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The Roles of Mesenchymal Stem Cells in Tissue Repair and Disease Modification

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Abstract: Mesenchymal stem cells (MSCs) are multi-potent cells which have been widely used for tissue regeneration and immunomodulation. The infusion of autologous and allogenic MSCs has been proved to be safe and effective in tissue repair and disease modulation. The inherent homing ability of MSCs ensures the transplanted cells migrating into the damaged tissue areas, but only a small percentage of the transplanted (allogenic) MSCs survive for long. However, the beneficial effects of MSCs transplantation could be noted within 1-2 days that are unlikely due to their proliferation and differentiation. The regulatory roles of MSCs in tissue repair are rather more important than their direct involvement of repair processes. The most important effect of transplanted MSCs is their immunomodulation function through crosstalk with the immune cells or the paracrine actions. The active factor secreted by MSCs may vary in the different disease conditions or tissue niches, and are under dynamic changes in various local environments. To understand and define the MSCs secretion factors in various disease settings could be a future research direction, and the findings could lead to potential new MSCs-based therapeutic products.

Keywords: Fate, immunomodulation, mesenchymal stem cells (MSCs), secretive factors, transplantation.

INTRODUCTION

Mesenchymal stem cells (MSCs) are multi-potent cells which have the ability to differentiate into multiple cell types, including osteoblasts, chondrocytes, and adipocytes [1]. It also has been proved that MSCs have the potential to differentiate into neural cells [2], germ cells [3], cardiomyocytes [4], etc. The history of MSCs could be traced back to 1970 when Friedenstein and his co-workers first isolated and cultured fibroblast-like clonogenic stromal cells from bone marrow which are multi-potent progenitors [5]. These cells can be easily expanded and promote tissue repair. Thus, the use of MSCs has been an innovative approach in treatment of various diseases. Currently, there have been more than 300 clinical trials using MSCs listed on the website of the United States National Institute of Health [6].

The International Society of Cellular Therapy has made a definition of MSCs based on three minimal criteria: First, these cells can be plastic-adherent in a standard condition; second, these cells express CD105, CD73 and CD90, and lack of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecule; third, these cells can be differentiated into osteoblasts, adipocytes and chondroblasts [7]. Recently, researchers have proved the potential of using MSCs for different organ regeneration and immunoregulation. The effects of MSCs treatments is contributed by the following factors: 1) secretion of growth factors and cytokines [8, 9]; 2) support for other cell types during tissue regeneration [10-12]; 3) immunomodulation properties [13, 14]; 4) differentiation into specific cells for damaged organ tissues [15, 16] (Fig. **1**). However, the cellular effects and the trace of MSCs after restoring transplantation appear to be lack of consideration and remain inconclusive [16-18].

Transplanted MSCs can be labeled with different markers, and tracing of transplanted MSC cell lineage can be based on polymerase chain reaction [19, 20], Y chromosome staining [21], green fluorescent protein labeling [22, 23] and so on [24, 25]. With the development of cell tracking technology, new methods like *in vivo* imaging techniques can be used for deep tissue and long-term tracing [26, 27]. It has been proved that systemic injection of MSCs reaches the lungs before redistributed to the liver, bone marrow and other organs [28]. In order to gain some insight into the fate and effects of transplanted allogeneic MSCs, we have reviewed available literatures and focused on function and fate of *in vivo* transplantated allogenic MSCs.

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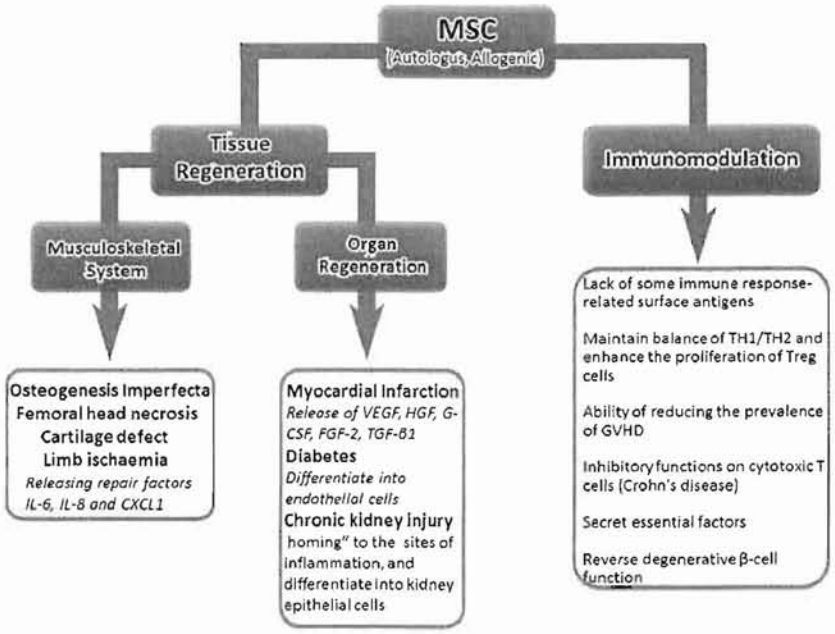

Fig. (1). Diagram illustrates the applications of autologous and allogenic MSCs in tissue regeneration and immunomodulation, and their potential underlying mechanisms.

The Tracking Methods of MSCs *In Vivo*

In vivo imaging and labeling methods are important tools for tracking cells. Fluorescence imaging is a suitable and easy way for visualizing labeled cells both *in vitro* and *in vivo*. The green fluorescent protein (GFP) transgenic animals and cells, which can be seen in a dark environment, were most widely used for cell transplantation experiments after first produced by Okabe in 1997 [22]. Although GFP has been documented to be biologically inert, it may cause dilated cardiomyopathy in GFP transgenic mouse [23]. DNA binding dyes like DAPI can provide a fluorescence imaging after staining and be applicable for live cell labeling [29]. But, DAPI has been proved to have growth-inhibitory effect on MSCs and possess ability to affect MSCs differentiation [30]. Transplanted cells can also be stained and tracked with red fluorescent Dil [31, 32]. While these labeling methods need an additional staining progress during resuspension and cannot be tested by bio-assay.

