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Review Article

Cell Therapy in Transplantation

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ABSTRACT

Organ transplantation is an established and practical definitive treatment option for patients with end-stage organ dysfunction. Unlike improvements in short-term graft survival, long-term graft survival is the main challenge due to the increased morbidity and mortality associated with the toxicity of immunosuppressive regimens and chronic rejection. Since a novel therapeutic strategy to fulfill allograft tolerance seems urgent, the attention of the transplant community is focusing on the development of the new safe approach to prolong graft survival. Various researches have focused on immune regulation in the context of organ transplantation with mesenchymal stem cells and regulatory T cells (Tregs) identified as cells that have the potential to suppress or optimize the immune responses in different situations. In this review article, we will provide an overview of human Tregs and different kinds of promising cells in the field of immune-suppressing, their phenotypic and functional characterization. Furthermore, we will review the different experiences of the clinical application of immunomodulatory cells in the setting of solid organ transplantation.

Keywords: Organ transplantation; Regulatory T cells; Mesenchymal stem cell; Cell therapy

INTRODUCTION

Solid Organ transplantation is the treatment of choice for end-stage organ failure and allograft acute rejection is a main challenge in recipients and can lead to the development and progression of chronic rejection [1]. Chronic use of immunosuppressive drugs imposes considerable risks of morbidity and mortality, including nephrotoxicity and an increased risk of cardiovascular diseases and diabetes. In addition, despite an impressive improvement in short-term graft survival of these drugs, prolong long-term graft survival is the main challenge in the past two decades so, finding an alternative strategy for long-term immunosuppression to achieve allograft tolerance in these patients seems necessary [2]. It has been established that the immune system can maintain tolerance to both self and non-self antigens through a vast spectrum of mechanisms in two main categories include central and peripheral tolerance. Central tolerance is consisting of clonal deletion, selection *via* using mTEC (medullary Thymic Epithelial Cells), clonal diversion, regulatory cell induction and peripheral tolerance is controlled by several mechanisms which restrict the development of potentially destructive autoimmune responses. These mechanisms include T cell ignorance through AICD (Activation-Induced Cell Death) and the induction of T cell anergy [3]. While these mechanisms are clearly important in the maintenance of self-tolerance, other mechanisms such as regulatory responses. Although characterization of these Treg cells defined their role in the maintenance of tolerance to self, it is now clear that such regulatory cells play an important role in suppressing immune responses against alloantigens expressed on tissues and transplanted organs directly.

Promising results in using Treg therapy in mice to mediate transplant tolerance suggests Treg-based therapies as mechanisms of long-term drug free transplant tolerance in human patients. Regulatory T cells (Tregs), formerly known as suppressor T cells, are a subpopulation of T cells which have a great role in suppressing or regulating other cells in the immune system naturally or during an immune response [4]. These cells can

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maintain tolerance to self-antigens and control the immune response to foreign antigens so can modulate the immune system and help prevent autoimmune diseases. There are two different types of Tregs produce in immune systems; first, Tregs produced by a normal thymus termed natural Tregs, and second, those formed by differentiation of naive T cells outside the thymus, i.e. the periphery, or in cell culture called adaptive Tregs. Treg cells are thought to suppress proliferation, activation and cytokine production of almost all immune cells such as CD4+ and CD8+ T cells, B cells and dendritic cells. These cells can produce different suppressive cytokines and express additional markers such as CD152 (CTLA-4) and GITR (Glucocorticoid-Induced TNF Receptor), which help them to control immune responses. Recent researches have shown that TGFβ is essential for differentiation of Tregs from naive CD4+ T cells and is important in maintaining Treg homeostasis [5].

