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How do Mesenchymal Stem Cells Repair?

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1. Introduction

Mesenchymal stem cells' field has flourished lately. It is undoubted that MSC have the ability to repair several damaged tissues. Multipotent mesenchymal stromal cells (MSC) can be isolated and efficiently expanded from almost every single body tissue and has the ability of self-renewal and differentiation into various mesodermal cell lineages. MSC can provide effective treatments for a wide range of diseases and posses several applications in regenerative medicine such as tissue repair and gene delivery. In fact, relevant data have been generated in animal models of human diseases and some clinical trials are even being started. However, little is known about how MSC can repair. It is suggested that the MSC has pleiotropic actions releasing pro-survival factors to cytoprotective microvesicles. In this chapter, we will review and discuss the main conjectures on the mechanisms of action of MSC in animal and human contexts.

2. Mesenchymal Stem Cells (MSC) biology: concept, terminology, sources, cell phenotype, gene profile and senescence

The so called "stem cell" called "stem cell" is the cell that by definition has two main properties: 1) Asymmetric division and 2) Differentiation capacity. Not all cells in our body follow these two properties.

In this sense, there are two main cells: embryonic stem cells and adult stem cells. For the purpose of this chapter, we will focus on adult stem cells.

The existence of adult stem cell is now well accepted. Tissue repair after injury and also the continuous homeostatic self renewal of some tissue consolidate this idea (1).

In 1970, Friendstein and collaborators described for the first time that bone marrow harbours not only hematopoietic stem cells (HSC), but also other type of cell that has clonogenic properties in vitro, characterizing these cells by their property to form fibroblast colonies in the primary passage in culture (CFU-F: colony-forming unit fibroblastic)(2). Later on, therapeutic approaches were achieved by using these cells in bone disorders (3, 4).

Years later, Caplan and co-workers named these cells as mesenchymal stem cells (MSC) (5, 6). In 1999, Pittenger et al demonstrated that these cells are multipotent stem cells with potential to differentiate into other cells from mesenchymal tissues (7).

Others sources of mesenchymal stem cells have been described since then. MSC are not only found at bone marrow. Adipose tissue has also been demonstrated as a potential niche (8). In addition, dental pulp (9), limbus (10), amniotic membrane (11) amniotic fluid (12), kidney

(13) and several other organs may harbor mesenchymal stem cell populations. In culture, all these cells possess a fibroblast-like phenotype and share similarities in their immunophenotype and differentiation assays.

Once it was seen that several organs and tissue have MSC, the name needed to be standardized. In 2005, the International Society of Stem Cell Research (ISSCR) termed these cells as multipotent mesenchymal stromal cells for fibroblast-like plastic adherent cells isolated from any organ (14). And if this cell follows the minimal criteria of stem cell, so this cell can be called mesenchymal stem cell. There are three main criteria in order to determine the identity of MSC: 1) must have adherence to plastic; 2) expression of CD105, CD73 and CD90, and lack of expression of CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR surface molecules; 3) must have differentiation potential (15). More recently, Caplan has suggested, due to its properties; to again rename MSC to "Medicinal Signaling Cells" because of its main mechanism of action (16).

Despite this phenotype similarity, gene profile among all these cells may be different. A molecular signature of markers of stem lineage markers and genes regulating developmental and regenerative processes is more elucidative (17). Peroni et al, in a detailed work, demonstrated that MSC from bone marrow have an identical molecular profile when compared to MSC from adipose tissue. Nevertheless, a difference in some genes expression may happen with culture conditions (17). However, some authors suggest that the site of origin of MSC leads to the expression of specific genes pathways. A comparative study of MSC from bone marrow and MSC from umbilical cord from Panepucci et al showed that there are some genes that are more expressed in one cell than another. For instance, genes related to antimicrobial activity and osteogenesis are more expressed in MSC from bone marrow; and genes related to matrix remodeling and angiogenesis are more expressed in MSC from umbilical cord (18). Proteome analysis of MSC also demonstrated a full list of proteins expressed by MSC as described by Park et al (19).

In fact, MSC population is not spread all over the organ. To maintain its properties, stem cells are located at niches. Niche is an environment defined by extracellular matrix and others cells that secrete several factors to maintain stem cells under its undifferentiated state and quiescence, since adult stem cells are highly sensitive to external signals (20-22). Thus, if the niche is not well regulated, for instance in a pathologic state, stem cells may not react as expected: to repair and maintain homeostasis. Moreover, a problem in this delicate balance between stem cells and its niche may also lead to cancer (23).

