TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

REVIEW

Caveats of mesenchymal stem cell therapy in solid organ transplantation

Jan Haarer, Christian L. Johnson, Yorick Soeder and Marc H. Dahlke

Department of Surgery, University Hospital Regensburg, Regensburg, Germany

Keywords
mesenchymal stem cells, risks, solid organ transplantation, stromal cells.

Correspondence
Marc H. Dahlke MD, PhD, Department of Surgery, University Hospital Regensburg, 11 Franz Josef-Strauss-Allee, Regensburg 93053, Germany.
Tel.: +49 941 944 6812;
fax: +49 941 944 6858;
e-mail: marc.dahlke@ukr.de

Conflicts of interest
The authors have declared no conflicts of interest.

Received: 6 May 2014
Revision requested: 26 May 2014
Accepted: 26 July 2014
Published online: 30 September 2014

doi:10.1111/tri.12415

Summary

In the past decade, therapeutic use of mesenchymal stem cells (MSCs) has increased dramatically. The weight of existing evidence supports that the short-term application of MSCs is safe and feasible; however, concerns remain over the possibility of unwanted long-term effects. One fundamental difference between MSCs and pharmacotherapy is that, once applied, the effects of cell products cannot be easily reversed. Therefore, a carefully considered decision process is indispensable before cell infusion. In addition to unwanted interactions of MSCs with the host immune system, there are concerns that MSCs may promote tumor progression or even give rise to cancer themselves. As animal models and first-in-man clinical studies have provided conflicting results, it is challenging to estimate the long-term risk of individual patients. In addition, most animal models, especially rodents, are ill-suited to adequately address questions over long-term side effects. Based on the available evidence, we address the potential pitfalls for the use of MSCs as a therapeutic agent to control alloimmune effects. The aim of this review was not to discourage investigators from clinical studies, but to raise awareness of the intrinsic risks of MSC therapy.

Introduction

Mesenchymal stem cells (MSCs) are versatile, multipotent adult stem cells. They are capable of differentiating into osteoblasts, chondroblasts, myocytes, and adipocytes [1]. Furthermore, neuronal progenitor cells, as well as lung epithelial and renal tubular cells, can be derived from MSCs [2–4]. In common with hematopoietic stem cells (HSCs) and endothelial stem cells, MSCs can be easily isolated from bone marrow, as well as various other tissues such as adipose, kidney, liver, and lung [4]. In addition to their use in regenerative medicine, MSCs have gained attention because of their immunoregulatory properties. It has been demonstrated that co-transplantation of MSCs together with HSCs fosters immune reconstitution while decreasing incidence of graft-versus-host disease (GvHD) [5]. MSCs have also been shown to enhance wound healing by promoting angiogenesis [6]. The immunogenicity of MSCs is low and associated with negligible rejection of human leukocyte antigen-mismatched (HLA-mm) cells when transferred into a HLA-mm host [7].

In the field of solid organ transplantation, an increasing number of clinical trials are now focusing on MSCs and attempting to harness their low immunogenicity and immunoregulatory properties for the use as novel therapeutics in the treatment of graft rejection [8–10]. In current clinical practice, pharmacological immunosuppression is essential for prolonging graft survival. Immunosuppressive regimens vary but typically require combinations of potent immunosuppressive drug including cyclosporin, mycophenolate, rapamycin, tacrolimus, and corticosteroids. An all-too-frequent complication experienced by patients receiving pharmacotherapy is an increased risk of opportunistic infections from potentially lethal bacteria, viruses, and fungi. Lifelong immunosuppression is also associated with an increased risk of *de novo* malignancies. These side

effects of immunosuppression lead to high transplant-related morbidity overall [11], which challenges the notion of transplantation as a long-term curative therapy. Thus, novel immunomodulatory strategies are urgently needed to overcome these limitations.