LITERATURE REVIEW

Regulatory T cells are essential to maintain the equilibrium of the immune response, and determined by the expression of the FOXP3 (Forkhead box P3) nuclear transcription factor, a master control gene in Tregs function and development, CD4 and CD25 molecules. Different types of Treg have been established including natural Treg (nTreg), develop in the thymus during the selection process, and recognized by expressing both the CD4 and CD25 (IL-2 receptor) biomarkers, thus they are CD4+ CD25+ in flowcytometry plots (Figure 1) and they also express CD152 or CTLA4 (cytotoxic T-lymphocyte-associated protein 4). Expression of the FoxP3, also known as scurfin, is crucial for maintaining suppression of the immune system [6]. Their suppressive activity is dependent on TGF-ß cytokine, and they can induce IDO in dendritic cells by CTLA4 mediated ligation of B7.1 and B7.2. Tr1 is another subset of Treg cells which are dependent on IL-10 for their regulatory properties and their differentiation. Instead of the FoxP3 transcription factor, in this type of regulatory cells, they express markers associated with Th2 lymphocytes and repressor of GATA (ROG) and high levels of CTLA4. They also can induce IDO and tryptophan catabolism in DCs. Antigen stimulation in the absence of co-stimulation may generate anergic CD4+ T lymphocytes characterized by an intrinsic raising of their threshold for antigen stimulation, that may be maintained by expression of E3 ubiquitin ligases include GRAIL, Itch and c-cbl. This kind of anergic cells can act as regulatory cells by competing at the sites of antigen presentation and consuming IL-2 and other stimulatory cytokines. Like Tr1, CD8+ CD28- suppressor T cells they are induced in the presence of IL-10. This inhibitory cytokine may be involved in the downregulation of DC co-simulation and the upregulation of ILT-3 and ILT-4 in DCs. Natural Killer like T (NKT) cells could be the other subset of Tregs that classified out of the routine classification, beacouse the role of NKTs during immune responses are diverse, ranging from antiviral and antitumor activity to the regulation of autoimmune diseases. In the classic classification of Treg cells, Tregs are divided into two subgroups include nTreg and iTreg (inducible Treg) which develop in the peripheral tissue from naive T cells following antigenic stimulation in semi specific conditions [7].

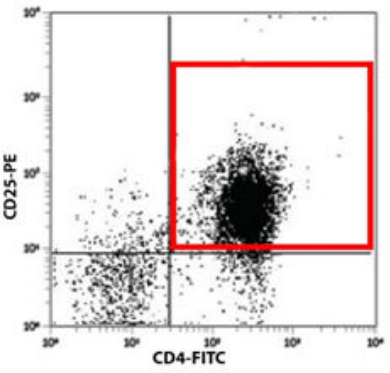

Figure 1: Flow cytometry plot gated on human CD4 T cells. The red rectangular show CD4+ CD25+ T cells.

Functions of Treg cells

Autoimmune diseases are the result of self or non-self-discrimination fails. In this situation, the immune system destroys cells and tissues of the body. Tregs suppress activation of the immune system activity and help to prevent pathological self-reactivity. The proposed molecular mechanism by which regulatory T cells exert their suppressor/regulatory activity is including: produce a number of inhibitory cytokines including TGF-ß, IL-35 and IL-10, induction of producing of immunosuppressive {Fallarino, 2011 #2399}IDO (Indole deaminase) in APCs, production of granzyme B which induce apoptosis in effector cells, production of adenosine (immunosuppressive molecule), signaling through the Consumption of IL-2 which is urgent for T effector cells activation, and suppression by regulatory T cells through the prevention of co-stimulation through CD28 on effector T cells and action of the molecule CTLA-4 (Figure 2).

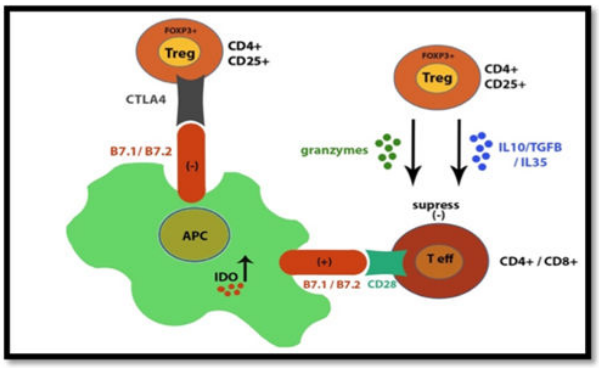

Figure 2: Inhibitory mechanisms of regulatory T cells.