The niche per se is very important; however stem cell stability is also necessary. DNA damage in melanocyte stem cells induce premature differentiation, leading to apoptosis and senescence (24). Regarding that cellular aging may be due to DNA alterations; this is probably an explanation for the inverse correlation between age and adult stem cell population and its functionality (25).

Despite all efforts, the potential niche for adult stem cell *in vivo* has not yet been defined. A perivascular niche is one possible place (26, 27). Some authors support the idea that mesenchymal stem cells are located throughout the body as pericytes, since it is related to tissue homeostasis and blood vessels stabilization (27). In this sense, da Silva Meirelles et al showed the direct correlation between the quantity of blood vessel and stem cells (28).

3. MSC therapy and its ability to repair several diseases

As previously written, all tissues per se have the capacity of homeostasis maintenance. However, after an injury, this process is somehow disturbed by inflammation or by extracellular matrix disruption, not allowing proper stem cell action.

Thus, in a way to assist the repair process, several works have focused on the administration of exogenous stem cells. Surprisingly, the administration of adult stem cell in several experimental diseases have showed to improve in its clinical outcome and moreover amelioration of tissue architecture.

However, the mechanism of action that leads to this improvement is not well defined. Fusion of dying cells with MSC, differentiation of MSC to other cell types or paracrine action, by secretion of several bioactive factors are the main mechanism of action suggested. New mechanisms have also been suggested with the knowledge of microRNA. These topics will be better explained in the next sections.

3.1 Animals models of human diseases: kidney, heart, CNS, liver, lung and pancreas

The main experimental models treated with mesenchymal stem cells are summarized in the next table (Table I).

	Experimental Model	Cell (amount/way/time)	Mechanism of Action suggested for better outcome of injury	Reference
Kidney	Acute Kidney Injury	Rat MSC, 2x10 ⁵ cell/rat, e.v., 6h after ischemia-reperfusion injury	Immunomodulation	(29)
		Microvesicles from human MSC, 15 µg/animal, e.v., 3 days after glycerol administration	mRNA and microRNA carried by microvesicles	(30)
		MSC, 1x10 ⁵ cell/mouse, intra-arterially, 30 min after inschemia-reperfusion injury	Paracrine action – VEGF, HGF, IGF-1 secretion	(31)
	Chronic Kidney Injury (remnant model)	Rat MSC, 2x10 ⁵ cell/rat, e.v., 2 nd week after 5/6 remnant model every other week until 8 th week.	Immunomodulation and paracrine action	(32)
		Rat MSC, 1x10 ⁵ cell/rat, e.v., 1 week after 5/6 nephrotomy	MSC engraftment and paracrine action	(33)
	Chronic Kidney Injury (unilateral ureteral obstruction)	Human MSC, 1x10 ⁶ cell/rat, intra-arterially, after ureter obstruction	Immunomodulation	(34)
	Glomerulonephritis	Rat MSC, 2x10 ⁶ cell/rat, intra-arterially, 2 days after Thy1.1 administration	Early results: paracrine effect Long-term results: maldifferentiation of MSC to adipocytes	(35)

	Experimental Model	Cell (amount/way/time)	Mechanism of Action suggested for better outcome of injury	Reference
Heart	Myocardial infarct model	Swine MSC, 6x10 ⁷ cell/swine, in situ at infracted area, two weeks after artery occlusion	Engraftment at myocardium	(36)
CNS	Spinal cord injury	Human MSC, 1.5x10 ⁵ cell/rat, injury in situ, at time of surgery	Immunomodulation and engraftment	(37)
	Parkinson model	Rat MSC, 1.106 cell/rat, intranasally, 3 days post surgery.	Immunomodulation, anti-apoptotic effect and engraftment	(38)
Liver	Liver Fibrosis (CCl4)	Rat MSC, 3x10 ⁶ cell/rat, e.v., 42 days after CCl4 administration	Paracrine and anti-apoptotic effect	(39)
Lung	Acute Lung Injury (LPS)	Mouse MSC, 1x10 ⁵ cell/mouse, e.v., 2h after the first LPS inhalation	Immunomodulation	(40)
	Chronic Lung Injury (Bleomycin)	Mouse MSC, 2.5x10 ⁵ cell/mouse, e.v., 7 days after bleomycin administration.	Engraftment, immunomodulation	(41)
Pancreas	Diabetes Autoimmune (NOD animal)	Mouse MSC, 1x10 ⁵ cell/mouse, i.p. or e.v., NOD mice at 4 weeks old.	Immunomodulation	(42)

Table I. Some pre-clinical data on MSC therapy

3.2 Human trials with MSC

Pre-clinical studies have stimulated human clinical trials. Searching for “adult stem cell” at Clinicaltrials.gov, nearly 3300 studies were found. Within these studies, 1530 are recruiting patients. Some of these clinical trials are related in Table II.

