Mesenchymal Stromal Cells: Role in the BM Niche and in the Support of Hematopoietic Stem Cell Transplantation

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Abstract

Mesenchymal stromal cells (MSCs) are key elements in the bone marrow (BM) niche where they interact with hematopoietic stem progenitor cells (HSPCs) by offering physical support and secreting soluble factors, which control HSPC maintenance and fate. Although necessary for their maintenance, MSCs are a rare population in the BM, they are plastic adherent and can be ex vivo expanded to reach numbers adequate for clinical use. In light of HSPC supportive properties, MSCs have been employed in phase I/II clinical trials of hematopoietic stem cell transplantation (HSCT) to facilitate engraftment of hematopoietic stem cells (HSCs). Moreover, they have been utilized to expand ex vivo HSCs before clinical use. The available clinical evidence from these trials indicate that MSC administration is safe, as no acute and long-term adverse events have been registered in treated patients, and may be efficacious in promoting hematopoietic engraftment after HSCT. In this review, we critically discuss the role of MSCs as component of the BM niche, as recent advances in defining different mesenchymal populations in the BM have considerably increased our understanding of this complex environment. Moreover, we will revise published literature on the use of MSCs to support HSC engraftment and expansion, as well as consider potential new MSC application in the clinical context of ex vivo gene therapy with autologous HSC.

Introduction

Human bone marrow (BM) niche includes several nonhematopoietic cells, including mesenchymal stromal cells (MSCs), osteoblasts, adipocytes, and endothelial and neural cells that offer physical support to hematopoietic stem progenitor cells (HSPCs) and regulate their homeostasis. In particular, MSCs are crucial elements of the BM niche where they provide newly formed osteoblasts for bone tissue regeneration and tightly control HSPC fate by direct interaction and through the secretion of soluble factors, thus playing a key role in the development and differentiation of the hematopoietic system.¹⁻³ MSCs were first described in 1968 by Friedenstein as a population of adherent cells present in the BM, which exhibited a fibroblast-like morphology and the ability to differentiate in vitro into mesodermal lineages.⁴ Due to the low frequency of mesenchymal progenitors in the human BM, where they only occur for approximately 0.001% to 0.01% of BM mononuclear cells (MNCs), ex vivo expansion of MSCs is necessary to reach sufficient numbers for clinical use.⁵,⁶ To this aim, standardized techniques are available to isolate and expand MSCs from MNCs or CD34 negative fraction of BM aspirates, including the use of culture media added with either fetal calf serum or platelet lysate.⁷,⁸ The International Society for Cellular Therapy has proposed more than 10 years ago minimal criteria for the definition of ex vivo-expanded MSCs based on their ability to adhere to plastic, expression of specific surface antigen expression (positivity for CD105, CD73, CD90; negativity for hematopoietic, endothelial and HLA class II markers) and capacity to differentiate in vitro into osteoblasts, chondroblasts, and adipocytes.⁹ Initially, the ready ability to expand and differentiate MSCs into several mesodermal lineages in vitro made these cells a promising tool for tissue engineering.¹⁰ More recently, several studies have demonstrated that MSCs display broad and potent immunoregulatory properties both in vitro and in vivo.¹¹,¹² In particular, MSCs are capable to sense inflammatory signals and adopt a pro- or anti-inflammatory phenotype to modulate innate and adaptive immunity.¹² These properties have prompted their clinical use in the setting of hematopoietic stem cell transplantation (HSCT), especially for the treatment of immune-mediated complications.¹³ MSCs were first demonstrated to suppress in vitro T-lymphocyte proliferation induced by mitogens and alloantigens by releasing soluble factor such as indoleamine 2,3-dioxygenase (IDO) and PGE2.¹⁴ Thereafter, it was shown that their coculture in vitro with peripheral blood MNCs is associated with the differentiation of CD4⁺ T cells into CD25⁺FoxP3⁺ regulatory T cells,¹⁵; this was confirmed in vivo in experimental models of autoimmune and inflammatory
diseases. The MSC-driven polarization of T cells toward a Treg phenotype, together with their ability to interact with cells of the innate immune system, highlight the role of MSCs in the control of inflammation and maintenance of tissue homeostasis. Indeed, MSCs are capable to regulate the polarization of monocytes (M0) toward M1 and M2 macrophages after sensing the surrounding microenvironment, thus contributing to deliver both anti- and pro-inflammatory signals. In vitro, coculture of monocytes with BM-derived MSCs induces the differentiation of monocytes into M2 macrophages and their secretion of large amounts of the immunosuppressive and anti-inflammatory cytokine IL-10. MSC licensing in an inflammatory environment seems to be fundamental to mediate their immunoregulatory properties. For example, proinflammatory stimuli like IFNγ, TNF, or LPS increase the expression of IDO and the inhibitory effect of MSCs on T cells is more robust when MSCs are pretreated with proinflammatory factors, such as INFγ and TNFα.