Another approach for tracking MSCs is to overexpress some reporter genes, then using specific antibody against the gene products incorporated in the genomic DNA such as bromodeoxyuridine (BrdU), β-galactosidase, luciferase and thymidine kinase [33, 34]. Other means of more advanced techniques have also been developed in order to track a long-term changes of the transplanted MSCs *in vivo*. Magnetic resonance imaging (MRI); single-photon emission CT (SPECT) and positron emission tomography (PET), are very effective ways to obtain three-dimensional image *in vivo* and some of these technologies have been successfully used for therapeutic tracing of transplanted cells [35]. Contrast reagents are needed for tracking cells, such as lanthanide chelates [36], superparamagnetic iron oxide [37], micron-sized iron oxide particles [38], some unique tracer dye [39] and others [40, 41]. Yet these methods still face many challenges like false positive signals, lack of whole body scan or a fast tracer decay [42]. Recently, a lineage tracing system has been employed to investigate the neuronal commitment role of MSC [43]. In this system, Cre is driven by a lineage specific promoter. Meanwhile, on the other cassate, followed Rosa26 promoter is a stop codon flanked by loxp sites and a report gene (LacZ). A very delicate example is simultaneously elaborate multiple fluorescent protein [44] based on different Cre-loxp combination. By changing the promoter sequence before Cre protein, this system could be a very flexible and useful method to trace the role of MSC in varies model and circumstance. Although all present image technologies of cell tracking have different disadvantages [45], there is no universal tracer for MSCs tracking *in vivo*, and to choose a most reliable way of labeling the transplanted MSCs is essential for studying the fate and function of MSCs *in vivo*.

The Use of MSCs in Repairing of Musculoskeletal System

The gold standard for clinical treatment of large musculoskeletal tissues injury is to restore or replace the damage tissues through surgical procedures. Numbers of therapies have been developed for managing bone defects, and it is clear that the bone formation or the healing of the defect can be enhanced by MSCs cell therapy. However, none of current therapeutic treatments have proved to be fully successful [46]. There are multiple ways of cell implanting during tissue regeneration, together with vehicles or scaffolds which are also known as systemic application or local application. The survival of cells after implantation and the total number

of cells delivered are the key factors of success [47]. But results from most studies proved that only 5% of transplanted cells survived after 2 weeks of their administration.

In 1999, Horwitz and his co-workers has proved the therapeutic effects of transplantation of allogeneic MSC into three children with osteogenesis imperfect [48]. This study also demonstrated the migrating capacity of allogeneic MSC which lead the transplanted MSCs migrating to the bone in these osteogenesis imperfecta children. This ability was first known as the "homing" capacity which marrow-derived MSCs can migrate and incorporate to musculoskeletal tissues of the recipient animals [49-51]. The following studies suggested that the mobilization of autologous MSCs can be induced by trauma [52]. And researchers also determined that the transplanted MSCs can migrate to the injury area. MSCs expressing *Firefly luciferase* were systemically injected into the mouse with stabilized tibia fracture. 1 day after transplantation, MSCs were found in the lungs. The MSCs started to localize in the fracture area on the day 3 of transplantation and this fluorescence lasted about 14 days. The following study confirmed this "homing" capacity is dependent on the presence of CXCR4 and the cell number reached a saturation point on day 7 of transplantation. The histology and mechanical analyses confirmed the improvement of fracture healing by more cartilage and newly mineralized bone formation [53].

In another study, researchers intravenously injected allogeneic MSCs into femoral head necrosis animals and traced for 6 weeks. Labeled MSCs reached the peak point at 6 weeks in the necrotic area of femoral heads while these cells were not seen after 2 weeks after transplantation in normal animals [16]. Trauma condition stimulated the migration of MSCs have also been confirmed conditions in other animal models such as brain injury, lung injury, liver injury and burn injury ect [54-57].

Chondrogenic differentiation is important characteristic of MSCs. The underlying mechanism using MSC cartilage repair are: (1) MSCs attenuates inflammatory reaction at the injury areas; (2) cartilage injury area defects replaced by chondrogenic MSCs [15]. A fluorescent dye CMTMR [5-[[[4-chloromethyl]benzoyl]amino]-tetramethylrhodamine] was first used by Quintavalla to label goat MSCs and implanted into the cartilage defect area with loaded on gelatin sponge scaffold [58]. During 14 days of implantation, the number of fluorescence labeled MSCs reduced over time. The implanted MSCs are found around the defect area and 6 mm away from the original defect. Compared with the scaffold cultured *in vitro*, over 70% of cells released from the implanted scaffold showed no fluorescence indicating that cells from the underlying bone marrow or the surrounding environment were recruited into the sponge scaffold during the healing progress. The cartilage healing cannot complete through implantation of allogeneic MSCs alone. Another study used DiI-labeled MSCs to repair the cartilage defect in pigs. Labeled cells were seen in the defected area at 1 week, but not at 4 and 12 weeks. The cartilage repair progress lasted for at least 3 months, so that the transplantation of allogeneic MSCs may act indirectly paracrine releasing repair factors for improving cartilage repair rather than directly repair the defect area [18].

Local injection of MSCs directly into the ischaemic area is a potential treatment for arterial occlusion and the limb ischaemia. In a pilot study, autologous bone marrow-mononuclear cells were injected locally into the ischaemic limbs. In all 45 legs, ankle-brachial pressure index level, transcutaneous oxygen pressure, rest pain and pain-free walking time were all significantly improved in 4 weeks and sustained at 24 weeks. The enhanced angiogenesis was due to the secreted angiogenic cytokines and the improved function of endothelial cells [59]. Lian also found MSCs, derived from human pluripotent stem cells, have the significant therapeutic efficacy in limb ischemia model of mouse [60] which indicated that the function of transplanted MSCs can successfully apply across species.

It was confirmed that the secreting of IL-6, IL-8 and CXCL1 from MSCs is important for enhancing function [9]. In diabetic rat models, the ischemic muscle metabolism neovasculogenesis were improved following MSCs transplantation and incorporation of MSCs to vessels was not observed, suggesting that neovasculalization induced by transplantation should be mediated through paracrine factors [61]. Another study confirmed that MSCs expressed and secreted higher level of bFGF, VEGF-A, IL-6 and IL-8 under hypoxic condition which can induce angiogenesis, cell migration, proliferation and so on [8]. Further study confirmed that transplanted MSCs could reduce the cytotoxicity and accumulation of natural killer cells under such hypoxic situation [62]. There were reports that MSCs could secret some crucial growth factors like BMP-2 for osteogenesis during bone healing progress; TGF-β for chondrogenesis during cartilage healing, etc. MSCs could also secrete many cytokines that could regulate inflammatory responses during injury. It is unclear which ones of these paracrine factors are the most important factors as they are mixture and constantly changing. During the regeneration of organs, the regulatory function of MSCs is more complex, and the factors secreted by MSCs are dynamic and responsive to the local environment.

