Myeloid-derived suppressor cells in transplantation: the dawn of cell therapy

Weitao Zhang1†, Jiawei Li1†, Guisheng Qi1†, Guowei Tu2, Cheng Yang1* and Ming Xu1*

Abstract
Myeloid-derived suppressor cells (MDSCs) are a series of innate cells that play a significant role in inhibiting T cell-related responses. This heterogeneous population of immature cells is involved in tumor immunity. Recently, the function and importance of MDSCs in transplantation have garnered the attention of scientists and have become an important focus of transplantation immunology research because MDSCs play a key role in establishing immune tolerance in transplantation. In this review, we summarize recent studies of MDSCs in different types of transplantation. We also focus on the influence of immunosuppressive drugs on MDSCs as well as future obstacles and research directions in this field.

Keywords: Myeloid-derived suppressor cell (MDSC), Transplantation, Cell therapy, Immunology, Regulation

Introduction of MDSCs
Regulatory myeloid cells are emerging as novel targets for immunosuppressive agents and hold considerable promise as cellular therapeutic agents [1]. Although myeloid-derived suppressor cells (MDSCs) were initially observed in tumor-bearing patients in the 1980s [2, 3], their exact biological role became appreciated in 2000 [4]. MDSCs develop and differentiate from a common myeloid progenitor (CMP). MDSCs play a significant role in tumor growth and progression, metastasis and resistance to different therapies [5]. Under pathological conditions such as cancer [6–8], infection [9, 10] and transplantation [11, 12], the pathway for CMP differentiation into granulocytes, macrophages, and dendritic cells is inhibited, in which case some CMPs may differentiate into MDSCs.

MDSCs are not a terminally differentiated population of cells. In mice, MDSCs are defined as CD11b+Gr1+ cells. It is now accepted that MDSCs can be divided into two major groups of cells which can be identified by a combination of specific markers. Granulocytic MDSCs (G-MDSCs) are defined as CD11b+Ly6ClowLy6G+ cells and monocytic MDSCs (M-MDSCs) are defined as CD11b+Ly6ChighLy6G− cells [13–16]. G-MDSCs are the largest population of MDSCs in tumor-bearing mice, representing >80% of all MDSCs. However, there is no consensus on the definition of MDSC subsets in humans. Historically, human MDSCs were defined as lineage marker (CD3, CD14, CD19, and CD56)-negative, human leukocyte antigen (HLA)-DR-negative and CD33-positive cells purified from mononuclear cells using a Ficoll gradient [17]. More recently, the existence of two subsets of cells (similar to murine models) has been reported in cancer patients, and G-MDSCs are commonly characterized as CD11b+CD14+ cells expressing a granulocytic marker, CD15 or CD66 [18]. M-MDSCs are defined by two combinations of markers: CD11b+CD14−CD15 (or CD66b−) or CD11b+CD14+HLA-DRlow (Fig. 1) [19].

Several types of induction can contribute to the accumulation of MDSCs, including induction by inflammatory cytokines and growth factors (such as granulocyte-macrophage colony stimulating factor (GM-CSF) [20, 21] and interleukin (IL)-6 [22]) and tumor-derived factors (such as vascular endothelial growth factor (VEGF) [23] and transforming growth factor
(TGF)-β1 [24]). Furthermore, the functions of MDSCs are highly dependent on the circumstances in which their expansion occurs. Significant cell-mediated immunosuppressive capacities were observed in infectious MDSCs (iMDSCs) and tumor-bearing MDSCs (tMDSCs) in vitro [25].

MDSCs were reported to be endowed with robust immunosuppressive activity in multiple pathophysiological conditions [26, 27]. The crosstalk between MDSCs and immune cells has been illustrated in recent years, including the following aspects: (1) the suppression of T cell proliferation [28] and increased T cell apoptosis [29]; (2) the potential suppression of the B cell reaction via nitric oxide (NO) [30, 31]; (3) the inhibition of dendritic cell development [32, 33]; (4) the impairment of the effect of natural killer cells on alloantigens [34]; (5) promotion expansion of protumorigenic T regulatory cells [35] and (6) the modulation of cytokine production of macrophages [36].

Even though different types of immune cells activity can be suppressed by MDSCs, the primary ‘targets’ of MDSCs are T cells [37]. There are several mechanisms concerning MDSCs’ suppression of T cells: (1) MDSCs suppress T cell proliferation by depletion of l-arginine via high expression of arginase 1 (Arg1) and inducible nitric oxide synthase (iNOS) [38]. (2) MDSCs nitrate T cell receptors and then inhibit their interaction with cognate antigen-MHC complexes by expressing high levels of reactive oxygen species (ROS) [39]. (3) Other factors such as IL-10, B7-H1 and MHC class II are also involved in the suppressive activity of MDSCs [40].