In addition to the notable clinical properties of MSC, their production bypasses the ethical issues associated with other stem cell sources, such as those derived embryonically. MSCs may contribute to improved graft outcome in solid organ transplantation via two modalities. The immunomodulatory capacity of MSCs can lower the need for immunosuppressive drugs [12,13], and increased wound and organ healing together with neovascularization may provide additional benefits [6,14].

Nevertheless, the therapeutic use of MSCs might be a double-edged sword. While the hypoimmunological or "immunoprivileged" state of MSCs can be beneficial for allogeneic organ transfer, there are concerns that precancerous MSCs will not be rejected by the host immune system and increase the risk of donor MSC-derived malignancies [15,16]. Furthermore, MSCs can promote the transformation and growth of pre-existing tumors in the host by suppressing the antitumor response of the host and promoting tumor vascularization [16–18]. In addition to the increased cancer risk, dedifferentiation of MSCs may lead to the emergence of more therapeutically desired cells but also give rise to cells with no therapeutic or even detrimental effects [9]. It has already been shown that unintended dedifferentiation of MSCs can affect healthy tissues and interfere with their physiological functions [4]. Taken together, it remains difficult to estimate the long-term side effects of MSC therapy. No severe side effects have been reported in phase I clinical trials using allogeneic MSCs, whereas conflicting results have been obtained from animal models.

MSC-derived tumors

A critical issue regarding the therapeutic use of MSCs in transplant rejection is the potential for induction of donor-derived *de novo* malignancies in the recipient. It is recognized that immunosuppressive pharmacotherapy inhibits the antitumor immune response that is essential in suppressing precancerous cell development. For example, 35% of patients treated with tacrolimus following liver transplantation had an overall risk of developing cancer up to 15 years after transplantation compared with 9% of patients in an age-matched control group. This study, which included more than 600 patients, demonstrated a clear link between the degree of HLA mismatch, therefore the extent of immunosuppressive drug usage, and the risk of cancer [19].

By applying this risk assessment to MSCs, two potential risk factors that facilitate MSC transformation were identified. Unlike HSCs that are adequately defined by markers such as CD34, thus permitting clinical-scale enrichment using magnetic-activated cell sorting, such markers have not been defined for MSCs [20]. A lack of a MSC-specific marker or signature has made it challenging to track the distribution and fate of MSCs after infusion with current technologies. Moreover, CD34+ stem cells can be administered directly without the need for an extended cultivation period. In contrast, MSC isolation is limited to cell culture techniques such as plastic adhesion. This procedure involves a certain degree of *in vitro* manipulation and cell expansion [21,22]. Importantly, a small proportion of freshly isolated human MSCs acquire chromosomal abnormalities at early passages (0–4) of cultivation [23]. In an immune-competent MSC recipient, programmed cell death and the immune response might be effectively control this risk of malignancy. However, in an immune-compromised host, a defect in cell cycle checkpoints and a lack of immune cells that are capable of detecting and clearing malignant cells might lead to the enrichment of these cells.

Currently, it is unclear which factors influence MSC differentiation and growth arrest *in vivo*. Cell culture conditions can have a strong influence on the development of chromosomal abnormalities *in vitro*. In cell culture studies using mouse and human MSCs, aneuploid karyotypes have appeared in both cell types after only 9–15 passages. In mice, chromosomal instability *in vitro* has been associated with malignant transformation *in vivo*. The mechanisms that drive MSC transformation remain largely unknown. Transformed cells grow independently from external growth arrest signals such as contact inhibition. During *ex vivo* cultivation, these cells will outgrow nontransformed cells. Therefore, prolonged cultivation may lead to the enrichment of transformed cells.

