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REVIEW

Potential of mesenchymal stem cells as immune therapy in solid-organ transplantation

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Summary

Over the last decade, there has been a rising interest in the use of mesenchymal stem cells (MSCs) for clinical applications. This interest stems from the beneficial properties of MSCs, which include multi-lineage differentiation and immunosuppressive ability, suggesting there is a role for MSC therapy for tissue regeneration and in immunologic disease. Despite recent clinical trials investigating the use of MSCs in treating immune-mediated disease, their applicability in solid-organ transplantation is still unknown. In this review, we identified topics that are important when considering MSC therapy in clinical organ transplantation. Whereas, from other clinical studies, it would appear that administration of MSCs is safe, issues like dosing, timing, route of administration, and in particular the use of autologous or donor-derived MSCs may be of crucial importance for the functional outcome of MSCs treatment in organ transplantation. We discuss these topics and assess the feasibility of MSCs therapy in organ transplantation.

What is already known?

Characteristics of MSCs

Over the last decade, various medical disciplines have become increasingly interested in mesenchymal stem cells (MSCs), whose unique characteristics are potentially useful for clinical therapy. MSCs are present in most tissues, including bone marrow, adipose tissue, skin, placenta and heart [1–5], and can be isolated and expanded *ex vivo*. They are selected on the basis of their capacity to adhere to plastic, and are characterized by their fibroblast-like morphology in culture, immunophenotype and multilineage differentiation capacity [1,2].

As no specific marker for MSCs has been found yet, MSCs are identified by a panel of cell-surface markers, including CD29, CD44, CD73 (SH3/4), CD90 (Thy-1), CD105 (SH2), CD106 (VCAM-1), CD166 (ALCAM) and HLA class-I. MSCs do not express hematopoietic or endothelial lineage markers such as CD11b, CD14, CD31, CD34, or CD45 [1,6,7]. Also, unless they are stimulated with IFN-γ, MSCs do not express the co-stimulatory molecules CD80 and CD86 or HLA class-II [8,9].

One of the main functional properties of MSCs is their capacity to differentiate into a variety of specialized cell types, such as osteoblasts, chondrocytes, adipocytes, myocytes (Fig. 1) or neuronal precursors cells [1,10,11]. This capacity makes them promising candidates for use in regenerative medicine. Human and animal studies have shown that MSCs have potential to repair bone [12,13], cartilage [14,15], skin [16,17], and neuronal tissue [18] and improve the function of cardiac muscle [19–21] and the kidney [22]. Recent clinical trials are investigating the use of MSCs in treating heart disease, liver cirrhosis and bone fractures.

It is unclear whether MSCs contribute to tissue repair by differentiation into tissue-specific cell types, or whether they produce trophic factors at the site of injury, which either stimulate tissue-repair [23,24] or which conceivably reduce self-inflicting damage by the immune system. In addition to their capacity for multilineage