These numbers are alarming. The real mechanism of action of MSC, as well as the long-term studies are not yet clarified. Despite it, others issues still hold doubts such as the amount of cells, site of injection, which cell is the best for each illness, which is the level of cell survival and engraftment, etc. These questions should be answered before clinical trials are started.

However, completed clinical trials have demonstrated efficient amelioration on clinical outcomes. MSC therapy has been focused on graft versus host diseases (GvHD) (43), limb

ischemia (44), acute kidney injury (45), lung injury (46), myocardial infarction (47), etc. Safety and efficacy will be discussed next in this article. How MSC leads to this better clinical outcome, despite which disease is it, is described below.

Study	Condition	Status
Evaluation of Circulating Levels of Adult Stem Cells in the Peripheral Blood of Patients With Acute Decompensated Heart Failure and Following Stabilization, in Comparison With Healthy Volunteers NCT01027403	Heart Failure	Recruiting
Adult Stem Cell Therapy in Liver Insufficiency NCT00147043	Liver Cirrhosis	Completed
Safety Study of Adult Stem Cells to Treat Patients With Severe Leg Artery Disease NCT00913900	Critical Limb Ischemia	Recruiting
Long-term Safety and Efficacy of Adipose-derived Stem Cells to Treat Complex Perianal Fistulas in Patients Participating in the FATT-1 Randomized Controlled Trial NCT01020825	Complex Perianal Fistula	Recruiting
Evaluation of PROCHYMAL[tm] Adult Human Stem Cells for Treatment-resistant Moderate-to-severe Crohn's Disease NCT00482092	Crohn's Disease	Recruiting
Autologous Mesenchymal Stem Cells From Adipose Tissue in Patients With Secondary Progressive Multiple Sclerosis NCT01056471	Multiple Sclerosis	Recruiting
Mesenchymal Stem Cell Infusion as Prevention for Graft Rejection and Graft-Versus-Host Disease NCT00504803	Hematological Malignancies	Recruiting
Intravenous Stem Cells After Ischemic Stroke NCT00875654	Stroke	Recruiting
Induction Therapy With Autologous Mesenchymal Stem Cells for Kidney Allografts NCT00658073	Renal Transplant Rejection	Completed

Table II. Some clinical trials ongoing

4. MSC mechanisms of action

4.1 Differentiation

Before talking about differentiation it is important to consider the two categories into which stem cells can be classified (according to their developmental status): embryonic and adult (postnatal). Each represents a diverse differentiation potential status and a different potential application. Embryonic stem are pluripotent cells isolated from the inner cells mass of blastocysts, and are capable of giving rise to cells found in all three germ layers of the embryo. They are considered to have the greatest range of differentiation potential. On the other hand, adult stem cells have the capacity renew tissue after trauma, disease, or aging. These cells are found in different scales of quantity and potentiality (uni-, di-, tri-, and multi-potent), and their differentiation status is related to cell plasticity, where cells of one type give rise to cells of another type, however closely related (cell flexibility) (48). Mesenchymal stem cells are adult stem cells with reduced differentiation capacity and higher plasticity capacity.

The differentiation and plasticity characteristics mentioned above exemplify the flexibility of MSC. It is well known that mesenchymal cells can shift from one differentiation pathway to another under modified external conditions, and can shift from quiescence to a proliferative state or that MSC differentiation can be reversed at least up to a certain stage (49, 50). MSCs have also been reported to differentiate into various epithelial cell types after systemic administration *in vivo*. Studies have shown that after bleomycin exposure, MSC lung engraftment was enhanced showing a small percentage of MSC localized to areas of lung injury. In addition, MSC also differentiated into type I pneumocytes (51) or assumed phenotypic characteristics of all major cell types in lung including fibroblasts, type I and type II epithelial cells, and myofibroblasts (52). MSCs have also been shown to differentiate into retinal pigment epithelial cells (53), skin epithelial cells (54) and tubular epithelial cells in kidney (55).

