mechanisms. These factors further enrich the tissue repair mechanisms reversing the pathology [18, 47]. The question of the resident stem cells and their failure to resolve the pathology is another important area which is unclear. In case, if the microenvironment is unfavorable for the resident or mobilized progenitor cells, how far can the transplanted cells create a conducive environment to sustain the hostile tissue for repair? There are few well-documented studies, which show the micro-physiology of the microenvironment, like changes associated with oxygen concentration and physiological stress, which can strongly affect the behavior of the MSCs [48–50]. The other factors, which affect the microenvironment, are the immune cells and other soluble and insoluble factors. These altogether affect the desired outcome of the transplanted stem cells. The local immune response to the MSCs results in the induction of the inflammatory mediators, which are not favorable for the MSCs to divide or differentiate [51, 52]. Therefore, microenvironment plays a crucial role in the success of therapeutic MSCs.

Basically, for any cell to act or react, stimuli or cell-to-cell interactions are required [53]. There are many modes by which these interactions or signal transmissions can take place. Further, these signal transmissions are different with the normal or pathological scenario. One explanation is that the release of the cytokines like IL-6 and Vascular Endothelial Growth Factor (VEGF) can induce pro-survival and oppose apoptosis as observed in the tumor microenvironment [54]. The best-explained mechanism is inter- and intra-cellular transmission of the mechanical stimuli, which affect the gene expression of the pro-survival factors [55]. It is unclear how the mechanical forces are tuned into biological signals of life and destruction. Further, these mechanostatic forces are responsible for large number of transcriptional gene regulations affecting the progression or repair of the tissue pathology. Many studies have explained the link between the mechanical stimuli and the Ca^{2+} homeostasis [56, 57]. Mechanical stimuli activate the Ca^{2+} from the ER within the cells or potentiate the entry of extracellular Ca^{2+} which further triggers the transcriptional regulation of the pro-survival cellular factors [58].

The repairing capabilities of MSCs have been reported in various tissues, including the brain, heart, kidney, pancreas and skin [59–62]. The mechanism through which the MSC-mediated tissue regeneration may vary from type of injury or tissues involved. For an instance, the increased expression of stromal cell-derived factor 1 (SDF-1) at the site of injury can attract the MSCs to the injured tissue [63, 64]. The expression of C-X-C chemokine receptor type 4 (CXCR4) by MSCs regulates the adhesion of MSCs to endothelial cells. This has been shown to be a critical step for MSCs to migrate to the target tissue. Thus, the expression of the CD184

(Fusin) is important to expedite the interaction between SDF-1 and CXCR4 system, which play an important role in the survival and migration of bone marrow stromal cells after transplantation into mice cerebral infarct [64]. MSCs can enhance the angiogenesis at the injured tissue, where the level of TGF-β1 is dramatically increased. TGF-β1 is known to stimulate the synthesis of VEGF in MSCs in order to promote the angiogenesis [65] which may augment the endothelial progenitor functions. Formation of new tissues and organs in the embryo requires the transitions from mesenchyme into epithelium that is the mesenchymal-epithelial transition [66]. We cannot speculate whether such a property of the mesenchymal-epithelial transition is observed at late progenitor stages of the MSCs. Further, such activity needs to be clearly elucidated.

Capabilities of MSCs to differentiate into hepatocytes, insulin-producing cells, neural cells, osteoblasts, chondrocytes, adipocytes, fibroblasts and so on are well documented and reproducible by many studies [67]. These properties are not only observed in in-vitro conditions but also in some in-vivo small animal studies, which have revealed the transformation (differentiation) of the MSCs into adult lineages [68]. These are further explained with the presence of the tracker-like GFP [69], indicating the newly formed cells with the presence of the GFP. In human studies, many types of the MSCs expressing pancreatic duodenal homeobox 1 (*Pdx1*) gene have been shown to differentiate into insulin-producing cells or functions of pancreatic β cells [70]. There are many studies showing successful regeneration of skeletal tissues such as bone, cartilage, tendon and intervertebral discs from various sources of MSCs, including MSCs from the foreskin and dental pulp [71–74]. In some preclinical studies, a set of MSCs expressing exogenous glial cell-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) have shown to reduce stroke-induced lesion volume and further improve neovascularization [75, 76].