Treg therapy in solid organ transplantation

Since the T cells respond to allogeneic (foreign) MHC molecules in the same fashion as to any foreign antigens, Polymorphisms in histocompatibility genes lead to generating a large population of activated effector cells, primarily T cells and macrophages, which are the main mediators of graft destruction, so finding a

fully matched donor in MHC locos seems to be urgent [8]. However, finding this fully matched donor is usually difficult so there is no choice except using semi-match or non-match donors. In this situation, to maintain the patient's tolerance to the semi-match or non-match graft, they have to use immunosuppressive drugs. Despite a lot of progress in the field of immunosuppressive drugs for transplanted patients in the last decades, drugs toxicity and their side effects and late graft loss associated with chronic rejection remains an ongoing challenge, Hence, cell therapy for these patients may be safer, so eliminating drug toxicities while maintaining graft acceptance has been the early aim of cell therapies. Regulatory T cells have been detected in the peripheral blood of transplanted patients, resulting in the suggestion that this type of regulatory cells play a critical role in the process of allograft acceptance that reduces immunological responses of acute rejection over time [9]. In murine models study, CD4+ CD25+ FoxP3+ Treg cells have been infused to prevent acute and chronic rejection effectively, Clinical evidence for using these regulatory cells is gathered from observations in recipients who do not reject their allograft unlike they stop taking immunosuppression medication (due to the medical necessity). Many studies have proven the ability of Tregs to maintain tolerance to allograft antigens in manipulated situations and slow down graft rejection. These studies also show the potential to use Tregs as a deliberate therapeutic tool clearly. This potential might be achieved by activation and expansion of Tregs *ex-vivo* and infusion to the recipient. Considering the low number of Tregs exists in circulation (5%-10%) or cord blood, the infusion of a large number of freshly isolated Tregs is difficult to achieve, so for having an adequate amount of Tregs we need to expand them *ex-vivo*.

Treg expansion

Clinical application of adoptive cell therapy with Tregs in solid organ transplantation and allogeneic Hematopoietic Stem Cell Transplantation (HSCT) has been reported recently. Due to the insufficient amount of Treg in circulation, the expansion of nTreg from the resting population of 1.3 × 1010/body to more than 5.8 × 1010/body is required [10]. For this purpose, after cell-sorting isolation, CD4+ CD25+ Tregs can be generated and expanded *ex-vivo* under GMP conditions. To have an adequate number of Tregs for infusion, they should co-cultured with anti-CD3/CD28-coated beads in the presence of a high dose of IL-2 as polyclonal expansion cytokine. To avoid contamination with effector T cells, Treg expansion protocols (all-trans retinoic acid) must be chosen. The positive effect of rapamycin on the viability of Tregs in the expansion protocols has been reported. Adding rapamycin to culture media can reduce contamination with Th1 cells, but not Th2 cells, which skew immunity away from inflammatory responses [11]. As Tregs are independent of the mTOR pathway for their cell cycle progression, rapamycin can significantly reduce the unwelcome proliferation of effector T cells *In vitro* by restraining the mTOR. ATRA with combination of TGF by affects T-cell deaths and contributing to Treg differentiation. Although its role in Treg induction is well established, the effects on Tregs are still controversial and no GMP expansion protocol has been developed yet.