Different techniques have been used for MSC differentiation: use of biological and pharmacological reagents (56-59); mechanical cues (60-62) and external mechanical and electrical forces (63-66). Both mechanical and electrical stimulation have been applied separately and combined with soluble factors to facilitate MSC differentiation (67).

The criteria for differentiation need to be rigorously defined. It appears difficult to ascertain about differentiation process. Some markers are specific for certain cells; however they do not have functional relation. In addition these markers are not unique to characterize a specific cell. Delorme et al have found that MSC express cytoskeletal proteins usually expressed in neural stem cells (nestin), hepatocytes (cytokeratin-8 and -18), biliary cells (cytokeratin-19), and sarcomeric muscle (troponins, α -C-actin), without the expression of proneural or neuronal, prohepatocytic, or myogenic key transcription factors (68). Although cytoskeletal markers remain adequate indicators of a differentiation pathways, there are numerous exceptions to the rule, such as the expression of cytokeratin-18 in vascular smooth muscle cells in the synthetic phase and other similar misleading expression factors as reported by Montzka (69).

Some of the observed differentiations may also result from reprogramming. Dezawa and colleagues have shown that rodent and human bone marrow MSC can be reprogrammed into cells with skeletal muscle potential after specific treatment comprising first cytokines and then gene transfer of the notch intracellular domain (70).

Differentiation induction can be also marked by the decline of one factor at the expense of the other, like *runt-related transcription factor-2* (RUNX2) downregulation and *peroxisome*

proliferator-activated receptor- γ (PPAR γ) upregulation in the adipogenic condition, which remains to be tested at the single cell level (71).

It has been shown that MSC of various species may undergo myogenic differentiation (72, 73). In a mouse model of myocardial infarction it has been seen that MSCs are capable of engrafting in the site of injury and differentiating into cardiomyocyte-like cells expressing typical cardiomyocyte markers (74). Another study showed that in mice undergoing cisplatin-mediated acute renal failure, systemic injection of MSCs resulted in accumulation of MSC in the kidney and differentiation into tubular epithelial cells that exhibited the characteristic brush border of the proximal tubule cells (55). Besides, there have been a number of reports suggesting that MSC differentiate into epidermal keratinocytes and endothelial cells *in vivo* (75, 76). *In vivo*, adipose-derived MSC can migrate through the hemato-encephalic barrier after adhesion to the endothelium (77), and they can differentiate into neuroglial lineages after intraventricular in utero injection in rats (78). However, in humans there is no evidence concerning the neural regenerative potential of MSC.

MSC obtained from different tissue sources show some differences regarding differentiation potential and gene expression profiles. Thus, it has become clear that the microenvironment in which MSCs are transplanted, growth factors and local cellular interactions, play a pivotal role in determining both MSC biology (survival, proliferation, and specific differentiation) and eventually a clinical measurable improvement.

4.2 Fusion

Cell fusion is a process that has an important biological role in the development, physiology and disease of multicellular organisms. For example, we have the zygote formation and organogenesis of various tissues, such as placenta, bone and skeletal muscle. There are different types of cell fusion: homotypic and heterotypic cell fusion. Homotypic fusion happens between cells of the same type; like fusion between myoblasts for the formation and growth of multinuclear myofibres and multinucleated cells during chronic inflammatory conditions. In a heterotypic cell fusion, which describes the fusion between cells of different lineages, we have stem cells, where in specific adult stem cells can be used for clinical therapy by introducing a nuclei or functional genes in aged or degenerating cells (79). Recent reports have indicated that stem cells can fuse with differentiated cells in a range of tissues, including the brain, kidney, heart, lung and liver.

It's known that inflammation promotes migration and infiltration of bone marrow-derived stem cells to sites of tissue injury. Moreover, inflammation also increases the frequency of stem cell fusion. In the brain, chronic inflammation can cause an increase in spontaneous fusion events through the increase of cytokine levels, by activating immune cells or by damaging the blood brain barrier leading to increased permeability (80, 81). Mechanistically, it is important to note that lipid bilayer membranes do not spontaneously fuse, and that fusion between membranes involves a highly intricate choreography of lipids and proteins. Alterations in the cell membrane that are likely to occur during chronic inflammation and the concomitant production of a variety of cytokines may predispose certain cells to fusion events.