Thanks to their immunoregulatory and pleiotropic functions, MSCs has been employed as a therapeutic tool in the clinical arena both in the context of HSCT and in strategies of Regenerative Medicine. MSC treatment has been employed both to enhance hematopoietic stem cell (HSC) engraftment and to treat therapy-resistant acute graft-versus-host disease (aGvHD) after HSCT. In GvHD phase III studies, MSC intravenous infusion has been shown to be safe and a valuable therapy for patients with the severe, refractory aGvHD, especially in children and when performed early in the course of the disease. Phase III, multicenter, academic studies are ongoing in Europe with the aim to define the role of MSCs in the management of aGvHD and to treat product and patient’s factors that able to predict response to MSCs in vivo (HO113, EudraCT 2012-004915-30). In this respect, Galleu et al have recently reported that delivery of MSC immunosuppressive effect occurs after induction of perforin-dependent apoptosis by recipient cytotoxic T-cells and suggests that patients affected by GvHD should receive ex vivo apoptotic MSCs. MSCs have also been successfully employed in approaches of Regenerative Medicine to re-establish tissue homeostasis and promote repair in autoimmune and inflammatory disorders, such as refractory Crohn disease.

In this review, we critically discuss the role of MSCs in the maintenance of HSPCs within the BM niche, as well in transplant strategies to facilitate HSC engraftment and expansion. Moreover, we will introduce their potential use in the context of ex vivo gene therapy with the aim to support both the expansion and the engraftment of gene-modified autologous HSCs (Fig. 1).

Role of MSCs in the BM niche

The understanding of the role of MSCs in the BM niche has been limited for a long time by the absence of in vivo MSC markers to track their phenotype and localization. However, the hypothesis that MSCs play a pivotal role in regulating the hematopoietic compartment in the BM niche was supported by data showing colocalization of MSCs with sites of hematopoiesis, starting from embryonic developmental stages.

Identification of novel markers of mesenchymal progenitors and development of genetic tools to conditionally delete key factors in the niche has greatly increased in the recent years our knowledge on the mesenchymal compartment of the BM niche and on some of the pathways controlling its complex regulation. In particular, recent studies have been focused on identifying the MSC subsets which are mainly involved in the regulation of HSPC homeostasis. Sacchetti et al first reported that CD146 marker labels human BM cells residing in the sinusoidal wall that are enriched for CFU-F activity and are capable to support hematopoietic activity when transplanted as heterotopic ossicles in immunodeficient mice, by transferring a hematopoietic microenvironment. These cells could be isolated from the ossicles and were found to display clonogenic capacity and self-renewal ability in vivo. Mesenchymal cells localized in the trabecular region of the human BM that stained positive for CD271 marker were later identified and differentiated by the CD146+ perivascular cells. Also these CD271+ MSCs showed high CFU-F capacity, ability to transfer a BM microenvironment upon transplantation and to differentiate in vitro into mesodermal mature cell lineages. Altogether these data indicate that different subtypes of MSCs exist in the BM niche and interact with HSCs in specific perivascular regions. In particular, CD271+ and CD271+/CD146+ hemMSCs have been described as bone-lining cells which are associated with long-term HSCs in low oxygen areas, whereas CD146+ and CD271+/CD146+ are located around BM sinusoids in association with activated and fast-proliferating HSPCs. However, a more dynamic concept of BM niche is emerging with primitive HSCs mainly localized along the sinusoidal vessels, closely associated with MSCs, integrating signals from the endosteal niche and able to migrate toward the bone-lining vessels, for example, after BM irradiation.

One of the critical functions of MSCs within the niche is the secretion of soluble factors, including CXCL12 and stem cell factor (SCF), which contribute to HSPC maintenance. Nestin+ MSCs, which are innervated through parasympathetic nerve fibers, have been identified by Mendez-Ferrer group in mouse BM as niche key elements thanks to the expression of high levels of CXCL12. These cells display a perivascular location in close proximity with HSPCs and participate to the prenatal development of the HSC niche. Nestin+ cell subsets such as Nes-GFPbright and Nes-GFPdim cells were also identified: while the first is a rare population associated with arterioles, the second is more abundant and mainly accompanying sinusoids. Nes-GFPbright cells were later identified as NG2+ which have been reported to constitute an important source of CXCL12 factor, and not SCF, in the niche. The deletion of these perivascular Nestin-GFP+ cells using Nestin-Cre was associated with depletion of HSCs, highlighting their fundamental role in the niche as major producers of key factors.