Clinical studies using Treg in transplant patients

There are limited clinical investigations identifying the percentage of Treg cells in stable transplanted patients as well as rejected kidney allografts, a concept which needs to be more studied. Treg-based therapies for transplant patients have many advantages include: selective, do not require harsh conditioning, and do not have a risk of Graves Versus Host Disease (GVHD). Several clinical trials are currently in progress worldwide utilizing a number of Treg therapies in transplantation. Todo et al. have reported a clinical trial on Treg therapy to induce tolerance in liver transplanted patients. In this clinical trial, 10 consecutive adult patients suffering from end-stage liver failure enrolled in the study. They underwent left lobe liver transplantation from living donors along with splenectomy and received a Treg-based therapy [12]. Post-transplantation immunosuppressive drugs included: mycophenolate mofetil, steroids, and tacrolimus which initiated at the time of transplantation. Steroids and mycophenolate mofetil were stopped in month 1 after transplant and tacrolimus was replaced with cyclosporine or rapamycin when tacrolimus-related adverse events occurred. Recipient received a single dose of cyclosporine and single infusion of Treg-enriched autologous peripheral blood mononuclear cells stimulated with irradiated donor PBMCs in the presence of anti-CD80 and anti-CD86 at day 5 and day 13 after transplant respectively. At the end of the first month, mycophenolate mofetil and steroid and over a first year after transplant, cyclosporine were stopped gradually. The result of the study showed that all patients were well with normal graft function and histology after threating. Seven of ten patients had completed successful weaning and stopped taking immunosuppressive agents completely without rejection for 16–33 months. Four patients had been drugged free for more than 24 months and the other 3 recipients with autoimmune liver diseases developed mild rejection.

Treg therapy in GVHD

Allo-HSCT is a curative therapy for patients suffering from bone marrow failure syndromes (hematological malignancies) such as leukemias, lymphomas, some anemias, myelomas and also inherited hematological disorders. Donors are selected by high-resolution HLA typing of class I and class II of MHC molecules, and typically selected by recipient matching at HLA-A, -B, -C, -DRB1, DQB1, and DPB. Mismatching within the minor histocompatibility antigens may stimulate donor T cells to induce GVHD [13]. GVHD is a severe and frequent complication following the receipt of Cell-rich solid organs and Hematopoietic stem cells from a genetically different donor and is a major cause of non-relapse mortality after allo-HCT. The pathophysiology of GVHD is complex, involving many different T-helper cell types that contribute to disease manifestation. Murine models have been shown that adoptive transfer of Tregs can prevent harmful immune responses in GVHD and donor bone marrow graft rejection, very likely sparing specific immune responses in leukemia, emerging hopes for less toxic and more specific immunosuppression than pharmacological inhibitor drugs. Given the considerable results of murine researches make Tregs an attractive therapeutic tool for preventing and/or

treating disease in humans, so the transplant society has intensively waited for news from the success of human clinical trials. Clinical application of Tregs has been severely hampered by their low frequency and unfavorable *ex-vivo* expansion properties.

As they demonstrated, purified Tregs could be expanded at least 50 million-fold by continues stimulation with APCs while maintaining suppressive function *in vitro* and *in-vivo*, and the degree of nTreg expansion could lead to the widespread application of Treg therapy for GVHD and graft rejection through the creation of an off-the-shelf therapy using Treg banks generated from HLA-typed donors with known safety and potency records. They also have shown that the plasticity of Tregs after expansion is to the point because Tregs are not terminally differentiated and can be reprogrammed TH17 *in vitro* or *in-vivo* when activated in the presence of IL-23 or IL-6 cytokines. Several findings from studies suggest that reprogramming of Treg may not be a serious issue in developing a cellular therapy for *ex-vivo* expanded Tregs because of two reasons: First, IL-17 cytokine was not detectable in the supernatants of all re-stimulation samples cultured with rapamycin and second, the number of IL-17+ expanded cells was very low and did not increase significantly over the 4 re-stimulation cycles. They also believed that Treg massive expansion with repetitive polyclonal stimulation might also allow relatively rare, auto-antigen-specific Treg clones to be expanded to treat autoimmune diseases. Finally, this strategy could be applied to the expansion of antigen-specific Tregs, which have a more effective suppressive function than polyclonal Tregs at disease. Ultimately, a Treg cell bank would be an effective treatment for multiple diseases because Tregs suppress third-party responses and ameliorate disease without long-term persistence and are also able to maintain suppressive function *ex-vivo*.

Hoffmann and his colleagues reported the results of the study to test the function of donor-type CD4+ CD25+ Regulatory T Cells in GVHD in the murine models after allogeneic bone marrow transplantation. They have shown that CD4+ CD25+ T cells isolated from the spleen or BM of donor C57BL/6 mice that have not been tolerized are still potent inhibitors of the alloresponse *in vitro* and of lethal acute GVHD induced by C57BL/6 CD4+ CD25+ cells in irradiated BALB/c hosts *in-vivo* (107). Adding Treg cells at a 1:1 ratio with effector T cells in that resulted in considerable inhibition of MLR (mixed leukocyte reaction) and remarkable protection from lethal GVHD. This inhibitory effect depended on the potency of the transferred Tregs to secrete IL-10 and occurred when the Treg were of the donor, but not host, origin. They had indicated that the balance regulatory T cells and effector T cells can determine the outcome of GVHD [14].