Human and mouse MSCs, as with all nucleated cell types, have tumorigenic potential. Aneuploid karyotypes have been found in both human and mouse MSCs at early passages (5–6) [15,24,25] and late passages (9–15) [11,26]. Immuno-incompetent nude and severe combined immunodeficient (SCID) mice injected with bone marrow-derived (BM) MSCs from syngenic Bl6 mice develop sarcomas alongside the injection sites [15]. These results were independent of pretreatment of the mice. Tumor development was also independent of the site of injection and the genetic background (nude, SCID, or immunocompetent BL6) as well as the passage number of the cells. Karyotypic analysis revealed that chromosomal alterations were common under the tested culture conditions, indicating that tumorigenesis is not the result of a single transformed cell clone. Interestingly, when the same protocol was used and the experiment repeated in rats, no tumor formation was observed [15]. Moreover, the rate of transformed cells in rat BM MSC cultures was markedly reduced compared

with that of their murine counterparts. These data emphasize that findings in mouse models may not apply to other (human) conditions, particularly in terms of tumorigenesis. Even short periods of culture are sufficient to induce alterations in DNA copy numbers in human MSCs [27]. However, these chromosomal aberrations do not result in transformation even when the cells are cultured beyond senescence (>15 passages). Interestingly, differences in the DNA content of one MSC cell clone at an early passage become undetectable at later passages, indicating that intracellular tumor suppression mechanisms function sufficiently to clear precancerous cells from culture. Investigation of epigenetic stability has revealed that DNA methylation patterns remain largely stable even in long-term culture [28].

Transformation of *ex vivo* cultivated MSCs may be a unique property of mice [29,30].

While inbred mouse strains will carry identical copies of the majority of their genes, it is unlikely that a human will carry identical copies of tumor suppressor genes and genes that regulate the cell cycle. In an inbred mouse, a deleterious gene mutation in one chromosome rarely can be compensated by a second functional copy of the gene. Thus, MSCs derived from inbred mouse strains will be more prone to transformation and tumor formation, especially because these mouse strains tend to form tumors upon aging. Therefore, the differences observed between humans and mice may be the result of comparing a wild-type population (humans) to an inbred model (mice). Indeed, the use of Bl6/129 hybrid mice results in a markedly reduced tendency for tumor formation when transferring Bl6/129 MSCs into immune-incompetent nonobese diabetic (NOD)/SCID mice [25] (see also Table 1).

Tumor formation in mice is largely dependent on the immune competence of the donor strain. When transferring MSCs between immune-incompetent NOD/SCID mice, all recipients develop tumors. When transferring MSCs from syngeneic but immune-competent Bl6/129 mice into NOD/SCID mice, tumor formation is reduced to one of six animals [25]. These data emphasize that *in vivo* MSC transformation depends on the donor rather than the recipient. In human MSCs, chromosomal abnormalities are detected less frequently. Recent studies show that *de novo* aneuploidy in human adipose-derived MSCs (ASCs) can develop upon cultivation, but it fails to induce tumor formation in immunodeficient mice [23]. One study reporting spontaneous malignant transformation of human MSCs *in vitro* was not reproducible [26].

Current evidence supports the view that the MSC recipient immune status is of relatively minor significance, while MSC donors require careful selection. As a precaution, genes known to be involved in tumor suppression in human MSCs (reviewed in [29]) might be sequenced prior to MSC transplantation. Thus, it would be possible to ensure that the donor does not carry disadvantageous gene variants and that both gene copies are diverse.

To date, there have been no reports of donor MSC-derived *de novo* malignancies in humans although more than 700 patients have been treated with MSC products as reviewed in [30].

MSCs promote tumor growth

Another important issue when considering MSCs as a therapeutic agent to control transplant rejection is the progression of host-derived tumors that do not originate from the infused cell product. In addition to the risk of MSCs transforming into cancerous or precancerous cells *in vitro*, MSCs reportedly can promote tumor growth or metastasis *in vivo* [31,32]. Human MSCs can migrate into tumor stroma where they inhibit proliferation and apoptosis of transformed cells [18]. An increased potential for metastasis was further reported in a mouse xenograft model. Human BM MSCs showed a markedly increased potential for metastatic tumor formation when a mixture of breast cancer cells and MSCs was transplanted into mice following cocultivation [31]. In a similar model, MSCs promoted the vascularization of transformed tissues [32].