Scolding et al hypothesized that endogenous factors associated with inflammation, such as tumour necrosis factor (TNF)- α and interferon (IFN)- γ , may also directly activate stem cells and Purkinje cells to promote fusion. They demonstrated that fusion

between MSCs and cerebellar neurons can occur spontaneously *in vitro*, associated with a markedly higher incidence of the inflammatory mediators such as TNF-alpha and IFN-gamma. The same group, has shown that human bone marrow-derived MSC also exhibit this potentially reparative action *in vivo*, fusing with Purkinje cells in the rodent cerebellum. These function events are also increased in the neuroinflammatory environment of experimental autoimmune encephalomyelitis (EAE), with no apparent loss in Purkinje cell numbers (82).

To confirm this, previous reports have demonstrated fusion between rodent haematopoietic stem cells and rodent Purkinje cells, with increased levels occurring in the context of central nervous system (CNS) or systemic inflammation (80). In another CNS study, Bae et al demonstrated that bone marrow-derived MSC/Purkinje neuron fusion-like events develop into electrically active neurons with functional synaptic formation in the cerebellum of mice with neurodegeneration. Thus, MSCs may be able to integrate into the CNS and contribute to the essential properties of mature neurons (83).

Alvarez-Buylla et al used a simple method based on Cre/lox recombination to detect cell fusion events, demonstrated that bone-marrow-derived cells (BMDCs) fuse spontaneously with neural progenitors *in vitro*. Furthermore, bone marrow transplantation demonstrates that BMDCs fuse *in vivo* with hepatocytes in liver, Purkinje neurons in the brain and cardiac muscle in the heart, resulting in the formation of multinucleated cells, suggesting that genetic material derived from BMDCs contribute through cell fusion to the survival and function of these cells (84).

Adnan and colleagues have show that BMDCs can fuse with a long-lived progenitor or intestinal stem cell population of gamma-irradiated damaged intestinal epithelium and can also fuse with tumor epithelium. Fusion of BMDCs with progenitors or stem cells may play an important role in the regeneration of damaged tissue, and the observation that BMDCs can fuse with tumor epithelium is an important finding also, since the study of this event will enhance the understanding of the biology of tumorigenesis and may provide a novel strategy for the development of anticancer therapies (85).

Other clear beneficial effects of heterotypic cell fusion of BMDCs with other cells types have been demonstrated in a mouse model of a lethal liver disease in which the enzyme fumarylacetoacetate hydrolase is absent, and a large numbers of wild-type BMDCs fused with mutant liver cells corrected the metabolic deficiency and ameliorated the disease phenotype (86).

These studies demonstrate that stem cells are able to fuse with cells of different tissues. However, additional studies in animal models will be required to determine whether this fusion can be used in reparative cell therapy.

4.3 Paracrine factors

Although there are many ways through which stem cells may ameliorate injury, the main mechanism is considered is through paracrine and endocrine functions. Today, a wide range of cytokines and factors are known to be involved in the beneficial interaction between MSC and other cells.

4.3.1 Immunomodulation

Among all theories regarding the paracrine action for MSCs, by far the most explored and discussed by research is immunomodulation. Considering the inflammatory nature of most injuries, studies have indicated that the predominant role of MSCs in resolving tissue

damage relies on toning down inflammation in specific sites of injury. While there are many factors suggested by literature, the main and most frequently pointed out factors and regulated immune cells are discussed ahead.

Monocytes/Macrophages

Since macrophages are one of the main cells responsible for cytokine production in injury sites, these cells are main focus points when immunomodulation is considered. Recent studies have indicated an important role in mesenchymal stem cell monocyte and macrophage immunomodulation. Maggini et al. amongst others have demonstrated that MSCs inhibit macrophage pro-inflammatory cytokine production, i.e. TNF- α , IL-6 and IFN- γ (87-89). MSC also stimulate anti-inflammatory cytokine, IL-10 and IL-12p40 production (87, 88). This way, immune cell activation and the local inflammatory process is contained, reducing tissue damage. MSC also enhance apoptotic cell phagocytosis which is important in clearing injury sites. In addition, these cells inhibit monocyte derived dendritic cell differentiation (90). These effects seem to be due mainly to MSC-derived PGE2 secretion, which has direct effects on macrophage activation.