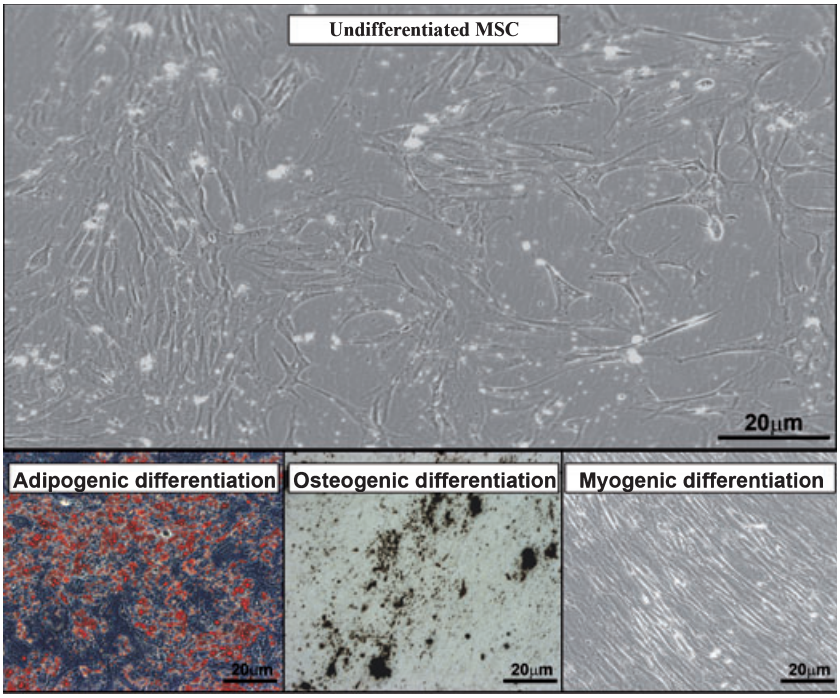

Figure 1 Multi-lineage differentiation capacity of MSCs. Figures show undifferentiated MSCs, MSCs stained with oil-red-O to detect lipid vesicles after adipogenic differentiation, MSCs stained by von Kossa staining to detect calcified minerals after osteogenic differentiation and MSCs after induction of myogenic differentiation.

differentiation, MSCs have a potent capacity to inhibit the activation and proliferation of immune cells, as has been demonstrated in *in vitro* studies.

The present review focuses on the immunosuppressive capacity of MSCs, and discusses their importance and applicability in cellular immune therapy in solid-organ transplantation.

Immunosuppression by MSCs

There is convincing data showing that MSCs have potent immunosuppressive capacity. It is important to consider that most of this data, as we will see below, has been generated in *in vitro* experiments under artificial conditions. An important question to ask is therefore whether this property of MSCs is present outside the culture dish? There are indeed indications that immunosuppression by MSCs is relevant *in vivo*. It has, for instance, been suggested that immunosuppression by MSCs plays a role in maternal acceptance of fetal (semi)-allografts [25]. Furthermore, there is now considerable evidence from clinical trials that MSCs can inhibit hematopoietic cells after *in vivo* administration [26]. Immunosuppression by MSCs therefore does not seem to be a freak property, seen only under laboratory conditions.

Under a variety of experimental conditions, it has been demonstrated that MSCs inhibit the proliferation of and production of pro-inflammatory cytokines by allo-activated and mitogen-activated PBMC [8,27,28]. A variety of mechanisms for this effect have been proposed [29]. The immunosuppressive effect of MSCs is dose-dependent and appears to be independent of major histocompatibility complex (MHC) [30] and mediation by antigen-presenting cells (APC) or regulatory T cells (Tregs) may not be required [31]. Experiments using transwell systems showed that the inhibitory effect of MSCs on PBMC proliferation was reduced, but not abolished, by the physical separation of MSCs and PBMC, indicating that MSCs affect PBMC both through cell-membrane contact and through soluble factors [31,32].

Mesenchymal stem cells constitutively secrete anti-inflammatory factors [28,29], albeit at low levels, as MSC-conditioned medium itself is not immunosuppressive [32]. Interaction of MSCs with immune cells through T-cell-produced or monocyte-produced pro-inflammatory cytokines such as interferon (IFN)-γ and interleukin (IL)-1 is necessary to enhance the MSC's secretion of anti-inflammatory factors [8,28,32,33]. Several MSC-derived soluble factors have been suggested to be involved in immunosuppression by MSCs: these include transforming growth factor-β1 (TGF-β1) [27,32], hepatocyte growth factor [27], prostaglandin-E_2 (PGE_2) [28], IL-10 [34], HLA-G [35,36], and nitric oxide [37]. Blocking each of these factors alone does not completely restore the proliferation of activated immune cells, indicating that multiple factors are involved. MSCs also inhibit T-cell proliferation by up-regulating the expression of indoleamine 2,3-dioxygenase (IDO) [38,39]. IDO is not constitutively expressed

by MSCs, but can be induced by exogenous factors such as IFN-γ, and catalyses the conversion of the amino acid tryptophan to kynurenine, leading to inhibition of lymphocyte proliferation. *In vitro* differentiation of MSCs into adipogenic, osteogenic and chondrogenic lineages preserves their immunosuppressive capacity [40] and it has been suggested that the immunosuppressive property of MSCs is shared among all stromal cell types [41].

The differences found by various studies in the immunosuppressive mechanisms of MSCs may reflect the different experimental setups used. The outcome of MSC-mediated effects is likely to be dictated by the type and magnitude of immune challenge. This should be borne in mind when MSCs are used in the treatment of immunologic disease.

Effects of MSCs on lymphocyte subsets

Many studies have demonstrated that MSCs inhibit immune responses by affecting various leukocyte subsets. Below, we discuss their specific effects on T cells, B cells, natural killer (NK) cells, and on other immune cells such as dendritic cells (DC).