In a CXCL12-GFP knock-in mouse, CXCL12-abundant reticular cells were identified as a population of mesenchymal progenitors within the BM intratrabecular space that are capable to differentiate into osteoblasts and adipocytes in vitro and in vivo and to produce large amounts of SCF. The majority of these cells were found to express Leptin receptor (Lepr) and their depletion was paralleled by reduction in quiescent HSCs. Lepre expression has been employed to identify primitive MSCs in the adult murine BM and Lepr+ cells were found near the sinusoids and small diameter arterioles. Ding and Morrison demonstrated that the majority of MSCs positive for SCF or CXCL12 express also Lepr and that the deletion of these genes in the mesenchymal precursors by using a Lepr-driven Cre-recombinase was associated with depletion of HSCs.

Mx-1 Cre-recombinase was found to identify a population of nonhematopoietic, nonendothelial mesenchymal progenitors in the bone which shows characteristics very similar to Nestin-GFP+ cells, including clonogenic capacity, ability to transfer hematopoietic activity and to undergo trilineage differentiation. Also paired related homeobox 1 (PRX1) and osterix (OSX) transcription factors have been reported to label mesenchymal progenitors in the BM with CFU-F activity and multilineage differentiation potential.
Gremlin1 (Grem1) has been recently described to identify a population of mesenchymal precursors that does not express Nestin and displays the ability to differentiate into osteoblasts, chondrocytes, reticular marrow stromal cells, but not adipocytes in vivo. Available knowledge does not allow to distinguish between these different MSC populations based on their function because they all display clonogenic and differentiation capacities. Moreover, the anatomical localization of mesenchymal progenitors in relation with the niche vasculature has never been systematically analyzed. It is reasonable to speculate that MSCs are more frequently associated to sinusoids, given their higher number, as compared with arterioles. Noteworthy, it should be noted that artificial models based on the deletion of single molecules may not properly reflect the in vivo situation where a plethora of factors are produced by different niche cells that interact in a complex regulatory network to maintain HSPC functions. Therefore, a more detailed characterization of the MSC subsets in vivo, based on their physical localization, function and cytokine secretion profile, is necessary to better understand their biology and exploit them for clinical use.

MSCs in preclinical models of HSCT

MSCs have been first demonstrated in experimental animal models to be capable to promote engraftment of HSCs and to prevent graft failure (see Table 1). Almeida-Porada et al observed that cotransplantation of human MSCs into preimmune fetal sheep resulted in enhancement of long-term engraftment of human cells in the BM and peripheral blood of the animals. Noort et al reported similar results in a cotransplantation model of fetal lung-derived MSCs and UCB-derived CD34+ cells in nonobese diabetic severe combined immunodeficient (NOD-SCID) mice and the enhanced engraftment could be maximized when low numbers of HSCs were coinfused with MSCs. In immunodeficient mice, cotransplantation of placenta-derived MSCs facilitated engraftment of double umbilical cord blood...
transplantation (UCBT) and reduced single cord predomi-
nance. Also in nonhuman primates, cotransplantation of
baboon-derived MSCs improved HSC engraftment after intrave-
nous infusion. Kuci et al reported that cotransplantation in
NOD-SCID mice of CD133+ HSCs and CD271+ MSCs, one of
the markers reported to label the most primitive and clonogenic
MSCs, was associated with significantly greater hematopoietic
engraftment, as compared to the coinfusion of an unselected
population of ex vivo-expanded MSCs. Fernandez-Garcia et al
showed that the coinfusion of not only BM-derived, but also
adipose tissue-derived MSCs with low numbers of HSCs
significantly enhanced short- and long-term hematopoietic
reconstitution in an autologous transplant setting in mice. Intra-
ossos cotransplantation of MSCs and HSCs could be also
employed as a strategy to improve hematopoietic engraftment,
as recently demonstrated in NSG mice human UCB-derived
HSCs.