Mesenchymal stem cells

Mesenchymal Stem Cells (MSCs) are non-hematopoietic multipotent stromal cells originally identified in the bone marrow but can be isolated from some other tissue including cord cells, Adipose tissue, Molar cells, and Amniotic fluid. In the bone marrow, MSCs control HSC homeostasis in the endosteal and the perivascular niche. MSC can differentiate into a variety of cell types including osteoblasts, adipocytes, and chondrocyte progenitors and are characterized by their fibroblast-like appearance, colony forming unit capacity. The functional characterization of MSC relies on their ability to adhere to plastic and their great capacity for self-renewal while maintaining their multipotency. Although several attempts have been made to select a homogeneous MSC population, no unique phenotype has been identified that allows the reproducible isolation of MSC pre-cursors. According to The International Society of Cellular Therapy, MSCs express stromal markers including CD73, CD90, and CD105, but be negative for hematopoietic markers including CD14, CD34, and CD45.

Immunological properties of MSCs

Immunomodulatory property is one of the most exciting findings of MSCs. the highlight of MSCs function is its immunemodulatory effects through central (Figure 3) and peripheral immune mechanisms (Figure 4). MSCs have shown great advantageous features such as metastasis throughout the body, and hypo immunogenicity due to the lack of MHC class II molecules and other co-stimulatory ligands such as CD80, CD86, and CD40. Interacting with the vast spectrum of immune cells and secreting soluble mediators such as cytokines in different microenvironment are the main mechanisms which MSCs uses to regulate innate and adaptive immune systems. Various researches have demonstrated that MSCs not only can regulate CD4+ and CD8+ T cells proliferation, activation, and differentiation but also can inhibit the proliferation and maturation of B cells and the secretion of immunoglobulin.

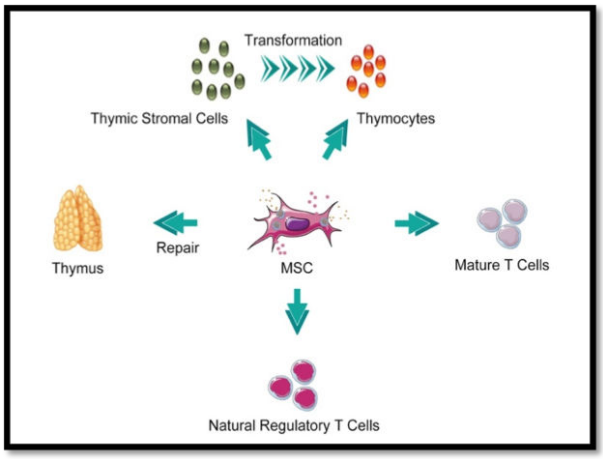

Figure 3: Immunomodulatory effects of MSC in central immune compartment. MSCs exert immunomodulatory effects mainly through central and peripheral immune compartments via produce many immunomodulatory molecules such as TGF-β, HLA-G5, PGE2, and IDO in response to inflammatory stimulants (IFN-γ, TNF-α, LPS). MSCs modulate central immune compartments by repairing damaged thymus, promoting T-cells maturation, inducing the proliferation of natural Tregs, and differentiating to thymocytes.