Interaction between MSCs and T cells

The effect of MSCs on T cells has been investigated in various experimental settings, showing that MSCs modulate the activation, proliferation and functioning of effector and regulatory T-cell subsets (Fig. 2). MSCs have a dose-dependent effect on the proliferation and cytokine production (e.g. IL-2, IFN-γ) of allo-activated and mitogen-activated $CD4^+$ T cells *in vitro* [27,31,42,43]. Although they strongly suppress the formation of cytotoxic $CD8^+$ T lymphocytes (CTL) in mixed-lymphocyte-cultures [44,45], MSCs are not capable of inhibiting the cytolytic activity of activated CTL [46]. Conversely, MSCs are themselves relatively resistant to CTL-mediated lysis [46], which may be explained by the low expression of HLA and co-stimulatory molecules on MSCs [47]. In addition to their effects on naïve T-cell populations, MSCs also inhibit the proliferation of memory T cells activated by their cognate peptide [27,31,46,48].

In addition to producing anti-inflammatory cytokines, MSCs express a number of adhesion molecules including ICAM-1, ICAM-2, VCAM-1, CD72, and LFA-3 that enable physical interaction with T cells [49]. MSCs have an increased affinity for activated T cells, as a result of the up-regulated expression of adhesion molecules on activated T cells. Furthermore, MSCs up-regulate adhesion molecules under inflammatory conditions Hoogduijn MJ, unpublished observation. Under inflammatory conditions, the physical interaction between MSCs and T cells is therefore enhanced. By keeping activated T cells in close proximity, the inhibitory effect of soluble mediators generated by MSCs may be potentiated [50].

In addition to the nonantigen-specific regulation of effector T cells by MSCs through the secretion of soluble factors and cell-membrane interactions, there is evidence that MSCs indirectly modulate immune responses through the induction of Tregs. Some studies have reported that, by selectively stimulating the proliferation of Tregs, MSCs increase the proportion of Tregs with strong suppressive capacities in the PBMC population [28,51–53]. However, the mechanism whereby MSCs induce Treg expansion is unclear, as is the specificity of the induced cells. If protocols could be developed whereby MSCs were used to induce Tregs in an antigen-specific manner, this would provide MSCs with the capacity to inhibit immune responses in an antigen-specific manner.

Interaction between MSCs and B cells

The effects of MSCs on B cells have been clarified to a lesser extent than their effects on T cells. Some studies have shown that MSCs effectively inhibit B-cell proliferation,

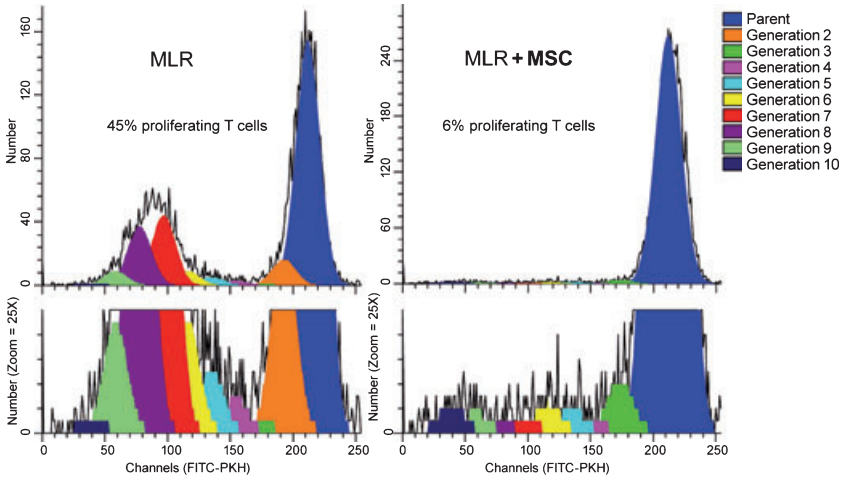

Figure 2 Immunosuppressive capacity of MSCs. MSCs inhibit the proliferation and number of cell divisions of PKH67-labeled responder T cells after 7 days in MLR. Analysis was performed by ModFit® software (Verity Software House, Topsham, ME, USA).

differentiation to plasma cells, and antibody production [54,55]. B-cell proliferation is inhibited by MSCs through an arrest in the G0/G1 phase of the cell cycle, and not through apoptosis [54,56]. On the other hand, some studies found that MSCs stimulated polyclonal expansion and antibody production by B cells [57,58]. Interestingly, it has been suggested that MSCs may resemble follicular dendritic cell-like cells, which rescue B cells from apoptosis and induce their differentiation [59]. This may explain the stimulatory effect of MSCs on B cells. The concentration of MSCs may be a decisive factor explaining such results, where high doses of MSCs have an inhibitory effect on B cells, while low doses stimulate B-cell activity. The absence or presence of T cells is of importance as well. Activated T cells produce IFN-γ, which activates MSCs to affect B cells through mechanisms that resemble those used to modulate T-cell activity.