In line with these results, a phase I clinical trial has shown marked reductions in the incidence and severity of acute GvHD (aGvHD) following MSCs/HSCs cotransplantation. Three of 10 patients treated with MSCs experienced grade I aGvHD, whereas 11 of 14 patients in the control group experienced aGvHD, of which nine had grade II

Table 1. Tumor formation in murine models.

Donor	Recipient	Genetic background	Tumor incidence	Immune-competent (donor/recipient)		Ref.
BL6	BL6	Inbred/inbred	100%	Yes	Yes	[16]
BL6	Balb/c	Inbred/inbred	100%	Yes	Yes	[15]
NSG	NSG	Congenic/congenic	100%	No	No	[25]
BL6/129	NSG	Crossbred/congenic	16%	Yes	No	[25]
BL6/129	BL6/129	Crossbred/crossbred	0%	Yes	Yes	[25]
Human	NSG	Crossbred/congenic	0%	Yes	No	[25]

aGvHD. Relapse occurred in seven of 10 patients treated with MSCs, whereas relapse only occurred in three of 14 patients in the control group [33]. However, in the previous study, both the HSCs and MSCs were derived from HLA-identical siblings. A study using HLA-mm HSCs and MSCs from unrelated donors for transplantation following a nonmyeloablative conditioning regiment indicated that MSCs might lower GvHD mortality without changing the graft-versus-tumor effect [34].

The risk of *de novo* malignancy has been examined in a mouse model in which a bioscaffold was repopulated with MSCs [16]. About 80% of animals treated with MSC-preseeded bioscaffolds developed sarcomas, whereas animals treated with MSCs or the bioscaffold alone did not develop sarcomas. In the previous study, development of host-derived sarcomas was found when MSC-preseeded bioscaffolds were transplanted into immunodeficient recipients. However, the formation of donor-derived sarcomas was not observed in allogeneic hosts. Interestingly, tumors were not formed when MSCs were injected directly. Further analysis revealed that tumor formation was facilitated by donor MSC-driven expansion of host $CD4^+CD25^+$ regulatory T cells (Tregs). *In vitro*, Tregs blocked splenocyte proliferation upon challenge with MSC-derived sarcomas, but not donor MSCs themselves. In the presence of MSCs, tumor-specific Tregs proliferated and sufficiently blocked splenocyte proliferation, whereas the splenocyte proliferative capacity was comparable to that induced by challenge with allogeneic cells.

In addition to MSC-mediated immunosuppression and promotion of angiogenesis, MSCs may influence the persistence of tumors by a third mechanism. Upon exposure to platinum analogs, MSCs release polyunsaturated fatty acids (referred to as platinum-induced polyunsaturated-trans-fatty acids, PIFAs) capable of mediating resistance to chemotherapy [35]. In a mouse tumor model, injection of a low number of MSCs at a distant site from the tumor was sufficient to induce systemic resistance to cisplatin. Interestingly, MSCs also mediated resistance to nonplatinum analog drugs such as 5-FU when they were preconditioned with cisplatin. Although clinical experience remains somewhat limited, we should nevertheless exercise caution when considering the use of cisplatin in patients previously treated with MSCs.

Dedifferentiation as a potential long-term effect

Replacement of disrupted tissues by MSC-derived cells, such as cardiomyocytes following myocardial infarction, has raised the expectations of MSC therapy, although differentiation mechanisms have remained elusive in some models. Furthermore, it is largely unclear how MSCs home to sites of injury and which factors drive their differentiation. For example, while human MSCs repopulate bone marrow in sheep and nonhuman primates, such a homing capacity cannot reproduced in mice [4, 36,37].