The Use of MSCs in Organ Regeneration

The use of MSCs transplantation for treating lung [63, 64], liver [65, 66], heart [67, 68] and brain injury [69, 70], has been tested in animal models. The therapeutic mechanisms are mainly due to modulating against the inflammatory responses while the engraftment or differentiation properties of MSCs were not involved [71-74]. GFP-labeled MSCs have been found crossed the blood–brain barrier and then engrafted to injured areas the hippocampus in rats [74]. The results suggested that the implanted MSCs can survive only a short-term in the brain (20 days) but promote a long-term change in hippocampal plasticity [72]. Results from another study showed that the labeled MSCs accumulated in the lung of rats with pulmonary hypertension compared with normal rats. After 14 days of transplantation, the number of MSCs was decreased from 7.5% to 4.2% indicating that these MSCs cannot survive too long *in vivo* [17].

As the most of organs are greatly vascularized tissues, the co-culturing of endothelial cells and MSCs can maximum simulate the co-existence of cells of normal tissues, which may promote the cell functions during reparation [75,

76]. A higher level of biochemical factors can be easily detected after co-culture *in vitro*, this increasing secretion can also be proved after transplanted *in vivo* [77-79]. The crosstalk of MSCs and endothelial cells or other cells can be bidirectional *in vitro*. The cell-cell interaction function and the higher level of factors can also improve osteogenesis function of MSCs [80].

MSCs have been proved to have therapeutic benefit for myocardial infarction. MSCs secreted factors and regulated the function of cardiomyocytes and immature cells during repair [81-83]. Vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), granulocyte colony stimulating factor (G-CSF), fibroblast growth factor (FGF-2) and transforming growth factor beta 1 (TGF-β1) have been identified as key factors of cardioprotection released by MSCs [84]. Some researchers reported that engrafted MSCs could differentiate into cardiomyocytes *in vivo* after local injection in addition to their secretion of paracrine factors [78, 79]. Following MSCs injection into the heart, most of transplanted MSCs were found in the lungs, liver, and spleen, only a small part of MSCs disperse within myocardium suggesting that the local integration at the injured area may not be necessary in myocardial repair progress [85]. It has been proved that transplantation of allogeneic MSCs was useful for managing acute myocardial infarction and the improved heart function last more than 4 weeks even after the transplanted MSCs disappeared [24, 86, 87]. Benefit of MSCs was also associated with the time and dose of injection [68, 74, 88]. However, large amount of MSCs injection can lead to massive pulmonary infarction and shall be avoided [88]. In 1999, Tomita injected both MSCs and 5-azacytidine treated MSCs were injected into the myocardial scar tissue 3 weeks after cryoinjury on the left ventricular wall, and found that only 5-azacytidine treated MSCs can inhibit ventricular scar formation and improve the contractile function, the MSCs transplantations have been proved to increase the capillary density [89]. But 5-azacytidine pre-differentiated MSCs increased their immunogenicity and only survived in the first few weeks, while the untreated MSCs could exert a longer-term survival [90]. The transplanted MSCs were capable of increasing blood vessel density and blood flow which are beneficial in protecting the myocytes from further ischemic damage [91]. A significant increase of VEGF level has been found after MSCs transplantation in rat hearts and the transplanted MSCs were further found in the newly formed blood vessels [92].

The higher expression of active factors by transplanted MSCs has also been found in other disease conditions. In the diabetic rats, both intramuscularly injected and subcutaneously injected MSCs can be detected in the wound area, and reached the peak point on day 5; MSCs granulation tissue formation and epithelialization of other cells in the wound area [93] were seen. The trace of labled-MSCs showed that they can be differentiated into endothelial cells and form collagen fibers in the blood vessels after 4 weeks transplantation [94]. The same protective effects of allogeneic MSCs on liver was also proved in both acute and chronic liver injury models [95-97]. The result of Moslem's study indicated that human pluripotent stem cell derived MSCs also can be an alternative cell source for mice liver repair [98].

In chronic kidney injury, MSCs have been found "homing" to the sites of inflammation during kidney injury and can be differentiated into kidney epithelial cells [99, 100]. Similar to the mechanism of MSCs promoting myocardial repair, current data suggested that direct kidney cell differentiation by allogeneic MSCs is not the case in kidney repair [11, 12]. Broekema traced labelled MSCs during kidney injury repair, MSCs were first found within the peritubular capillaries and interstitium; 8 days later, MSCs were found within tubules and only about 2–2.5% of recovered tissues were derived from the labelled MSC [101]. On the other hand, the paracrine function of the transplanted MSCs play a more important role in kidney injury repair [102]. It has been proved that MSCs-derived GM-CSF, EGF, CXCL1, IL-6, IL-8, MCP-1, PDGF-AA, and CCL5 can be identified which may promote repair of kidney injury by promoting macrophage polarization, while which of these factors is the most important one still remains unknown [77].

The Immunomodulatory Function of MSCs *In Vivo*

Activation and proliferation of T lymphocytes are the main cause of allogeneic transplant rejection [103]. MSCs are lack of some immune response-related surface antigens including CD40, CD40L, CD80 and CD86, hence the transplanted allogeneic MSCs don't trigger acute immune attack. When co-culturing with peripheral blood lymphocytes, allogeneic MSCs don't cause lymphocyte proliferation [13]. The immune suppressive function of MSCs against T lymphocytes may be due to the contact between the cells and the cytokines secreted by MSCs, such as indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), transforming growth factor-beta (TGF-β), hepatocyte growth factor (HGF), interleukin-10 (IL-10), human leukocyte antigen-G (HLA-G5), etc [104-107]. It is also found that MSCs can help to maintain balance of TH1/TH2 and enhance the proliferation of Treg cells [14]. After 48h of MSCs transplanted into sensitized and non-sensitized rats, the MSCs can be detected mainly in spleen of sensitized ones while in non-sensitized rats the MSCs were mainly found in the bone marrow, where MSCs exert their immunemodulatory functions [108].

MSCs have also been used in treating autoimmune diseases such as autoimmune encephalitis, inflammatory bowel diseases and graft versus host diseases [109, 110]. MSCs transplantation improved the survival of mice with the lethal dosage radiation-induced injury and attenuated radiation-induced hematopoietic toxicity, indicating the potential immuneprotective role of MSCs [111].