Interaction between MSCs and natural killer cells

While MSCs suppress IL-2- and IL-15-driven NK-cell proliferation and IFN-γ production [28,46,60], they do not inhibit the cytotoxic activity of activated NK cells [46,61]. The inhibition seems to be independent of cell-membrane contact, and PGE_2 and TGF-β appear to play a role the regulation of NK-cell activity [62]. While MSCs are not lysed by freshly isolated allogeneic NK cells, they are susceptible for lysis by IL-15-activated NK cells [46,60,63].

Interaction between MSCs and antigen-presenting cells

In addition to directly affecting lymphocytes, MSCs modulate immune responses via DC. MSCs can reduce the formation and maturation of both monocyte-derived and $CD34^+$-derived dendritic cells (DCs) [64–66]. MSCs also reduce the expression of co-stimulatory molecules such as CD40, CD83 and CD86 on mature DC [67] and alter cytokine secretion by stimulating IL-10 [65], IL-12 [67] and TGF-β1 [27] production, while decreasing tumor necrosis factor-α secretion. It has been reported that MSCs require activation through IL-1β production by $CD14^+$ monocytes to suppress allo-reactive T cells [32]. Thus, MSCs modulate the activation, proliferation and function of DC, thereby indirectly regulating T- and B-cell activity.

Interaction between MSCs and other immune cells

There is little data on the effects of MSCs on other immune cells. MSCs secrete soluble factors such as monocyte-chemo-attractant protein, macrophage-inflammatory protein, IFN-inducible protein-10 and IL-8, all of which may attract immune cells such as monocytes, macrophages and neutrophils. Secretion of these factors by MSCs is affected by inflammatory conditions (Hoogduijn MJ, unpublished data). The relevance of the production of these factors by MSCs to the function of monocytes, macrophages and neutrophils in an inflammatory environment is unknown.

Interaction between MSCs and hematopoietic stem cells

It has previously been shown that MSCs promote hematopoietic engraftment [26,68,69]. This is likely to relate to the important role of MSCs in the hematopoietic niche, where they support hematopoietic stem cell survival and self-renewal. It can thus be speculated that MSCs have indirect effects on the formation of antigen-specific T cells by their interference with hematopoietic development.

Mesenchymal stem cells as immune therapy

Use of MSCs in inflammatory disease and graft-versus-host-disease

On the basis of the available *in vitro* data, it is proposed that MSCs can contribute to controlling inflammatory diseases. The question remains whether the *in vitro* effects of MSCs can be translated to an *in-vivo* setting. So far, results from animal models have been ambiguous. Whereas MSCs have shown both adverse and beneficial effects in rheumatoid arthritis (RA) [70,71], there is certainly evidence that they can reduce inflammation in myocarditis [72] and renal ischemia-reperfusion injury [73]. In experimental autoimmune diseases, the infusion of MSCs has also been effective, for instance by reducing demyelination and the number of inflammatory infiltrates in mice with autoimmune encephalomyelitis [74,75], and by reducing inflammation of the ileum in mice with autoimmune enteropathy [76]. The effectiveness of MSCs in the treatment of inflammatory diseases such as multiple sclerosis, inflammatory bowel disease and RA in humans is currently under investigation in clinical trials.

The immunologic properties of MSCs suggest that they may facilitate bone marrow and solid-organ transplantation by preventing rejection and by improving the function of the graft. Such a role has been demonstrated in murine models of allogeneic bone marrow transplantation, where infusion of MSCs prevented graft-versus-host disease (GVHD) [77]. The application of MSCs in bone marrow transplantation has been further elaborated in human studies; a number of groups have demonstrated that the administration of MSCs not only increased bone marrow engraftment after hematopoietic stem cell transplantation, but also that it reduced conventional therapy-resistant GVHD [26,78–80]. Recently, clinical trials

started to investigate the effect of MSCs on GVHD on a larger and more controlled scale [81].