Dendritic Cells

Dendritic cells (DCs) have essential roles in antigen presentation and lymphocyte profile modulation. MSC are capable of inhibiting DC maturation through cell to cell contact and PGE2 and IL-6 production, as seen through downregulated expression of CD1a, IL-12p70, MHC class II molecules, CD80 and CD86 (91, 92). As T cells depend importantly on antigen presenting cells to become activated, dendritic cell modulation is considered a possible mechanism for T lymphocyte tolerance induction. In addition, MSC treatment also impacts DC migration, as seen in reduced CCR7 expression and reduced migration in response to CCL19 (92). Also, mature type 1 DCs decrease TNF- α production and type 2 DCs increase IL-10 expression which may also induce Th2 profile lymphocytes (93).

T Lymphocytes

Research has shown that T lymphocyte modulation has an important role in the therapeutic character of MSC. For starters, in a disease setting, a considerable percentage of exogenous MSCs tend to accumulate in the spleen and lymph nodes, in particular around immune cells such as DCs, T and B lymphocytes, suggesting cell-specific interaction (94). MSCs are not considered to display important allogenic properties, being immune-privileged, due to low HLA -DR and costimulatory molecule expression and its basic immunomodulatory properties, although a full consensus does not exist towards the degree in which this happens (95, 96). *In vitro*, MSC inhibit phytohemagglutinin mitogen-induced and mixed lymphocyte reaction allo-antigen driven T cell proliferation (97-99). This is done by both cell-to-cell contact and humoral factors in specific, secreting IDO and Galectin-1. These stem cells also decrease TNF- α and IFN- γ T cell production and raise IL-10 secretion, possibly mediated by IDO, PGE2 and B7-H amongst other molecules (100-102). MSCs also induce Th2 type lymphocyte and T regulatory cell differentiation through, HLA-G5 and other molecules (103-105).

B lymphocytes

Although many works have associated MSC and T lymphocyte regulation, few have indicated a direct role in B lymphocyte function, and many published studies are

controversial. Yanfei et al have shown that B lymphocytes have decreased proliferation and antibody production when cultivated with MSC regulated allogenic DCs (106). In addition, other studies suggest that MSC directly inhibit B lymphocyte plasma cell differentiation through humoral factors (107, 108). On the other hand, other studies indicate that mesenchymal stem cells induce B-cell proliferation and differentiation into plasmocytes, when stimulated with a Toll-like receptor 9 agonist (109). These different results are probably due to the different stimuli used and its detailed effect on B cell outcome is still to be discovered.

NK / iNKT Cells

Little information is still known on MSC-mediated NK / invariant natural killer T Cells (iNKT) in comparison to other cell types. Studies demonstrate that MSCs inhibit NK and iNKT cell activation and IFN- γ production by secretion of mediators as HLA-G5 and PGE2 respectively (110, 111). It is also important to mention that NK cells induce MSC lysis, probably due to low HLA class I molecule expression (112, 113). Also, important consideration needs to be given to MSC effects on the immune system in regards to tumor surveillance, due to NK cell inhibition (114).

4.3.2 Angiogenic factors

Angiogenic support provided by MSC can be considered one more supportive effect, since the re-establishment of blood supply is fundamental for recovery of damaged tissues. The pro-angiogenic effect of MSC have been demonstrated in several studies *in vitro* and *in vivo* (115-118).

It is known that MSCs express and secrete *Stromal cell-derived factors 1* (SDF-1), *vascular endothelial growth factor* (VEGF), and other cytokines important for angiogenesis (*Basic Fibroblast Growth Factor* (bFGF); *Matrix metalloproteinases* (MMPs)). VEGF has been identified as a key component in the development of blood vessels, but VEGF alone may be insufficient to achieve functional and mature development of the vasculature. VEGF-induced vessels are often leaky and do not connect appropriately to the existing vasculature (119, 120). SDF-1 activity is essential for endothelial cell survival, vascular branching and pericyte recruitment (121). Interestingly, SDF-1a is not only a mobilization signal capable of recruiting CXCR4- positive progenitor cells into hypoxic tissues but also a retention signal for angiocompetent bone marrow-derived stem cells. It also recruits pericytes and smooth muscle cells to stabilize and mature newly formed blood vessels (122, 123). Thus, SDF-1 has been shown to augment neovascularization by the acceleration of *endothelial progenitor cell* (EPC) recruitment into ischemic foci (122, 124). In addition, VEGF is one of the powerful angiogenic cytokines that can also mobilize EPCs from bone marrow and inhibit EPC apoptosis (125). In the mouse ischemic hind limb model, VEGF-A-mediated angiogenesis partly depends on the activation of the SDF-1 – CXCR4 pathway (124). Taken together, the chemokine SDF-1 likely plays a pivotal role in ASC-mediated angiogenesis (126).