Graft-versus-host disease (GVHD) is a series of severe complications during allogeneic tissue/organ transplant which is due to the attack form donor T cells. MSCs have been proved to have the ability of reducing the prevalence of GVHD [112]. The use of MSCs instead of immunosuppressive drugs during solid organ transplantation has proved to be safe and effective against GVHD. In the patients with kidney transplantation, the infusion of MSC can improve graft survival and reduce the dose of immunosuppression [113-117]. Koch *et al.* compared the intra-arterial and intravenous MSCs and found that many animals died following intra-arterial injection because MSCs may block the capillary

system of kidney or other abdominal organs. Whereas the intravenous injection of MSCs is relatively safe. The reason for this is the directly reaching to the capillary system of MSC through intra-arterial injection [118]. The graft protection function of MSCs is T cell related, with the increase of Treg cells and the reduction of T-memory cells [41]. MSCs is capable of reversing miR-155 expression which can led to Th2 differentiation induced by organ transplantation [116]. However, the multi-potentiality of MSCs did have the ability of restoring vessel endothelium in systemic lupus erythematosus [119]. Now, the using of MSCs as treatment for autoimmune diseases such as Crohn's disease, ulcerative colitis, multiple sclerosis, amyotrophic lateral sclerosis, systemic lupus erythematosus has been accepted as an alterative clinical therapy method [119-124].

Focal segmental glomerulosclerosis is known as a dysregulation of the immune system resulting in renal failure. A 13-years-old boy, who presented an immediate recurrence after transplantation, received allogeneic MSCs infusion 3 times and was fully recovered and remain stable after a follow up of 22 months [125]. This renoprotection function of infusion MSCs was also detected in patients of systemic lupus erythematosus [126]. More importantly, multiple transfusions of MSCs provided a better strategy compared to that of single dose infusion [119]. Nearly a quarter of patients suffering form Crohn's disease need major abdominal surgery [127]. The rational of using MSCs for the treatment of Crohn's disease is based on their inhibitory functions on cytotoxic T cells, which is highly active in Crohn's disease patients [128]. The transplantation of MSCs improved the intestinal injury and inhibit ulceration through regulating the intestinal epithelial cell niches directly or indirectly [129, 130].

It is believed that immune response also plays an important role in the development of diabetes. The transplantation of MSCs can successfully depress autoimmunity against islets and enhance survival of islets. Also, transplanted MSCs has been proved to lower blood glucose levels in diabetic animals [131]. However, these results showed the infusion of MSCs had no significant effect on pancreatic β-cell differentiation [132]. It is known that transplanted MSCs can secret essential factors for pancreatic tissue regeneration, such as HGF [133] and MSCs could reverse degenerative β-cell function through their immunosuppressive property [10]. Allogeneic, labeled MSCs can only be detected in pancreas and kidney in MSCs-treated diabetic mice, whereas no MSCs was seen in the lung, liver, and spleen [134].

SUMMARY

The beneficial function of transplanted MSCs has already been proved in many therapeutic areas, such as hematopoietic reconstitution, immunomodulation, hepatic regeneration and cardiac reperfusion. The inherent homing ability of MSCs ensures the transplanted cells migrating into the damaged tissue areas, but only a small percentage of the transplanted (allogenic) MSCs survival for long. The beneficial effects of MSCs transplantation could only be noted within 1-2 days which is not sufficient for cellular growth, division and differentiation. During last few years, the using of MSCs has had a great change. Researchers paid more and more attention on their regulatory role instead of their differentiation ability. The regulatory function of transplanted MSCs includes both immunomodulation function and secretion function. Both of these two functions may change according to the disease conditions or tissue niches. To understand and define the MSCs secretion factors in various disease settings could be future research direction. The findings could lead to potential new MSCs-based therapeutic products.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Knight MN, Hankenson KD. Mesenchymal Stem Cells in Bone Regeneration. Adv Wound Care (New Rochelle) 2013; 2(6): 306-316.

[2] Ma L, Feng XY, Cui BL, *et al.* Human umbilical cord Wharton's Jelly-derived mesenchymal stem cells differentiation into nerve-like cells. Chin Med J (Engl) 2005; 118(23): 1987-93.

[3] Huang P, Lin LM, Wu XY, *et al.* Differentiation of human umbilical cord Wharton's jelly-derived mesenchymal stem cells into germ-like cells *in vitro*. J Cell Biochem 2010; 109(4): 747-54.

[4] Qian Q, Qian H, Zhang X, *et al.* 5-Azacytidine induces cardiac differentiation of human umbilical cord-derived mesenchymal stem cells by activating extracellular regulated kinase. Stem Cells Dev 2012; 21(1): 67-75.

[5] Friedenstein AJ, Chailakhjan RK, Lalykina KS. The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. Cell Tissue Kinet 1970; 3(4): 393-403.

[6] Ikebe C, Suzuki K. Mesenchymal stem cells for regenerative therapy: optimization of cell preparation protocols. Biomed Res Int 2014; 2014: 951512.

[7] Dominici M, Le Blanc K, Mueller I, *et al.* Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006; 8(4): 315-7.

[8] Chen L, Xu Y, Zhao J, *et al.* Conditioned medium from hypoxic bone marrow-derived mesenchymal stem cells enhances wound healing in mice. PLoS One 2014; 9(4): e96161.

[9] Yew TL, Hung YT, Li HY, *et al.* Enhancement of wound healing by human multipotent stromal cell conditioned medium: the paracrine factors and p38 MAPK activation. Cell Transplant 2011; 20(5): 693-706.

[10] Izumida Y, Aoki T, Yasuda D, *et al.* Hepatocyte growth factor is constitutively produced by donor-derived bone marrow cells and promotes regeneration of pancreatic beta-cells. Biochem Biophys Res Commun 2005; 333(1): 273-82.

[11] Lin F, Moran A, Igarashi P. Intrarenal cells, not bone marrow-derived cells, are the major source for regeneration in postischemic kidney. J Clin Invest 2005; 115(7): 1756-64.