In a few attempts, the use of MSCs in solid-organ transplantation has been examined in animals. Under particular conditions, MSCs were shown to prolong the survival of skin [82] and liver [83] grafts in primate and rat models. Other studies failed to find any beneficial effect of MSCs on renal graft survival or showed that, when infused before transplantation, MSCs of donor origin may actually accelerate heart and skin graft loss, possibly through the induction of a memory immune response [84–86]. Beyond a limited number of studies, the effectiveness of MSCs in solid-organ transplantation remains unexplored.

It is unknown whether MSCs can play a beneficial role in human organ transplantation. The *in vitro* properties of MSCs, together with the reported effects of MSCs in GVHD and some data from animal studies would suggest they might. At this stage, there are many relevant questions regarding the potential role of MSCs in cellular immune therapy. Below, we identify and discuss several aspects of this that should be taken into consideration.

Factors to be considered regarding MSC immune therapy in organ transplantation

Source of MSCs – tissue type

Traditionally, MSCs are isolated from bone marrow. Currently, this source is used for most clinical applications. But although the bone marrow is a reliable source of MSCs, bone marrow procurement procedures are painful and invasive, and may yield relatively low numbers of MSCs upon processing [87].

One alternative bone marrow is subcutaneous adipose tissue [88]. This is a suitable source of MSCs that can be obtained under local anesthesia through a simple, less invasive surgical procedure that provides repeatable access to large quantities of tissue. Adipose-tissue-derived MSCs also expand faster than bone marrow MSCs, and have comparable phenotype, multilineage differentiation capacity and immunosuppressive properties [89].

Umbilical-cord blood (UCB) may be another suitable source of MSCs. UCB MSCs seem to have a greater expansion capacity than bone marrow MSCs and have phenotypical and functional characteristics comparable to bone marrow and adipose tissue MSCs [87]. The two disadvantages of UCB MSCs are the low success rate of isolation and its need preservation from birth until use.

Although the functional properties of the MSCs derived from these different sources appear to be similar, they are not identical and MSCs from different tissues vary with regard to their gene expression [87,90]. When MSCs are used in clinical applications, such differences may affect their function.

There is some evidence that chromosomal abnormalities develop in MSCs, in particular those originating from adipose tissue, after long-term expansion [91,92]. However, other studies found such aberrations to be negligible. [93]. It is therefore unclear whether adipose-tissue-derived MSCs are more prone to chromosomal changes than bone marrow MSCs, which show very little chromosomal abnormalities after culture [94]. Chromosomal aberrations in adipose-tissue MSCs appear to occur mainly after culturing for more than 25 passages. Thus, for safety reasons, the use of high-passage MSCs for clinical applications should be, and can easily be, avoided.

Source of MSCs – autologous or allogeneic

One of the major questions concerning the clinical application of MSCs is whether MSCs of autologous or allogeneic origin should be used. This is especially important for their application in organ transplantation. In an organ-transplantation setting, there is theoretically a choice of MSCs from three origins; they can be derived from the recipient, from the donor, or from a third-party. In planned living-organ transplantation, there is an opportunity to isolate and expand MSCs of recipient or donor origin; in contrast, the transplantation of organs from deceased donors would limit the options to recipient and 'off-the-shelf' third-party MSCs.

Although it has been suggested that allogeneic MSCs are better immunosuppressors [61], we, like others, have found that autologous and allogeneic MSCs have a comparable immunosuppressive capacity to inhibit alloreactivity *in vitro* [30,42,45]. It is not known what the case is in a clinical setting. MSCs are considered to be immunoprivileged by their low immunophenotype, i.e. not to provoke proliferation of allogeneic lymphocytes in co-culture experiments [40,43], and to escape lysis by $CD8^+$ cytotoxic lymphocytes and NK cells [52,54]. Theoretically, this low immunogenicity would reduce the clearance of allogeneic MSCs by the allogeneic immune system, suggesting that transplantation of MSCs across MHC barriers may be possible. This is supported by a case report on the transplantation of fully mismatched allogeneic MSCs into an immunocompetent fetus suffering from osteogenesis imperfecta [95]. Donor MSCs showed engraftment in bone whereas no signs of alloreactivity against donor MSCs were observed. In addition, Sundin *et al.* [96] also reported that in GVHD patients, no specific T cells against MSCs were recovered after the therapy, whereas BSA-specific T cells were (most likely generated from the fetal bovine serum used for amplification).