There are undoubtedly many in-vitro and in-vivo studies addressing the direct repair potential and the uses of providing conducive environment for the repair by the MSCs. What needs to be addressed here is whether all the subsets of the MSCs located at various anatomical niches are capable of performing the repair irrespective of their small deviations in the surface marker expression. Looking at the other functions of the MSCs, such as immune suppressive or modulatory effects, the therapeutic infusions of MSCs in experimental models of autoimmune encephalomyelitis showed reduced infiltration of T cells and macrophages followed by a reduction of demyelination in the brain and in the spinal cord [77–80]. Repeated administration of MSCs derived from a patient's mother completely cured a young patient suffering from severe grade IV graft-versus-host disease (GVHD); this is another observation, which clearly showed modulation of the properties of the infused MSCs paving a way for another dimension of the MSCs repairing property [21].

4. Mesenchymal stem cells: A tailor-made therapeutic approach in the future of medicine

Today, there is a growing need for novel technologies to restore, maintain and enhance organ function. Since the 1990s, stem cells have originated as a novel therapeutic option for

regenerative medicine. Human embryonic stem (ES) cells, mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSC) have appeared as potential sources for therapeutic intervention for future.

There has long been a need for unique approaches to challenge the world of diseases and disorders. The skeletal tissue damage is one such clinical condition which requires restoration, maintenance and enhanced organ function. The use of skeletal-derived stromal cells (MSCs) is a better option and an attractive choice. Though human ES cells, MSCs and iPSCs are regarded as potential sources for regenerative medicine and tissue engineering applications [81], they remained predominantly in the realm of laboratory-based in vitro investigation and in vivo animal modeling; however, more recently, a number of research centers have bridged the translational gap, from bench to clinic with few successes. Although the potential of MSCs to regenerate various tissues is known, it is increasingly renowned that the MSCs can exert immune and inflammation modulatory effects [82] through a large number of secreted bioactive factors including anti-scarring, angiogenic, anti-apoptotic as well as factors enhancing tissue remodeling [83, 84]. This mechanism may elucidate the interesting observation of the presence of therapeutically relevant outcomes of MSCs after systemic or local transplantation in a number of tissue injury models, for example, ischemic brain injury and myocardial infarction in the presence of low tissue engraftment of MSCs [85]. Though we do not know the success of these cases in humans, it is still promising unless trials are initiated in these areas of translational research.

The number of the clinical trials using MSCs till 2017 is furnished in **Figure 2**. Interestingly, both autologous and allogeneic MSCs have been employed in these studies as they are believed to be less immunogenic. According to National Institutes of Health (NIH) clinical trials database, predominantly bone and cartilage regeneration (23%), neuronal (21%), cardiovascular (16%) and autoimmune disorders [9] have been highly focused among other therapeutic approaches using MSCs.

The source and environmental niches are playing the critical role on MSCs; they have to be considered while studying their biological activity and clinical applications. Furthermore, the continuous search for novel and potent sources that might be suitable for specific regenerative applications is needed. Recently, we compared the MSC-like cell populations obtained from alternative sources: the human adipose tissue, adult skin and newborn foreskin, with the standard phenotype of human bone marrow MSC. Our whole genome analysis has revealed a common MSC molecular signature composed of 33 CD markers including known MSC markers and several novel markers, for example CD165, CD276 and CD82. MSCs obtained from different sources exhibit significant differences in their proliferation, multipotency and molecular phenotype, which should be considered before applications in the clinical protocols [86]. The skin-derived stromal cells have shown the endothelial lineage differentiation in-vitro, and the angiogenic role with potential contribution to blood vessel formation in ex-vivo Chorioallantoic Membrane Assay (CAM) model is an excellent start for the pre-clinical considerations for the skin-derived MSCs. Therefore, human skin stromal cells are valuable resources that might be useful in applications requiring enhanced angiogenesis or in areas such as ischemic diseases [87–89]. Furthermore, these cells could be employed in tissue engineering and cell-based therapy in which vascularization is an essential component.