Bone marrow-derived HSCs can home to the bone marrow and other known stem cell niches, whereas the migratory pathways for MSCs are unclear. In a mouse model using green fluorescent protein (GFP)-tagged BM MSCs, the MSCs did not follow a defined migration pattern. In a variety of tissues, GFP-tagged MSCs were present alongside blood vessels. Most MSCs were located in the lung, likely a result of mechanical impedance in the capillary system. It was further shown that a large proportion of these MSCs transdifferentiated into fibroblasts rather than lung epithelial cells. The mice became dyspneic, lost weight, and were sacrificed at 28 days post-MSC injection [25].

In a mouse heart infarction model, infusion of MSCs or unfractionated BM-derived cells resulted in calcification and ossification at the injection sites. Moreover, MSCs infused via the tail vein did not migrate to sites of injury or transdifferentiate into cardiomyocytes [9]. On the other hand, in a study addressing the long-term effects of human ASCs in a SCID mouse model, subcutaneously injected human ASCs were neither found to be dedifferentiated nor transformed up to 17 months post-transplantation [38]. To the best of our knowledge, no clinical trials published to date contain reports of harmful dedifferentiation.

In humans, hypoxic conditions induce dedifferentiation in various kinds of tumors including ductal breast cancer, neuroblastoma, and lung cancer cells [39–41]. Hypoxia affects Jagged/Notch signaling and OCT3/4 expression, both of which are critical for differentiation and self-renewal of stem cells [42-45]. In addition, it is becoming more evident that oxygen tension is a key regulator of the fate of MSCs [46,47]. The dedifferentiation described in references [25] and [9] may have been fostered by hypoxic conditions induced either by cryoinjury of the heart or embolization of the lung capillaries. In line with these findings, osteosarcoma-like lesions were restricted to the lung and were not found in other organs such as the kidney, liver, or heart [25].

Immuno-challenge

Yet to be fully evaluated are the long-term effects of MSCs on the immune system. From an immunological viewpoint, two major risks arise from the therapeutic use of MSCs. In the short term, MSCs are hypoimmunogenic both *in vitro* and *in vivo*; however, allorejection might develop over time, lowering the therapeutic efficacy of MSCs. Second, it is unclear whether terminally differentiated tissues that arise from MSCs will be hypoimmunogenic as well. Rejection might either be driven by donor HLA-reactive host T cells

or by donor antibodies against minor histocompatibility complexes or to blood group antigens (AB0 antigens) [48,49]. The latter are expressed by neither native MSCs nor *in vitro* differentiated MSCs [50]. In a recent study, it was demonstrated that clinical-grade MSCs do not express AB0 antigens or upon treatment with interferon-γ (IFN-γ), in a mixed lymphocyte reaction (MLR), or following adipogenic or osteogenic induction [51]. However, exposure of MSCs to AB plasma (ABP) induces subsequent blood clotting *in vitro*. Furthermore, blood group 0 recipients treated with ABP-exposed MSCs show a tendency for a lower clinical response, indicating that rejection can also be triggered by transfer of culture medium components rather than antigens expressed by MSCs [51]. In line with these findings, antibodies against fetal calf serum (FCS) have been found in patients treated with MSCs and HSCs up to 12 months post-transplantation [52]. The same study also revealed that antibodies against MSCs were detectable at 6–12 months post-transplantation in patients that did not show MSC-reactive antibodies prior to transplantation. Notably, two of 10 patients had MSC-reactive antibodies prior to MSC transplantation. Even if MSCs are hypoimmunogenic, it should be kept in mind that patients might have been presensitized to non-HLA antigens by previous treatment with blood products or by disease-associated AA amyloidosis as examples [48,49]. Therefore, while initially MSC infusion might be well tolerated, rejection may be triggered by successive treatments because of the carryover of cell culture components used in MSC production, such as FCS or ABP [51,52]. However, as both studies focused on HSC transplantation (HSCT), all patients were heavily immunocompromised. In a pediatric patient treated with MSCs for osteogenesis imperfect, FCS-reactive antibodies were detected [53]. However, anti-FCS antibodies are also found in the vast majority of healthy individuals, indicating that preformed FCS-reactive antibodies might have been present before MSC treatment [52].