Interestingly, studies have demonstrated that mesenchymal stem cells have the same angiogenesis property. Shintani et al demonstrated that implantation of autologous bone marrow mononuclear cells into ischemic skeletal muscles successfully augmented angiogenesis and collateral vessel formation in both animal studies and human trials (127-129). The same group found that implantation of ASC significantly augmented angiogenesis in a mouse model of hind limb ischemia, by release chemokines such as SDF-1 (126). Kim et al. demonstrated in a preliminary clinical trial that implantation of

human cord blood-derived mesenchymal stem cells enhanced angiogenesis and collateral vessel formation in human cases with Buerger's disease (130). Kamihata and colleagues have reported that bone marrow mononuclear cells that survived engrafting can synthesize angiogenic factors such as VEGF, bFGF, and angiopoietin-1 to induce angiogenesis in the ischemic myocardium (128).

In summary, engrafting MSC in clinical therapy has a beneficial effect, which may be attributable to paracrine action. MSC secrete a number of angiogenic factors and stem cell homing factor that are able to re-establishment of blood supply, being this fundamental for the recovery of damaged tissues.

4.3.4 Anti-apoptotic factors

An important role in MSC-mediated protection is its inhibition of tissue apoptosis and augmentation of tissue turnover. Studies show that MSC are capable of inhibiting apoptosis in kidney, liver and brain injuries (30, 131-133). Recent evidence shows that this is done through increasing pro-survival factors as Akt expression in injured cells (55), BDNF and growth factors as IGF, VEGF and HGF expression which inhibit apoptosis and stimulate cell proliferation (134, 135). Together, this dynamic permits high cell turn-over, renewing damaged cells and decreasing excessive cell death, thus restoring normal tissue physiology.

4.3.5 Anti-oxidative factors

It is well known that MSC mediate tissue repair through paracrine mechanisms. Besides mediating directly in the inflammatory process, some studies have suggested that MSC also possess anti-oxidative characteristics. MSC have been observed to produce many anti-oxidative mediators such as IGF, PDGF, superoxide dismutase (SOD), HGF and IL-6 (136-139). MSC-conditioned media has also been seen to contain these anti-oxidative factors including G-CSF, GM-CSF and IL-12, as reviewed by Kim et al (140). In addition, evidence has supported that MSC and its conditioned media respectively decrease oxidative damage in culture when fibroblast cells are exposed to oxidative damage-inducing environments such as UVB (141) or tert-butyl hydroperoxide (tBOOH) (142).

In addition, research indicates that MSC possess not only considerable ability to support oxidative stress by producing anti-oxidative mediators, but may actually be stimulated by hypoxia-induced ROS (reactive oxygen species). During oxidative stress, MSC seem to have increased proliferation and migration mediated by the Akt and Erk pathways and platelet-derived growth factor receptor- β (PDGFR- β) phosphorylation (143, 144). This however is still controversial. Other studies indicate that oxidative stress correlates with MSC senescence (145, 146). These different results may be consequent to different ROS inducers, and consequently, different levels of ROS production and environmental contributing factors involved.

4.4 Microvesicles and miRNA

The paracrine action of MSC is now well accepted. In this sense, administration of conditioned medium of stem cell in an animal model of kidney injury has demonstrated to improve in clinical parameter outcomes correlated with decreased apoptosis and ameliorated histological parameters. Despite the bioactive molecules secreted by MSC, Bruno et al have showed that inside the conditioned medium also there are some microvesicles.

These microvesicles (MVs) are circular membranes fragments that shed from the cell surface membrane carrying protein and lipids from the membranes of the cells from which they

originate. Besides this, MVs may also carry mRNA and microRNA establishing a communication between one cell and another (147). Shedding of microvesicles is a physiologic process, however some stress conditions lead to an increase in the number of MV shed (148).

Camussi's group has described that mesenchymal stem cells are able to shed microvesicles, and moreover, these MVs carry mRNA and microRNA leading to amelioration of acute and chronic experimental models of renal injury, accelerating regeneration of hepatectomized rats and activating endothelial cells (30, 149-151).