[12] Duffield JS, Park KM, Hsiao LL, *et al.* Restoration of tubular epithelial cells during repair of the postischemic kidney occurs in-

dependently of bone marrow-derived stem cells. J Clin Invest 2005; 115(7): 1743-55.
[13] Le Blanc K, Tammik L, Sundberg B, *et al.* Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 2003; 57(1): 11-20.
[14] Bai L, Lennon DP, Eaton V, *et al.* Human bone marrow-derived mesenchymal stem cells induce Th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. Glia 2009; 57(11): 1192-203.
[15] Ryan AE, Lohan P, O'Flynn L, *et al.* Chondrogenic differentiation increases antidonor immune response to allogeneic mesenchymal stem cell transplantation. Mol Ther 2014; 22(3): 655-67.
[16] Li ZH, Liao W, Cui XL, *et al.* Intravenous transplantation of allogeneic bone marrow mesenchymal stem cells and its directional migration to the necrotic femoral head. Int J Med Sci 2011; 8(1): 74-83.
[17] Takemiya K, Kai H, Yasukawa H, *et al.* Mesenchymal stem cell-based prostacyclin synthase gene therapy for pulmonary hypertension rats. Basic Res Cardiol 2010; 105(3): 409-17.
[18] Nakamura T, Sekiya I, Muneta T, *et al.* Arthroscopic, histological and MRI analyses of cartilage repair after a minimally invasive method of transplantation of allogeneic synovial mesenchymal stromal cells into cartilage defects in pigs. Cytotherapy 2012; 14(3): 327-38.
[19] Bocker W, Rossmann O, Docheva D, *et al.* Quantitative polymerase chain reaction as a reliable method to determine functional lentiviral titer after ex vivo gene transfer in human mesenchymal stem cells. J Gene Med 2007; 9(7): 585-95.
[20] Rollin R, Alvarez-Lafuente R, Marco F, *et al.* Human parvovirus B19, varicella zoster virus, and human herpesvirus-6 in mesenchymal stem cells of patients with osteoarthritis: analysis with quantitative real-time polymerase chain reaction. Osteoarthritis Cartilage 2007; 15(4): 475-8.
[21] Jiang W, Ma A, Wang T, *et al.* Homing and differentiation of mesenchymal stem cells delivered intravenously to ischemic myocardium *in vivo*: a time-series study. Pflugers Arch 2006; 453(1): 43-52.
[22] Okabe M, Ikawa M, Kominami K, *et al.* 'Green mice' as a source of ubiquitous green cells. FEBS Lett 1997; 407(3): 313-9.
[23] Huang WY, Aramburu J, Douglas PS, *et al.* Transgenic expression of green fluorescence protein can cause dilated cardiomyopathy. Nat Med 2000; 6(5): 482-3.
[24] Amsalem Y, Mardor Y, Feinberg MS, *et al.* Iron-oxide labeling and outcome of transplanted mesenchymal stem cells in the infarcted myocardium. Circulation 2007; 116(11 Suppl): I38-45.
[25] Park SK, Won JH, Kim HJ, *et al.* Co-transplantation of human mesenchymal stem cells promotes human CD34+ cells engraftment in a dose-dependent fashion in NOD/SCID mice. J Korean Med Sci 2007; 22(3): 412-9.
[26] Ni M, Rui YF, Tan Q, *et al.* Engineered scaffold-free tendon tissue produced by tendon-derived stem cells. Biomaterials 2013; 34(8): 2024-37.
[27] Joo SY, Cho KA, Jung YJ, *et al.* Bioimaging for the monitoring of the *in vivo* distribution of infused mesenchymal stem cells in a mouse model of the graft-versus-host reaction. Cell Biol Int 2011; 35(4): 417-21.
[28] Gao J, Dennis JE, Muzic RF, *et al.* The dynamic *in vivo* distribution of bone marrow-derived mesenchymal stem cells after infusion. Cells Tissues Organs 2001; 169(1): 12-20.
[29] Davani S, Marandin A, Mersin N, *et al.* Mesenchymal progenitor cells differentiate into an endothelial phenotype, enhance vascular density, and improve heart function in a rat cellular cardiomyoplasty model. Circulation 2003; 108 Suppl 1: II253-8.
[30] Leiker M, Suzuki G, Iyer VS, *et al.* Assessment of a nuclear affinity labeling method for tracking implanted mesenchymal stem cells. Cell Transplant 2008; 17(8): 911-22.
[31] Sun S, Chen G, Xu M, *et al.* Differentiation and migration of bone marrow mesenchymal stem cells transplanted through the spleen in rats with portal hypertension. PLoS One 2013; 8(12): e83523.
[32] Shao CH, Chen SL, Dong TF, *et al.* Transplantation of bone marrow-derived mesenchymal stem cells after regional hepatic irradiation ameliorates thioacetamide-induced liver fibrosis in rats. J Surg Res 2014; 186(1): 408-16.
[33] Yaghoubi SS, Barrio JR, Namavari M, *et al.* Imaging progress of herpes simplex virus type 1 thymidine kinase suicide gene therapy in living subjects with positron emission tomography. Cancer Gene Ther 2005; 12(3): 329-39.
[34] Kicic A, Shen WY, Wilson AS, *et al.* Differentiation of marrow stromal cells into photoreceptors in the rat eye. J Neurosci 2003; 23(21): 7742-9.
[35] Kooreman NG, Ransohoff JD, Wu JC. Tracking gene and cell fate for therapeutic gain. Nat Mater 2014; 13(2): 106-9.
[36] Crich SG, Biancone L, Cantaluppi V, *et al.* Improved route for the visualization of stem cells labeled with a Gd-/Eu-chelate as dual (MRI and fluorescence) agent. Magn Reson Med 2004; 51(5): 938-44.
[37] Kustermann E, Himmelreich U, Kandal K, *et al.* Efficient stem cell labeling for MRI studies. Contrast Media Mol Imaging 2008; 3(1): 27-37.
[38] Shapiro EM, Gonzalez-Perez O, Manuel Garcia-Verdugo J, *et al.* Magnetic resonance imaging of the migration of neuronal precursors generated in the adult rodent brain. Neuroimage 2006; 32(3): 1150-7.
[39] Gambhir SS, Barrio JR, Phelps ME, *et al.* Imaging adenoviral-directed reporter gene expression in living animals with positron emission tomography. Proc Natl Acad Sci USA 1999; 96(5): 2333-8.
[40] Yamada M, Yang P. *In vitro* labeling of human embryonic stem cells for magnetic resonance imaging. J Vis Exp 2008; 17. pii: 827.
[41] Berger C, Rausch M, Schmidt P, *et al.* Feasibility and limits of magnetically labeling primary cultured rat T cells with ferumoxides coupled with commonly used transfection agents. Mol Imaging 2006; 5(2): 93-104.
[42] Sohni A, Verfaillie CM. Mesenchymal Stem Cells Migration Homing and Tracking. Stem Cells Int 2013; 2013: 130763.
[43] Zhao H, Feng J, Seidel K, *et al.* Secretion of shh by a neurovascular bundle niche supports mesenchymal stem cell homeostasis in the adult mouse incisor. Cell Stem Cell 2014; 14(2): 160-73.
[44] Livet J, Weissman TA, Kang H, *et al.* Transgenic strategies for combinatorial expression of fluorescent proteins in the nervous system. Nature 2007; 450(7166): 56-62.
[45] Nguyen PK, Riegler J and Wu JC. Stem cell imaging: from bench to bedside. Cell Stem Cell 2014; 14(4): 431-44.
[46] Cancedda R, Giannoni P and Mastrogiacomo M. A tissue engineering approach to bone repair in large animal models and in clinical practice. Biomaterials 2007; 28(29): 4240-50.
[47] Eberli D, Atala A, Yoo JJ. One and four layer acellular bladder matrix for fascial tissue reconstruction. J Mater Sci Mater Med 2011; 22(3): 741-51.
[48] Horwitz EM, Prockop DJ, Fitzpatrick LA, *et al.* Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta. Nat Med 1999; 5(3): 309-13.
[49] Ferrari G, Cusella-De Angelis G, Coletta M, *et al.* Muscle regeneration by bone marrow-derived myogenic progenitors. Science 1998; 279(5356): 1528-30.
[50] Chamberlain G, Fox J, Ashton B, *et al.* Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. Stem Cells 2007; 25(11): 2739-49.
[51] Pereira RF, Halford KW, O'Hara MD, *et al.* Cultured adherent cells from marrow can serve as long-lasting precursor cells for bone, cartilage, and lung in irradiated mice. Proc Natl Acad Sci USA 1995; 92(11): 4857-61.
[52] Richert L, Golubic S, Guedes RL, *et al.* Characterization of exopolysaccharides produced by cyanobacteria isolated from Polynesian microbial mats. Curr Microbiol 2005; 51(6): 379-84.
[53] Granero-Molto F, Weis JA, Miga MI, *et al.* Regenerative effects of transplanted mesenchymal stem cells in fracture healing. Stem Cells 2009; 27(8): 1887-98.
[54] Ortiz LA, Gambelli F, McBride C, *et al.* Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. Proc Natl Acad Sci USA 2003; 100(14): 8407-11.
[55] Chen Y, Xiang LX, Shao JZ, *et al.* Recruitment of endogenous bone marrow mesenchymal stem cells towards injured liver. J Cell Mol Med 2010; 14(6B): 1494-508.
[56] Mahmood A, Lu D, Lu M, *et al.* Treatment of traumatic brain injury in adult rats with intravenous administration of human bone marrow stromal cells. Neurosurgery 2003; 53(3): 697-702; discussion 702-3.