T-cell-mediated "classical" allorejection, in addition to the humoral immune response, has been described in a mouse model [54]. Erythropoietin-expressing MSCs were administered to immune-competent syngenic and allogeneic mice, and the latter resulted in allorejection of MSCs. Allo-MSCs systemically infused into sublethally irradiated mice to promote allo-bone marrow engraftment are sufficient to not only induce rejection, but also generate memory T cells [55]. These two examples illustrate that, under certain conditions, MSCs can lose their "immunoprivileged" status. In animal models, the route of administration is another major risk factor for the induction of allorejection. Systemically infused allo-MSCs are more potent to induce rejection compared with that of locally infused MSCs (reviewed in [56]). IFN-γ pretreatment of MSCs, which is associated with upregulation of major histocompatibility complexes I and II on MSCs, as well as rechallenging the host with allo-MSCs also appears to trigger rejection of allo-MSCs in animal studies [56–58]. In contrast, MSC rejection is not elicited in animal models with at least mild immunosuppression and in most clinical settings. Our own clinical trial for liver transplant recipients employs a bottom-up approach in which immunosuppressive drugs are initially administered at low doses and only increased as needed [59].

It is further unclear whether MSCs promote the development of tolerogenic T cells. Interestingly, in a mouse model, T cells do not overcome MSC-induced anergy even after the removal of MSCs and supporting T-cell growth with interleukin-2 [60]. Furthermore, a slow reduction of immunosuppression can foster systemic tolerance to donor MSCs, because MSCs also migrate into tissues that take part in T-cell selection, such as bone marrow and the thymus [36,61,62]. Recent studies using human MSCs further demonstrate that rejection of MSC by cytotoxic T cells increases following secondary exposure to allo-MSCs. In particular, pretreatment of MSCs with IFN-γ induces allorejection [63]. Interestingly, when comparing BM MSCs and ASCs, the latter do not induce a potent T-cell response. However, ASC hypoimmunogenicity can be overcome by IFN-γ pretreatment [63]. Taken together, despite the hypoimmunogenicity of MSCs, there have been concerns that MSC-derived cells might lose immunoprivilege. For example, glycoantigen expression differs between MSCs and MSC-derived osteogenic cells [64]. However, upon *in vitro* induction of differentiation into adipose, bone, or cartilage cells, no increased alloreactivity has been reported *in vitro* [62]. *In vivo* data from MSC-derived osteogenic cells implanted into New Zealand white rabbits appear to underline these findings [65].

Current clinical experience

A major goal of ongoing clinical trials into the use of MSC in solid organ transplantation was to avoid or reduce the detrimental side effects associated with pharmacological immunosuppression including renal and neural toxicity [8,10,66]. To date, the majority of these trials have utilized autologous or third-party-derived MSCs, applied shortly either before or after transplantation. While many trials have investigated BM MSCs, MSC can also be readily isolated from other sources among which are umbilical cord blood, Wharton's jelly, adipose tissue, and dental pulp.

While clinical trials using MSC in context with HSCT to control GvHD appear to show that cell source is not a key factor (see also Table 2), it is too early to conclusively evaluate the individual merits and weaknesses of each MSC type. Precisely how MSCs are able to exert a long-lived

Table 2. clinical experience using mesenchymal stem cells (MSC) in context with HSC transplantation (HSCT).