However, it has been demonstrated in murine models that infusion of allogeneic MSCs can induce memory

T-cell responses, and that MSCs can be immune-rejected in MHC mismatched hosts [84,97,98]. Priming with donor MSCs may thus induce hypersensitivity to donor-antigens, and thereby accelerate graft rejection. Nevertheless, recognition of donor MSCs by the host immune system does not necessarily lead to hypersensitivity. It may also be possible that recognition of donor MSCs desensitizes the host to donor-antigens. Such a mechanism would resemble the effect seen in the past with the use of pretransplant donor-blood transfusions, which in some cases led to donor-specific hypo-responsiveness [99]. If MSCs have the capability of inducing donor hypo-responsiveness, this is likely to rely on a balanced dosing and timing of MSC administration.

Route of administration and migration of MSCs

Mesenchymal stem cells used for immune therapy in solid-organ transplantation can be administered via two routes: systemic or local. It is unknown where MSCs would exert their potential beneficial effect. This could be in the target organ or perhaps in the lymph nodes. It is therefore unknown whether it is more effective to administer MSCs into the target organ – i.e. the graft – or via intravenous injection. An important point to consider is that *ex vivo*-expanded MSCs are trypsinized before administration, which may damage cell adhesion molecules and thereby affect the homing behavior of MSCs. Sackstein *et al.* [100] demonstrated that modification of the cell surface molecule CD44 on *ex vivo* expanded MSCs can influence the migration of MSCs after infusion. This is of great interest for the specific delivery of MSCs for clinical applications.

Clinical studies have shown that MSCs can be infused intravenously without infusion-related adverse events [81,101,102]. Although MSCs express homing receptors [103], it is unclear whether such receptors would lead systemically administered MSCs to the target organ. Data from a number of studies suggest that intravenously injected MSCs home to sites of inflammation [104–108]. However, other studies reported that selective homing of MSCs to lymphoid tissues [109] or sites of inflammation [107,110] is limited, and that MSCs get trapped in lungs and liver by space constrictions [111]. To increase the number of MSCs in the target organ, intra-arterial infusion can be considered [112,113]. Alternatively, this might also be achieved by local administration [114,115]. As MSCs migrate poorly in tissue, repeated multi-focal injections with MSCs may be required to obtain an effective dose of MSCs in the graft.

Dose of MSCs

An important issue in the clinical application of MSCs involves establishing the dosing that will achieve the best results. *In vitro* studies show immunosuppressive effects at (MSC:PBMC)-ratios of (1:10) or higher [27]. These high concentrations of MSCs may not be achievable in clinical applications, as the majority of MSCs may disappear as a result of distribution to other organs and because of the cell-loss caused by immunologic or mechanical stress after infusion.

In a human setting, there is some experience with dosing of MSCs in the treatment of bone marrow transplant patients with severe GVHD. A recent multi-center trial showed that doses of 0.5×10^6–9×10^6 cells per kg body weight did not lead to adverse side-effects [81]. Interestingly, in this study, the effect of MSCs appeared to be independent of the dose. It should thus be investigated whether this is the case in solid-organ transplantation, or whether an optimal dose of MSCs can be established. If local administration of MSCs is considered in organ transplantation, an optimal number of MSCs per target organ may have to be established rather than a number of MSCs per kg body weight.

Timing

In vitro studies have shown that MSCs effectively suppress lymphocyte activity in the afferent phase and not in the cytotoxic phase of an allo-response [44,46,48]. *In vivo*, it has been shown that MSCs were effective when infused before onset of inflammatory processes, and that they could prevent the development of autoimmune encephalitis in a murine model [74]. Moreover, in the same model, MSCs were also effective when administered at the peak of disease, suggesting that they can ameliorate active inflammatory processes. This was further demonstrated in patients with severe drug-resistant GVHD whose clinical condition was improved by treatment with MSCs [78,81]. Consequently, MSC-based therapy may be effective in preventing anti-donor reactivity and in reducing active rejection in organ transplantation.

Modulation of MSCs immunosuppressive capacity

Mesenchymal stem cells are responsive to their environment and adapt their function to local circumstances, their immunosuppressive properties apparently being induced under inflammatory conditions [8]. Modification of culture medium by specific factors can modulate the properties of MSCs: for example, enhancing their immunosuppressive function and reducing their susceptibility for lysis by cytotoxic T cells [116]. Thus, for instance, pretreatment of MSCs with IFN-γ may transform normal MSCs to immune-enhanced MSCs [8,117].