Altogether, these preclinical data confirm the ability of MSCs
to support HSC engraftment in vivo in animal models of both
autologous and allogeneic HSCT, in the absence of toxicity. This
opens the possibility of employing MSCs also in the context of ex
vivo HSC gene therapy where autologous, patient-derived HSCs
are genetically modified ex vivo before infusion into patients. In
this view, MSCs can be adopted in vitro as a tool to maintain
primitive HSCs during the gene correction procedures and
eventually employed in vivo to promote the engraftment of gene-
corrected HSCs (see also Fig. 1 for a schematic representation). In
this regard, Fernandez-Garcia et al have recently reported that the

Table 1

| Animal Model                  | MSC Origin | Outcome                                           | Ref. No. |
|------------------------------|------------|---------------------------------------------------|----------|
| Preimmune fetal sheep        | Human BM   | Enhancement of human HSC engraftment               | 40       |
| NOD-SCID mouse               | Human BM   | Enhancement of human HSC engraftment               | 41       |
| NOD-SCID mouse               | Human placenta | Enhanced engraftment of double UCBT, reduced single donor predominance | 42       |
| Nonhuman primate             | Baboon BM  | Enhancement of HSC engraftment                     | 43       |
| NOD-SCID mouse               | Human BM   | Promoted lymphoid engraftment after CD133+ HSC Tx | 44       |
| NOD-SCID mouse               | Human BM   | Promotion of engraftment after intraosseous transplation of human HSC | 46       |

Ex vivo-expanded MSCs have been administered to patients in a
number of phase II/III clinical trials of HSCT with the aim of
facilitating HSC engraftment (see Table 2) and to treat steroid-
resistant aGvHD. While feasibility and safety of MSC infusions
have been demonstrated in these studies, clinical efficacy needs be further proved in phase III randomized trials,
together with the identification of product and patient’s variables
predicting response to MSC treatment.

The first phase II/III clinical trial testing the coinfusion of MSCs
in the context of HSCT enrolled 28 patients affected by breast
cancer who received autologous peripheral blood mobilized
HSCs and MSCs at a dose of 1 to 2 x 10^6 MSC/kg with the aim of
accelerating hematological recovery. Patients showed rapid
hematopoietic reconstitution in the absence of any toxicity.

In another phase II/III, multicenter trial 46 patients undergoing
allogeneic HSCT from an HLA-identical sibling for hematologi-
Similar results were reported in a larger group of 44 patients affected by severe aplastic anemia (SAA) and undergoing haplo-HSCT without T-cell depletion received the coinfusion of third-party donor UCB-MSCs with the double aim of facilitating HSC engraftment and preventing GvHD development. All patients showed sustained hematopoietic engraftment without any adverse reaction and a low incidence of severe aGvHD (5%).

In the setting of UCB transplantation, ex vivo-expanded MSCs and unrelated donor UCB HSPCs were administered to 8 children; also in this study safety record was good and neutrophil recovery was prompt (median time: 19 days) and sustained. In another phase II/I study, UCB-derived HSCs and parental MSCs were cotransplanted in 13 pediatric patients with no differences in the engraftment kinetics of UCB-HSCs between study patients and controls, while a protective effect on acute and chronic GvHD occurrence and no GvHD-associated transplant-related mortality were noted.

Overall, these data demonstrate the feasibility and safety of cotransplanting HSCs and MSCs in the clinical setting; moreover, this approach was associated with prompt hematological recovery and low graft failure rate. A formal proof of the benefit of MSCs over standard HSCCT (ie, no MSC coinfusion) should be obtained in randomized clinical trials.

The exact mechanisms by which MSCs exert their functions have not been completely clarified, although it is commonly believed that both cell-to-cell contact and secretion of soluble factors play a role. A potential mechanism through which MSCs might contribute to the engraftment of donor HSCs, thus reducing the risk of graft failure, is their ability to restore the BM microenvironment which has been damaged by the conditioning regimen through the secretion of paracrine mediators. This aspect may be particularly important in the context of genetic diseases affecting both the hematopoietic compartment and the BM niche, where the restoration of a proper environment is fundamental to facilitate the engraftment of gene-corrected HSCs. In the context of mismatched transplants such as haploidentical HSCT, MSCs may also be capable to modulate residual host alloreactivity thanks to their immunoregulatory properties, which include cell-to-cell contact mechanisms and release of soluble factors. It is well known that MSCs release extracellular vesicles (EVs) that contain several classes of RNAs involved in the control of transcription, cell proliferation, and immune regulation. Recent studies have reported that the immune regulatory and anti-inflammatory signals delivered by MSCs may be mediated at least in part by MSC-derived EVs. A recent paper demonstrated the existence of an EV-mediated powerful cross-talk between MSCs and UCB-derived CD34+ cells capable to influence HSC biological functions, such as viability, differentiation, and migration. Moreover, MSC-EVs have been already employed in the clinical setting to alleviate symptoms of aGvHD in a patient with treatment-resistant, grade IV manifestations likely due to reduction of the proinflammatory cytokine response, in the absence of side effects.