Study aim	Result	Adverse effect in MSC group	Conditioning regime	MSC source	Follow-up	Author/Year [Ref.]
Treatment of high-risk AML	No GvHD	Not reported	Myeloablative, TBI	BM HLA-haplo-identical related	31 months	Lee *et al.* 2002 [5]
Treatment of steroid-resistant GvHD	No significant effect	Not reported	Myeloablative TBI	BM HLA-identical sibling		Lazarus *et al.* 2005 [68]
Increase recurrence rates	aGVHD and cGvHD incidence and severity significantly decreased	Higher rate and earlier time point of relapse (60% vs. 20% and 63 vs. 117 days, respectively)	Myeloablative TBI	BM from HLA-identical sibling	3 years	Ning *et al.* 2008 [33]
Increase engraftment of cord blood HSC co-infusion, decrease aGvHD	No sever aGvHD in MSC group	Not reported	Myeloablative	BM from third-party HLA-mm-unrelated donor	22 months	Gonzalo-Daganzo *et al.* 2009 [67]
Weaken GVHD	Increased 1-year overall survival (80% vs. 44%) and increased 1-year progression-free survival (60% vs. 38%)	Not reported	Nonmyeloablative	BM from third-party HLA-mm-unrelated donor	1 year	Baron *et al.* 2010 [34]
Impact of MSC cotransplantation on lung function	Lung function not affected	Significantly increased risk of fungal lung infection	Nonmyeloablative	Not mentioned	1 year	Moermans *et al.* 2014 [69]

GvHD, graft-versus-host disease; BM, bone marrow-derived; HLA, human leukocyte antigen; HSC, hematopoietic stem cells.

Table 3. Potential long-term health risks related to mesenchymal stem cells (MSC) therapy.

Study type	*In vitro*		*In vivo* animal study		
MSC origin	Animal	Human	Animal	Human	Clinical trial/case report
Induction of *de novo* malignancies	Yes [15]	No [23,26,27]	Yes [16,24,25]	No [23,25,26]	No reports [30]
Progression of pre-existing malignancies	n/a	n/a	Yes [32]	Yes [18,31]	Increased risk of relapse following HLA-matched HSCT MSC cotransplantation [33] No increased incidence of relapse following HLA-mm HSCT MSC cotransplantation [34]
Induction of chemoresistance	Not investigated	Yes [35,70]	Not investigated	Yes [70,71]	Not investigated
Dedifferentiation	n/a	Oxygen tension biases MSC differentiation [46,47]	Yes [4,9,25]	No [38]	Not reported
Rejection of donor MSC-derived tissues	n/a	n/a	No [62,65]	Not investigated	Not reported
Presensitization	Not investigated	Clinical-grade MSC grown in medium supplemented with ABP cause blood clotting [51]	Yes [55,57,72]	Not investigated	Blood group 0 patients treated with ABP-exposed MSC show lower clinical outcome [51] FCS-reactive antibodies in patient treated with FCS-exposed MSCs [52,53]

n/a, not applicable; ABP, AB plasma FCS, fetal calf serum; HLA, human leukocyte antigen.

immunoregulatory influence remains unclear. Experiences from HSCT show that donor-derived MSCs do not necessarily migrate to the bone marrow, making it at least possible that MSCs exhibit their immunoregulatory function "in-trans" without the need for a specific niche [5,33,34]. This observation is further supported by animal data [35]. In clinical trials investigating the impact of MSC cotransplantation for GvHD [5,33,34], it was suggested that the observed reduction in acute and chronic GvHD was not only a result of donor MSC infiltration into recipient bone marrow [5,67]. It also remains unclear whether MSCs are capable of migrating to tissues forming a stable MSC niche or whether MSCs need only be present transiently at an early phase to promote a tolerogenic phenotype. Observations from a number trials investigating MSC in the context of GvHD therapy demonstrate that early administration of MSC is associated with a reduction in the severity and incidence of GvHD (see also Tables 2 and 3). At the same time, an increased engraftment was reported.

Conclusions

The use of immunosuppressive drugs is associated with severe side effects such as renal failure, reactivation of viral infections, and *de novo* malignancies. In this context of solid organ transplantation, infusion of MSCs may promote long-term graft acceptance and lower the need for immunosuppressive drugs. It may also lead to tumor formation by the infused cell product or promote tumor growth of recipient tissues. Sensitization of the MSC recipient and dedifferentiation of cell products are possible. Detailed observation and follow-up of MSC recipients should be a key competent in all future MSC trials.

Funding

The authors have declared no funding.

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