Moreover, increase CD5+ Bregs by the productions of the IL-10. MSCs may also act as an important part of peripheral immune tolerance by induction of Tregs. LFA-3, ICAM-1, and VCAM-1 are the main adhesion molecules that MSCs express to interact MSCs also modulate immune responses by inhibition of proliferation and maturation of NK cells and T cells and by decreasing the activation of DCs as well as suppressing DCs maturation by producing IL-6 and Macrophage Colony-Stimulating Factor (M-CSF) (Figure 4). Also, since the MSCs induced the activation of T cells, the generation of Immature DCs in the presence of MSCs is significantly decreased. Finally, regardless to cell-to-cell contact inhibitory mechanisms, MSCs also indirectly modulate the immune response by producing inhibitory agents and anti-inflammatory mediators, including; prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase, Transforming Growth Factor (TGF)-β and Hepatocyte Growth Factor (HGF) (Figure 4). Recent progress in MSC-based cyto therapies has shown a great potential to treat various immune-based disorders, such as cancers, Crohn's disease, rheumatoid arthritis, diabetes, and multiple sclerosis. MSCs are one of the most promising cell populations for cell-based immunomodulatory therapy in solid organ transplantation too.

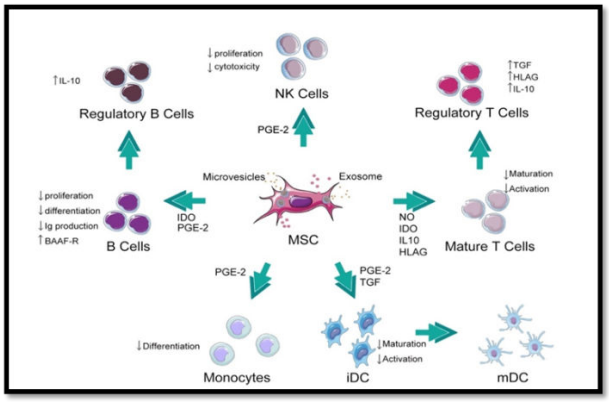

Figure 4: Immunomodulatory effects of MSC in the peripheral immune compartment. MSCs modulate peripheral immune compartments, including interacting with various immune cells and secreting various soluble mediators involved in different microenvironments. They suppress T cell subtypes (such as TH1, TH17, CTL) and B cell proliferation by the potent immunomodulatory molecules such as TGF-β, PGE2, and HLA-G5, induce the generation and proliferation of Tregs and Bregs, inhibit differentiation of precursors into DCs, inhibition of DCs maturation, and reduce proliferation, cytotoxicity, and IFN-γ production activity of NK cells Trough the secretion of TGF-β and prostaglandin E2 (PGE2). Also, IDO and PGE2 secreted by MCSs can induce the switch of M1 macrophages to the anti-inflammatory M2 macrophages.

Abundant studies have demonstrated the potential of human MSCs to generate a local immunosuppressive microenvironment by restraining allorecognition, interfere with T-lymphocytes and dendritic cells function and by secreting immunomodulatory cytokines so these cells have recently emerged as promising candidates for cell-based immunotherapy in solid organ transplantation. Based on animal experiments and clinical studies, the most successful clinical application of MSCs is involved in hematological disease. A comprehensive list of current clinical trials on the effects of Treg in the recipient after transplant with their identifier is depicted in Table1. According to this table, many clinical trials are passing Phase 1 successfully and some are in phase 2.

Target tissue or condition	Tregcell type administered	Trial phase	Clinical trial identifier
Liver	Alloantigen tregcells	I	NCT02188719
Kidney	Alloantigen tregcells	I	NCT02244801
Kidney	Alloantigen tregcells	I/II	NCT02711826
Liver	Alloantigen tregcells	I/II	NCT02474199
Liver	Autologous tregcells	I/II	NCT02166177
Islet cell	Autologous tregcells	I	NCT03444064
Refractory chronic GVHD	Alloantigen tregcells	I/II	NCT02749084
Refractory chronic GVHD	Alloantigen tregcells	I/II	NCT02385019
Refractory chronic GVHD	Alloantigen tregcells	II	EudraCT 2012-002685-12
Refractory chronic GVHD	Alloantigen tregcells	II	EudraCT 2016-003947-12
Refractory chronic GVHD	Alloantigen tregcells	II	EudraCT 2012-000301-71
SLE (skin)	Autologous tregcells	I	NCT02428309
Pemphigus vulgaris	Autologous tregcells	I	NCT03239470
Type 1 diabetes	Autologous tregcells	I	NCT02772679

Table 1: Current clinical trials studying Treg cells in transplantation and autoimmunity.