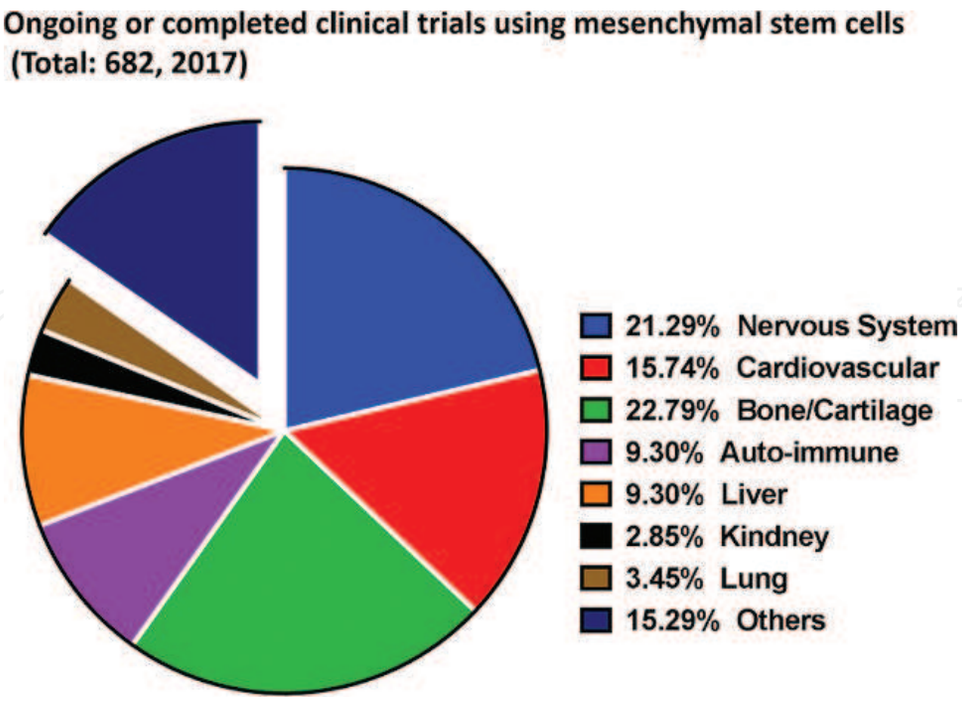

Figure 2. A pie chart showing the ongoing and/or completed clinical trials with MSCs (total of 682, 2017), adapted from http://clinicaltrials.gov.

Currently, several MSC-based therapeutic protocols are being tested in an increasing number of clinical conditions in phase I/II and III clinical trials. At the website of the National Institutes of Health, the USA (http://clinicaltrials.gov), overall, till 2017, the status pertaining to hMSCs-based clinical trials shows 682 studies and in that 438 were closed (including completed, 168, and withdrawn 12), 134 are unknown and finally 244 are under recruiting conditions. Results from these clinical trials are expected to have major impact on the treatment of several disease conditions.

Much progress has been made over the last decade in stem cell technology, and a steady stream of clinical applications and trials have followed on these advances. However, the approaches outlined above provide only limited evidence of current status [90, 91]. To date, there remains a paucity of randomized controlled trials to demonstrate the efficacy of many of these tissue-engineered/stem cell approaches. Thus, to date, it is difficult to recommend any of these strategies as standard therapy. Nevertheless, advances in basic research as well as from clinical trials of MSC-based therapy are expected to provide options for therapeutic interventions for tissue regeneration in multiple organs that will address the current unmet needs of an increasing number of patients suffering from age-related degenerative diseases.

5. Conclusion

Though MSCs have shown some promising therapeutic and transplantation potential, its use in regenerative medicine is primitive. In many aspects of the therapeutic approach, the results

of the MSC applications are varied as well as affirmative, suggesting that more research needs to be carried out. The critical feature of the MSCs is their activation in the microenvironment or modulation of or by the host immune system, which makes it much more difficult to understand and study the mechanism of regeneration. There are various opinions on the route of administration of MSCs like in vivo, or local transplantation on site of the organ on the tissue repair is still a subject of debate. Many studies cited in these chapters are individual observations at various centers and still need translation to bedside from the bench. The few clinical trials listed are at different phases and collectively may require more time for MSCs successful clinical applications.

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