5. Long term aspects of MSC therapy: cancer, immunosuppression or maldifferentiation?

The majority of pre-clinical and clinical studies, which are going on, are incipient. They analyzed the results of treatment in few months or years, not allowing long-term analysis. In these early results, MSC therapy has not shown adverse effects, being designated safe by FDA (152). Thus it is difficult to tell if MSC treatment *per se* may lead to cancer. Nevertheless, several studies have showed that MSC after infusion do not engraft in any tissue, emphasizing the paracrine mechanism of action (152). However, if the treatment is continuous or the MSC administration is repeated, MSC can be found in the injured tissue (32). When MSC is engrafted or even when there is an *in situ* administration, MSC may maldifferentiate. In a model of glomerulonephritis, MSC maldifferentiate to adipose cells in the kidney (35). *In situ* administration of human autologous stem cell therapy in a patient with lupus nephritis has induced angiomylproliferative lesions at the sites of injection and hematuria (153).

All bioactive molecules secreted by MSC are prone to stimulate cancer cells to proliferate and migrate. Some works correlate MSC to suppression of tumor growth, others to supporting it. Several questions may be related to its discrepancy: animal host, timing of injection of MSC, differences in tumor models, etc (154). In addition, MSC may differentiate to tumor associated fibroblast (TAF), cells that support tumor growth (155). Thus, MSC therapy should exclude patients with cancer family history.

Also, the immunosuppression level of MSC therapy cannot be controlled. Once MSC are injected endovenously, immunosuppression is achieved. MSC therapy may compromise the host's defense against infections agents (156).

6. Final considerations

Many advances have been made in the field of mesenchymal stem cells. Nowadays much is known about what the MSC is and how is the mechanism of action. Currently, existing therapies administered exogenous MSC to treat several diseases. Perhaps, a deeper knowledge on endogenous stem cells may bring advances on cell therapy. To activate endogenous stem cells, via stimulation of the niche is an interesting therapeutic perspective. In addition, try to understand what happens to this endogenous stem cell in pathological state is one of the highlights to be discovered.

In the conventional therapy - administration of exogenous MSC - many issues are yet to be solved: amount of injected MSC, the best route of administration, the culture conditions which are not standardized with the use of materials of animal origin, which is the best source for these cells, etc. In conclusion, the field of MSC is very fruitful and still requires to be further studied.

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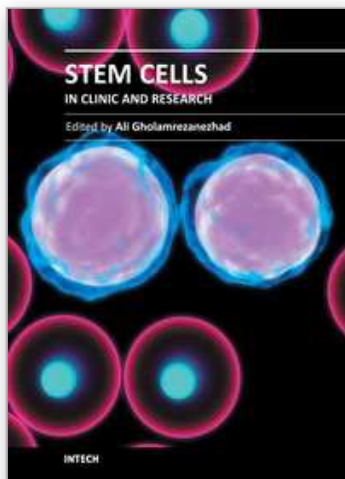
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Based on our current understanding of cell biology and strong supporting evidence from previous experiences, different types of human stem cell populations are capable of undergoing differentiation or trans-differentiation into functionally and biologically active cells for use in therapeutic purposes. So far, progress regarding the use of both in vitro and in vivo regenerative medicine models already offers hope for the application of different types of stem cells as a powerful new therapeutic option to treat different diseases that were previously considered to be untreatable. Remarkable achievements in cell biology resulting in the isolation and characterization of various stem cells and progenitor cells has increased the expectation for the development of a new approach to the treatment of genetic and developmental human diseases. Due to the fact that currently stem cells and umbilical cord banks are so strictly defined and available, it seems that this mission is investigational more practical than in the past. On the other hand, studies performed on stem cells, targeting their conversion into functionally mature tissue, are not necessarily seeking to result in the clinical application of the differentiated cells; In fact, still one of the important goals of these studies is to get acquainted with the natural process of development of mature cells from their immature progenitors during the embryonic period onwards, which can produce valuable results as knowledge of the developmental processes during embryogenesis. For example, the cellular and molecular mechanisms leading to mature and adult cells developmental abnormalities are relatively unknown. This lack of understanding stems from the lack of a good model system to study cell development and differentiation. Hence, the knowledge reached through these studies can prove to be a breakthrough in preventing developmental disorders. Meanwhile, many researchers conduct these studies to understand the molecular and cellular basis of cancer development. The fact that cancer is one of the leading causes of death throughout the world, highlights the importance of these researches in the fields of biology and medicine.

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