Limited evidence is available also on the engraftment of human MSCs after infusion in vivo, which seems to occur for a very limited fraction of the cells, at least when ex vivo-expanded MSCs are employed. A recent paper from Abbuehl et al indicate that, after intrabone transplantation, primary, but not culture-expanded murine MSCs can engraft in the BM after irradiation. Another important limitation of our knowledge on MSC biology comes from the fact that experimental and clinical data available have been largely obtained with ex vivo cultured cells. Whether primary human MSCs in vivo display the same biological and functional properties of expanded cells is not clearly understood because of their low frequency in the BM which requires in vitro expansion.

In addition, MSCs have been shown to stimulate ex vivo expansion of HSCs before infusion into patients. In a 2D system, the coculture of UCB-derived HSCs and MSCs resulted in higher numbers of total nucleated cells, CD34+ and CD133+ HSCs and CFU-F activity, as compared with standard liquid culture. In a phase I/I clinical trial of double UCBT, 2 UCB units, 1 expanded ex vivo over MSCs and 1 unexpanded, were infused into 31 adult patients with hematological malignancies. Significantly improved neutrophil and platelet engraftment, as compared with historical controls receiving 2 unmanipulated UCB units, was registered together with a good safety profile of the approach. The same group recently confirmed these results in 27 patients undergoing double UCBT after a reduced intensity conditioning regimen and reported a cumulative incidence of neutrophil engraftment on day 26 of 73% with UCB expansion versus 50% without expansion.

The demonstration that the human niche can be modeled in vitro by MSC-HSC coculture has been widely reported; however, the spatial relationship between these 2 cell types in a 2D culture system during ex vivo expansion has been investigated by Jing et al. The authors identified 3 distinct localizations of HSPCs in vitro in relation to the stromal layer: cells floating in the supernatant, phase-bright cells adhering to the MSC surface and containing the highest proportion of proliferating progenitors and phase-dim cells localized beneath the MSC layer cells and characterized by a lower cycling rate and a more immature phenotype. Thanks to these hematopoietic supportive properties, MSCs could also be adopted to maintain and expand ex vivo primitive HSCs during gene correction procedures in gene therapy approaches. Preliminary data from our group support the finding that MSCs are capable not only to expand HSCs in 2D cultures, but also to preserve their primitive phenotype (Crippa et al, unpublished) defined according to specific surface markers able to identify primitive HSC subsets among CD34+ cells. Moreover, 3D scaffold models based on bioreactors are now available to reproduce ex vivo the BM niche and to sustain more efficiently primitive HSCs. Another possible approach could be the selection of a specific MSC subset to improve the hematopoietic supportive capacity of MSCs in vitro and in vivo.
in vivo in NSG mice a humanized BM niche are becoming available; these models will greatly improve our understanding of the biology and architecture of the mesenchymal compartment, as well as of their interactions with HSPCs in healthy subjects and in patients (Fig. 1 for a schematic representation).

Conclusions and future directions

Clear evidence from preclinical and clinical data indicates that MSCs are key elements in the BM niche where they participate to the regulation of HSPC homeostasis and fate through complex regulatory networks.1–3 The use of putative markers for the prospective isolation of primary MSCs in vivo and of genetically modified mice with conditional deletion of key niche factors have significantly improved our understanding of MSCs; however, further studies are needed to augment our knowledge on the biology of the different MSC subsets and their hierarchical organization within the BM niche. In vivo models, in which a single factor in a specific mesenchymal cell subset is deleted, have clear limitations and may not reflect the in vivo situation and the relationship between different MSC subpopulations endowed with different functions.4–6 A thorough comparison between MSC subsets in vivo and their ex vivo-expanded counterparts in terms of immunophenotype, functional abilities, and secretome profile is also needed to better instruct the clinical application of the cells.

Clinical data from phase I/II studies support the clinical use of MSCs in the setting of autologous and allogeneic HSCT with the aim to facilitate engraftment of HSCs. Two different strategies can be considered: the ex vivo expansion and maintenance of primitive HSCs in 2D or 3D culture systems before infusion into patients and the coadministration of MSCs and HSCs in transplantation strategies (Fig. 1).19,49,50 These approaches could be employed in the future not only in the setting of standard autologous and allogeneic transplantation, but also in ex vivo HSC-gene therapy approaches to optimize its outcome when low numbers of corrected cells are available (ie, after gene editing).71

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