[57] Mansilla E, Marin GH, Drago H, *et al.* Bloodstream cells phenotypically identical to human mesenchymal bone marrow stem cells circulate in large amounts under the influence of acute large skin damage: new evidence for their use in regenerative medicine. Transplant Proc 2006; 38(3): 967-9.

[58] Quintavalla J, Uziel-Fusi S, Yin J, *et al.* Fluorescently labeled mesenchymal stem cells (MSCs) maintain multilineage potential and can be detected following implantation into articular cartilage defects. Biomaterials 2002; 23(1): 109-19.

[59] Tateishi-Yuyama E, Matsubara H, Murohara T, *et al.* Therapeutic angiogenesis for patients with limb ischaemia by autologous transplantation of bone-marrow cells: a pilot study and a randomised controlled trial. Lancet 2002; 360(9331): 427-35.

[60] Lian Q, Zhang Y, Zhang J, *et al.* Functional mesenchymal stem cells derived from human induced pluripotent stem cells attenuate limb ischemia in mice. Circulation 2010; 121(9): 1113-23.

[61] Madonna R, Pizzi SD, Tartaro A, *et al.* Transplantation of mesenchymal cells improves peripheral limb ischemia in diabetic rats. Mol Biotechnol 2014; 56(5): 438-48.

[62] Huang WH, Chen HL, Huang PH, *et al.* Hypoxic mesenchymal stem cells engraft and ameliorate limb ischaemia in allogeneic recipients. Cardiovasc Res 2014; 101(2): 266-76.

[63] Moodley Y, Vaghjiani V, Chan J, *et al.* Anti-inflammatory effects of adult stem cells in sustained lung injury: a comparative study. PLoS One 2013; 8(8): e69299.

[64] Curley GF, Ansari B, Hayes M, *et al.* Effects of intratracheal mesenchymal stromal cell therapy during recovery and resolution after ventilator-induced lung injury. Anesthesiology 2013; 118(4): 924-32.

[65] Li DL, He XH, Zhang SA, *et al.* Bone marrow-derived mesenchymal stem cells promote hepatic regeneration after partial hepatectomy in rats. Pathobiology 2013; 80(5): 228-34.

[66] Du Z, Wei C, Cheng K, *et al.* Mesenchymal stem cell-conditioned medium reduces liver injury and enhances regeneration in reduced-size rat liver transplantation. J Surg Res 2013; 183(2): 907-15.

[67] Katare R, Riu F, Rowlinson J, *et al.* Perivascular delivery of encapsulated mesenchymal stem cells improves postischemic angiogenesis via paracrine activation of VEGF-A. Arterioscler Thromb Vasc Biol 2013; 33(8): 1872-80.

[68] Richardson JD, Bertaso AG, Psaltis PJ, *et al.* Impact of timing and dose of mesenchymal stromal cell therapy in a preclinical model of acute myocardial infarction. J Card Fail 2013; 19(5): 342-53.

[69] Calio ML, Marinho DS, Ko GM, *et al.* Transplantation of bone marrow mesenchymal stem cells decreases oxidative stress, apoptosis, and hippocampal damage in brain of a spontaneous stroke model. Free Radic Biol Med 2014; 70: 141-54.

[70] van Velthoven CT, Kavelaars A, Heijnen CJ. Mesenchymal stem cells as a treatment for neonatal ischemic brain damage. Pediatr Res 2012; 71(4 Pt 2): 474-81.

[71] Coquery N, Blesch A, Stroh A, *et al.* Intrahippocampal transplantation of mesenchymal stromal cells promotes neuroplasticity. Cytotherapy 2012; 14(9): 1041-53.

[72] Rojas M, Parker RE, Thorn N, *et al.* Infusion of freshly isolated autologous bone marrow derived mononuclear cells prevents endotoxin-induced lung injury in an *ex-vivo* perfused swine model. Stem Cell Res Ther 2013; 4(2): 26.

[73] Wang T, Tang W, Sun S, *et al.* Intravenous infusion of bone marrow mesenchymal stem cells improves brain function after resuscitation from cardiac arrest. Crit Care Med 2008; 36(11 Suppl): S486-91.

[74] Wolf D, Reinhard A, Seckinger A, *et al.* Dose-dependent effects of intravenous allogeneic mesenchymal stem cells in the infarcted porcine heart. Stem Cells Dev 2009; 18(2): 321-9.