Mesenchymal stem cells therapy in solid organ transplantation

Cell therapies have been proposed as updated approaches to induce immune tolerance in solid organ and hematopoietic stem cell transplantation. Various researches have shown that the administration of immunoregulatory cells to transplant recipients could adjust the regulatory and effector pathways, eventually promoting the potential of the recipient immune

system to control the harmful immune response to the allograft tissue. Since MSCs potentially affect immunological, inflammatory and regenerative pathways, MSC therapy has been designed as a feasible tactic to modulate immune responses. Experimental transplant models have demonstrated that MSCs play a critical role in immune modulation and their regenerative effects have been shown in murine models. The tendency for administratingMSCs in solid organ transplantation comes not only from their anti-inflammatory properties but also from their potential to repair tissue damage. Various clinical trials have demonstrated the safety and feasibility of the administration of MSCs in kidney transplant recipients, and further studies have focused on improving the long-term transplant survival by minimization of immunosuppression. To increase wider usage of MSC in solid organ transplantation, it is urgent to specify efficacy, to increase the understanding of the mechanism of action, and to develop tools to identify eligible patients.

Clinical applications of MSCs in HSCT

Allogeneic hematopoietic stem cell transplantation is a common therapeutic method in hematologic malignancies. Currently, MSCs are widely used in hematological diseases, especially in HSCT, which mainly includes promoting HSCs engraftment, treating engraftment failure, poor graft function, and preventing GVHD. The plasticity, inhibitory effects, having the potential to produce a wide range of cytokines and migratory potential of MSC offer a promising source for stem cell therapy applications, so MSC could be a novel approach after HSCT. Since the hematopoietic microenvironment of bone marrow in HSCT recipients is damaged by irradiation, chemotherapy and malignant hematological diseases, MSCs can act as a repairer to fix damaged stroma with secretion of a group of hematopoietic cytokines, including IL-11, IL-6, IL-8, Flt-3 ligand, IL-7, and Stem Cell Factor (SCF). By regulating the inflammatory microenvironment and inducing the generation of Tregs, MSCs can also improve hematopoiesis.

MSC therapy in GVHD

About the therapeutic application of MSC, there are big challenges in efficacy and efficiency despite the wide investigation of MSCs. The immunosuppressive potential of MSCs are well documented that they have been successfully used in patients to amend GVHD. Allogeneic transplantation of MSCs is believed to involve a diminish risk of transplant rejection because it has shown that MSCs may avoid the recognition of circulating T cells and suppressing the immune responses according to their inhibitory potentials. This hypothesis giving rise to the idea of an allogeneic MSC preparation to be a “one-size-fits-all, off-the-shelf” therapy. The efficiency of MSCs for preventing GVHD varies in different researches have been reported that 28% of patients developed acute GVHD after co-infusion of MSCs with HSCs, while the incidence of acute GVHD in patients who received only HSCs (control group) was 56%. According to the vast spectrum of studies, different results have been shown in the fields of application of MSCs in GVHD patients. For example, a Germany and an American clinical trial have been shown that MSCs failed to achieve a significant increase in response rate in steroid-resistant GVHD patients compared with the control group.

In another clinical trial in Finland, keto et al. assessed the immunological response to MSC treatment in 16 acute GvHD patients by evaluating lymphocyte profiles and proposed acute GvHD serum markers during the MSC treatment. Surprisingly, they saw that there were no significant differences in the lymphocyte profiles between the responders and non-responders. The total numbers of lymphocytes include CD4+ T helper cells, B cells, and NK cells were below the normal reference interval in all patients and also remained particularly low throughout the follow-up period while regulatory T cells remained unaltered.