For particular applications, *in vitro* predifferentiation of MSCs may be desired. Interestingly, it has been reported that predifferentiated MSCs still have immunosuppressive capacity [40]. Modulation of the properties of MSCs

offers the opportunity to adapt the function of MSCs for use in specific clinical applications.

Mesenchymal stem cells and immunosuppressive drugs

When immune therapy with MSCs is used in solid-organ transplantation, the immunosuppressive drugs used by the recipients may affect the function of MSCs. While it has been reported that MSCs and cyclosporine A have synergistic immunosuppressive effects [61], there is also evidence that there are no additional, or even adverse, effects [85].

Our own group recently investigated the effect of tacrolimus, mycophenolic acid (MPA) and rapamycin on MSCs; while the molecular targets of these drugs are expressed in MSCs, their effect on the immunosuppressive capacity of MSCs is unknown. We found that clinical doses of these drugs induced no MSC-toxicity, but that the proliferation of MSCs was inhibited by MPA and rapamycin. And whereas MSCs and MPA also had additive effects on the inhibition of allo-reactivity, MSCs reduced the immunosuppressive efficacy of tacrolimus and rapamycin [118]. It is not unlikely that inhibition of the allo-response by immunosuppressive drugs removes the trigger that MSCs need to exert their immunosuppressive function. This may mean that the addition of MSCs to the immunosuppressive regimen allows the dose of conventional immunosuppressive drugs to be reduced without affecting the efficacy of the therapy.

Potential pitfalls of MSC immune therapy in organ transplantation

Numerous studies, mainly *in vitro*, convincingly show that MSCs can modulate the function of immune cells. Despite little scientific background on their biology *in vivo*, MSCs have already been introduced into phase I studies on the treatment of a number of diseases. However, before they are used in organ transplantation, some possible pitfalls should be considered.

Perhaps most importantly, the outcome of clinical therapy may be determined by the choice of autologous or allogeneic MSCs. Because allogeneic MSCs may induce memory responses, which could accelerate graft rejection, the use of autologous MSCs would be safest. Conversely, to induce donor-specific hypo-responsiveness comparable with the donor-specific transfusions in the past [99], immune recognition of allogeneic donor MSCs may be beneficial. Clearance of MSCs may be beneficial when only a temporary effect is desired. In short, the clinical consequence of allogeneic or autologous MSCs should be further investigated.

Another concern is the multi-lineage differentiation potential of MSCs, which may not always be beneficial, as it may lead to the formation of the 'wrong' cell types. It has been reported that treatment of mice with myocardial infarcts with MSCs induced increased calcification of the heart [119]. Alternatively, differentiation of MSCs in the wrong cell type may lead to tumor formation. This has not been observed so far in a human setting. Perhaps more likely is the induction of fibrosis by MSCs. As intravenously administrated MSCs end up in several organs, in particular in the lungs, it is possible that fibrosis is stimulated by growth factors present in these tissues. Although some evidence for this is provided by a recent clinical study in which progenitor-enriched adipose-tissue induced fibrosis [118], it is unclear whether MSCs that have been expanded in culture will act in the same way.

Other safety issues that involve systemic administration of MSCs are the potential modulation of the overall immune system, thereby reducing resistance to infections or supporting the development of pre-existing tumors [120]. However, in baboons treated with multiple administrations of high dose allogeneic MSCs, allo-reactive immune responses were affected but there was no compromise of the overall immune system [121]. In addition, although to date a considerable number of humans has been treated with MSCs for several diseases, serious short-term side-effects have not been reported [81]. It is too early to determine long-term effects of MSCs treatment.

Conclusions

While there is an accumulation of evidence from *in vitro* and animal studies that MSCs have tissue repair and immunosuppressive properties, it is currently unknown whether these capacities are functional or beneficial in a human organ transplantation setting. This review has discussed several factors that should be considered when MSCs are used as cellular therapy in organ transplantation. On the basis largely of their immunosuppressive capacity, we believe that MSCs have unique properties that allow them to improve graft acceptance and function. We therefore subscribe to the current high hopes regarding their use in cell therapy, but future research and clinical trials in organ transplantation will show whether this is justified.

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