[75] Ma J, Both SK, Ji W, *et al.* Adipose tissue-derived mesenchymal stem cells as monocultures or cocultures with human umbilical vein endothelial cells: performance *in vitro* and in rat cranial defects. J Biomed Mater Res A 2014; 102(4): 1026-36.

[76] Pedersen TO, Blois AL, Xue Y, *et al.* Osteogenic stimulatory conditions enhance growth and maturation of endothelial cell microvascular networks in culture with mesenchymal stem cells. J Tissue Eng 2012; 3(1): 2041731412443236.

[77] Wise AF, Williams TM, Kiewiet MB, *et al.* Human mesenchymal stem cells alter macrophage phenotype and promote regeneration via homing to the kidney following ischemia-reperfusion injury. Am J Physiol Renal Physiol 2014; 306(10): F1222-35.

[78] Toma C, Pittenger MF, Cahill KS, *et al.* Human mesenchymal stem cells differentiate to a cardiomyocyte phenotype in the adult murine heart. Circulation 2002; 105(1): 93-8.

[79] Orlic D, Kajstura J, Chimenti S, *et al.* Bone marrow stem cells regenerate infarcted myocardium. Pediatr Transplant 2003; 7 Suppl 3: 86-8.

[80] Hong M, Jo H, Ankeny RF, *et al.* Influence of mesenchymal stem cells on the response of endothelial cells to laminar flow and shear stress. Cells Tissues Organs 2013; 198(4): 289-99.

[81] Wollert KC, Drexler H. Cell-based therapy for heart failure. Curr Opin Cardiol 2006; 21(3): 234-9.

[82] Pittenger MF, Martin BJ. Mesenchymal stem cells and their potential as cardiac therapeutics. Circ Res 2004; 95(1): 9-20.

[83] Iso Y, Spees JL, Serrano C, *et al.* Multipotent human stromal cells improve cardiac function after myocardial infarction in mice without long-term engraftment. Biochem Biophys Res Commun 2007; 354(3): 700-6.

[84] Crisostomo PR, Wang M, Markel TA, *et al.* Stem cell mechanisms and paracrine effects: potential in cardiac surgery. Shock 2007; 28(4): 375-83.

[85] Imanishi Y, Saito A, Komoda H, *et al.* Allogenic mesenchymal stem cell transplantation has a therapeutic effect in acute myocardial infarction in rats. J Mol Cell Cardiol 2008; 44(4): 662-71.

[86] Williams AR, Suncion VY, McCall F, *et al.* Durable scar size reduction due to allogeneic mesenchymal stem cell therapy regulates whole-chamber remodeling. J Am Heart Assoc 2013; 2(3): e000140.

[87] Wang T, Tang W, Sun S, *et al.* Mesenchymal stem cells improve outcomes of cardiopulmonary resuscitation in myocardial infarcted rats. J Mol Cell Cardiol 2009; 46(3): 378-84.

[88] Everaert BR, Bergwerf I, De Vocht N, *et al.* Multimodal *in vivo* imaging reveals limited allograft survival, intrapulmonary cell trapping and minimal evidence for ischemia-directed BMSC homing. BMC Biotechnol 2012; 12: 93.

[89] Tomita S, Li RK, Weisel RD, *et al.* Autologous transplantation of bone marrow cells improves damaged heart function. Circulation 1999; 100(19 Suppl): II247-56.

[90] Xia C, Cao J. Imaging the survival and utility of pre-differentiated allogeneic MSC in ischemic heart. Biochem Biophys Res Commun 2013; 438(2): 382-7.

[91] Li P, Li SH, Wu J, *et al.* Interleukin-6 downregulation with mesenchymal stem cell differentiation results in loss of immunoprivilege. J Cell Mol Med 2013; 17(9): 1136-45.

[92] Tang YL, Zhao Q, Zhang YC, *et al.* Autologous mesenchymal stem cell transplantation induce VEGF and neovascularization in ischemic myocardium. Regul Pept 2004; 117(1): 3-10.

[93] Wan J, Xia L, Liang W, *et al.* Transplantation of bone marrow-derived mesenchymal stem cells promotes delayed wound healing in diabetic rats. J Diabetes Res 2013; 2013: 647107.

[94] Fang SM, Du DY, Li YT, *et al.* Allogeneic bone marrow mesenchymal stem cells transplantation for stabilizing and repairing of atherosclerotic ruptured plaque. Thromb Res 2013; 131(6): e253-7.

[95] Xagorari A, Siotou E, Yiangou M, *et al.* Protective effect of mesenchymal stem cell-conditioned medium on hepatic cell apoptosis after acute liver injury. Int J Clin Exp Pathol 2013; 6(5): 831-40.

[96] Kaibori M, Adachi Y, Shimo T, *et al.* Stimulation of liver regeneration after hepatectomy in mice by injection of bone marrow mesenchymal stem cells via the portal vein. Transplant Proc 2012; 44(4): 1107-9.

[97] Seki T, Yokoyama Y, Nagasaki H, *et al.* Adipose tissue-derived mesenchymal stem cell transplantation promotes hepatic regeneration after hepatic ischemia-reperfusion and subsequent hepatectomy in rats. J Surg Res 2012; 178(1): 63-70.

[98] Moslem M, Valojerdi MR, Pournasr B, *et al.* Therapeutic potential of human induced pluripotent stem cell-derived mesenchymal stem cells in mice with lethal fulminant hepatic failure. Cell Transplant 2013; 22(10): 1785-99.

[99] Togel F, Isaac J, Hu Z, *et al.* Renal SDF-1 signals mobilization and homing of CXCR4-positive cells to the kidney after ischemic injury. Kidney Int 2005; 67(5): 1772-84.

[100] Wong CY, Cheong SK, Mok PL, *et al.* Differentiation of human mesenchymal stem cells into mesangial cells in post-glomerular injury murine model. Pathology 2008; 40(1): 52-7.

[101] Broekema M, Harmsen MC, Koerts JA, *et al.* Determinants of tubular bone marrow-derived cell engraftment after renal ischemia/reperfusion in rats. Kidney Int 2005; 68(6): 2572-81.