CONCLUSION

In conclusion, no obvious markers for MSC therapy response were revealed in this study, but the results suggest that allogeneic MSCs do not provoke overt T cell-mediated immune responses at least in immunosuppressed acute GvHD patients. Significant improvement has been reported in refractory chronic GVHD patients after MSCs administration. MSCs regulate chronic GVHD by affecting the function of B cells. many kinds of researches have indicated that MSCs may ameliorate Treasure of B cells renovation and retain their homeostasis by proliferating subsets of B lymphocytes include memory and naive cells in GVHD patients, and by adjusting levels of B cell activating factor and B cell activating factor receptor expression on B lymphocyte. In 2009 evaluated 19 patients with chronic GvHD treated with MSCs and reported a response rate of 73.7%. In this research, overall, complete and PR rates for acute GvHD were in line with the literatures.

Although co-transplanting MSCs with HSCs may reduce the occurrence of acute GVHD somewhat, different researches have shown that no statistical significance was shown in comparison with the control group. Of 11 pediatric patients diagnosed with acute or chronic GVHD, a limited profit after one or two injections of MSCs in only 5 patients with chronic GvHD was seen in the report of introna. Recent studies revealed that MSCs may boost the proliferation of Bregs (CD5+ B cells) in responsive chronic GVHD patients as well. Available evidence supported that administration of MSCs for acute GVHD prophylaxis was safe and efficient. In addition, researches have shown that MSCs can improve aGVHD by improving thymic output function and regenerating damaged thymic tissue which induced a long-term immune tolerance. MSCs can also reduce the possibility of bone marrow graft rejection by improving hematopoiesis, modulating the inflammatory microenvironment, and T-cell subtypes.

Tregs play a definitive role in inducing peripheral immune tolerance and MSCs can promote the generation of these cells to prevent GVHD. Various researches proved that MSCs can reduce the incidence and severity of chronic GVHD in acute GVHD patients by ameliorating thymic function. Based on these researches, it has proposed that MSCs could exert immunomodulatory effects through central immune compartments. Low efficacy of engrafted cells in a number of phase III clinical trials of MSC immunotherapy has led to unclear primary clinical endpoints.

DISCUSSION

The emergence of cell therapy as a regulator of peripheral tolerance has raised the exciting possibility that Treg and mesenchymal stem cells can be manipulated for improving outcomes of transplant. Recent clinical trials have been promising and using cell therapy in solid organ transplantation seems feasible and safe, however, dose and timing of the infusions are still challenging. Multiple studies have demonstrated that adoptive immunotherapy with purified fresh CD4+ CD25+ Tregs counteracts the GVHD potential of a high number of donor conventional Tcells in HSCT. Polyclonal recipient Tregs induced engraftment of conventional doses of allogeneic bone marrow in recipients conditioned with rapamycin and costimulation blockers, leading to donor-specific tolerance due to the emerging of mixed chimerism. Although data from animal models cannot be extrapolated well, several aspects are likely to be related to translation to the clinical application. First, the therapeutic administration of MSC and Treg is not likely to be successful in preventing rejection. Second, alloreactive Treg can be expanded for therapeutic administration. Third, alloreactive natural Treg exist and adaptive alloreactive Treg can be induced under some conditions. Fourth, the importance of antigen specificity for optimal Treg activity has been established well.

The different expressions of these markers are reliable predictors for disease occurrence, resolution, and survival. Therefore, it would be useful to explore more specific markers for diagnostic and prognostic applications. Despite increasing experimental and clinical interest in using MSCs as regenerative medicine especially in the field of transplantation, clinical MSC-based therapeutic approaches have not been well established, because of poor cell viability and low engraftment which limit the therapeutic efficacy of MSC transplantation. To overcome low-level engraftment output and long-term MSC engraftment loss, genetic modification has been suggested as a potentially effective approach to tissue repair and regeneration to promote therapeutic efficacy.

Various aspects of MSC and Treg biology that have a particular role in organ transplantation remain to be fully elucidated. Understanding the effects of these regulatory cells on the direct and indirect pathways, on effectors T and B cells, memory cells, primary immune system, and antibody production will provide novel insights into Treg and MSC functions and may afford new opportunities to restrain Treg function to modulate these important players in clinical outcomes. Further animal studies need to be performed to understand the exact effect and outcome of MSC and Treg therapy and for optimization for clinical application. It will also be needed to describe how current immunosuppressive drugs affect Treg in transplant patients and correlate immunologic outcomes to changes in Treg/Teff ratio.

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None

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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