[102] Asanuma H, Meldrum DR, Meldrum KK. Therapeutic applications of mesenchymal stem cells to repair kidney injury. J Urol 2010; 184(1): 26-33.
[103] Boeckh M, Nichols WG, Marr KA. Long-term care after hematopoietic-cell transplantation in adults. N Engl J Med 2002; 347(20): 1625-6; author reply 1625-6.
[104] Dorronsoro A, Fernandez-Rueda J, Fechter K, *et al.* Human Mesenchymal Stromal Cell-Mediated Immunoregulation: Mechanisms of Action and Clinical Applications. Bone Marrow Res 2013; 2013: 203643.
[105] Larocca RA, Moraes-Vieira PM, Bassi EJ, *et al.* Adipose tissue-derived mesenchymal stem cells increase skin allograft survival and inhibit Th-17 immune response. PLoS One 2013; 8(10): e76396.
[106] Shi M, Liu ZW, Wang FS. Immunomodulatory properties and therapeutic application of mesenchymal stem cells. Clin Exp Immunol 2011; 164(1): 1-8.
[107] Yagi H, Soto-Gutierrez A, Parekkadan B, *et al.* Mesenchymal stem cells: Mechanisms of immunomodulation and homing. Cell Transplant 2010; 19(6): 667-79.
[108] Xu LH, Fang JP, Hong DL, *et al.* Application of mesenchymal stromal cells in bone marrow transplantation for sensitized recipients. Acta Haematol 2012; 127(2): 105-9.
[109] Ren G, Chen X, Dong F, *et al.* Concise review: mesenchymal stem cells and translational medicine: emerging issues. Stem Cells Transl Med 2012; 1(1): 51-8.
[110] Uccelli A, Moretta L and Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol 2008; 8(9): 726-36.
[111] Qiao S, Ren H, Shi Y, *et al.* Allogeneic compact bone-derived mesenchymal stem cell transplantation increases survival of mice exposed to lethal total body irradiation: a potential immunological mechanism. Chin Med J (Engl) 2014; 127(3): 475-82.
[112] Tobin LM, Healy ME, English K, *et al.* Human mesenchymal stem cells suppress donor CD4(+) T cell proliferation and reduce pathology in a humanized mouse model of acute graft-versus-host disease. Clin Exp Immunol 2013; 172(2): 333-48.
[113] Vanikar AV and Trivedi HL. Stem cell transplantation in living donor renal transplantation for minimization of immunosuppression. Transplantation 2012; 94(8): 845-50.
[114] Vanikar AV, Trivedi HL, Feroze A, *et al.* Effect of co-transplantation of mesenchymal stem cells and hematopoietic stem cells as compared to hematopoietic stem cell transplantation alone in renal transplantation to achieve donor hypo-responsiveness. Int Urol Nephrol 2011; 43(1): 225-32.
[115] Zhou HP, Yi DH, Yu SQ, *et al.* Administration of donor-derived mesenchymal stem cells can prolong the survival of rat cardiac allograft. Transplant Proc 2006; 38(9): 3046-51.
[116] Forbes GM, Sturm MJ, Leong RW, *et al.* A phase 2 study of allogeneic mesenchymal stromal cells for luminal Crohn's disease refractory to biologic therapy. Clin Gastroenterol Hepatol 2014; 12(1): 64-71.
[117] Pileggi A, Xu X, Tan J, *et al.* Mesenchymal stromal (stem) cells to improve solid organ transplant outcome: lessons from the initial clinical trials. Curr Opin Organ Transplant 2013; 18(6): 672-81.
[118] Koch M, Lehnhardt A, Hu X, *et al.* Isogeneic MSC application in a rat model of acute renal allograft rejection modulates immune response but does not prolong allograft survival. Transpl Immunol 2013; 29(1-4): 43-50.
[119] Sui W, Hou X, Che W, *et al.* Hematopoietic and mesenchymal stem cell transplantation for severe and refractory systemic lupus erythematosus. Clin Immunol 2013; 148(2): 186-97.
[120] Herreros MD, Garcia-Arranz M, Guadalajara H, *et al.* Autologous expanded adipose-derived stem cells for the treatment of complex cryptoglandular perianal fistulas: a phase III randomized clinical trial (FATT 1: fistula Advanced Therapy Trial 1) and long-term evaluation. Dis Colon Rectum 2012; 55(7): 762-72.
[121] Garcia-Olmo D, Herreros D, Pascual I, *et al.* Expanded adipose-derived stem cells for the treatment of complex perianal fistula: a phase II clinical trial. Dis Colon Rectum 2009; 52(1): 79-86.
[122] Kassis I, Vaknin-Dembinsky A, Karussis D. Bone marrow mesenchymal stem cells: agents of immunomodulation and neuroprotection. Curr Stem Cell Res Ther 2011; 6(1): 63-8.
[123] Yamout B, Hourani R, Salti H, *et al.* Bone marrow mesenchymal stem cell transplantation in patients with multiple sclerosis: a pilot study. J Neuroimmunol 2010; 227(1-2): 185-9.
[124] Krabbe C, Zimmer J, Meyer M. Neural transdifferentiation of mesenchymal stem cells--a critical review. APMIS 2005; 113(11-12): 831-44.
[125] Connick P, Kolappan M, Crawley C, *et al.* Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-label phase 2a proof-of-concept study. Lancet Neurol 2012; 11(2): 150-6.
[126] Belingheri M, Lazzari L, Parazzi V, *et al.* Allogeneic mesenchymal stem cell infusion for the stabilization of focal segmental glomerulosclerosis. Biologicals 2013; 41(6): 439-45.
[127] Gu Z, Akiyama K, Ma X, *et al.* Transplantation of umbilical cord mesenchymal stem cells alleviates lupus nephritis in MRL/lpr mice. Lupus 2010; 19(13): 1502-14.
[128] Bouguen G and Peyrin-Biroulet L. Surgery for adult Crohn's disease: what is the actual risk? Gut 2011; 60(9): 1178-81.
[129] Kudo K, Liu Y, Takahashi K, *et al.* Transplantation of mesenchymal stem cells to prevent radiation-induced intestinal injury in mice. J Radiat Res 2010; 51(1): 73-9.
[130] Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. Gut 2009; 58(8): 1152-67.
[131] Lee RH, Seo MJ, Reger RL, *et al.* Multipotent stromal cells from human marrow home to and promote repair of pancreatic islets and renal glomeruli in diabetic NOD/scid mice. Proc Natl Acad Sci USA 2006; 103(46): 17438-43.
[132] Semont A, Mouiseddine M, Francois A, *et al.* Mesenchymal stem cells improve small intestinal integrity through regulation of endogenous epithelial cell homeostasis. Cell Death Differ 2010; 17(6): 952-61.
[133] Lechner A, Yang YG, Blacken RA, *et al.* No evidence for significant transdifferentiation of bone marrow into pancreatic beta-cells *in vivo*. Diabetes 2004; 53(3): 616-23.
[134] Urban VS, Kiss J, Kovacs J, *et al.* Mesenchymal stem cells cooperate with bone marrow cells in therapy of diabetes. Stem Cells 2008; 26(1): 244-53.

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