Considering their immunosuppressive function, many studies have reported the significance of MDSCs in transplantation [1, 41, 42], from bench to bedside, in order to establish immune tolerance and to promote the long-term survival of transplants. This review summarizes recent advances on the effect and application of MDSCs on transplantation.

**Solid organ transplantation**

**Kidney transplantation**

Kidney transplantation is the most mature and common type of solid organ transplantation worldwide. The first report of MDSCs in an experimental kidney transplantation animal model was in 2008. A rat model of anti-CD28-induced kidney allograft tolerance showed an accumulation of plastic-adherent CD11b+ myeloid cells expressing CD80/86 that were defined as MDSCs. This study indicated that MDSCs had nonspecific immunosuppressive activity in vivo and in vitro involving the action of inducible nitric oxide synthase (iNOS), which was upregulated after contact with activated effector T cells but not with regulatory T cells (Tregs) [28]. Dilek et al. analyzed gene expression in blood-derived MDSCs from rat recipients of kidney allografts using DNA microarray [43]. They found that CCL5 (Rantes), a chemokine for Tregs, was strongly downregulated after treatment with a tolerizing regimen. The results indicated the
contribution of MDSCs to the establishment of a graft-to-periphery CCL5 gradient in tolerant kidney allograft recipients, which controlled the recruitment of Tregs to the graft where they likely contributed to maintaining tolerance [43].

In the clinic, Hock et al. reported renal transplant recipients had elevated frequencies of circulating CD11b+CD33+HLA-DR- MDSCs (both M-MDSCs and G-MDSCs) [44]. They further traced the change in MDSCs for 1 year post-transplantation. These observational studies showed that MDSC numbers increased rapidly and peaked following commencement of immunosuppression [45]. Luan et al. also found an increase in CD11b+CD33+HLA-DR- MDSCs in renal transplant recipients [46]. It is well known that Tregs play a key role in immune tolerance induction and maintenance [47]. The authors found that MDSCs isolated from kidney transplant recipients were highly efficient in suppressing the proliferation of CD4+ T cells in mixed leukocyte reactions. In addition, CD11b+CD33+HLA-DR- MDSCs were capable of expanding Tregs in vitro, and their accumulation over time after transplantation was linearly correlated with an increase in Tregs in vivo. This was the first study to link the presence of MDSCs with the emergence of Tregs in vivo in transplant recipients, and to define the subpopulation of MDSCs derived from transplant recipients responsible for generation of Tregs [46]. The results of Meng et al. also supplement the previous findings of MDSCs in kidney transplantation [48]. In this study, 50 renal transplant recipients with acute T cell-mediated rejection were enrolled. The patients were divided into two groups according to the ratio of MDSCs in the peripheral blood mononuclear cell population tested by flow cytometry. As expected, the 1- and 5-year graft survival rates in the high-MDSC group were 93 and 79%, respectively, but were only 68 and 36%, respectively, in the low-MDSC group. As expected, interferon (IFN)-γ- and tumor necrosis factor (TNF)-α-related renal tissue injury was significantly alleviated in the high-MDSC group compared with the low-MDSC group. Furthermore, IL-17, a strong pro-inflammatory cytokine, was inhibited by Tregs expanded by MDSCs [48]. These results indicated that the number of MDSCs in the renal allograft recipients was associated with long-term graft survival and that MDSCs may regulate the imbalance between Tregs and Th17 cells.

**Cardiac transplantation**

In a prolonged murine cold ischemia time-mediated donor cardiac injury model [49], Gong et al. detected three MDSC subsets, CD11b+Gr-1low, CD11b+Gr-1int and CD11b+Gr-1high. It should be noted that the definition of MDSC subsets was based on Gr-1, without Ly6C. The findings revealed that CD11b+Gr-1low MDSCs had strong suppressive activity. MDSC subsets from the tolerant mice exhibited higher suppressive capacities compared with subsets from naive (untreated) mice. Depletion of Tregs increased peripheral and intragraft CD11b+Gr-1low MDSC frequency. Intriguingly, boosting Tregs caused a remarkable increase in CD11b+Gr-1low MDSC frequency in the graft, peripheral blood and spleen. This study indicated for the first time the possible interaction between MDSCs and Tregs in cardiac transplantation [49]. Furthermore, Nakamura et al. demonstrated that MDSCs induced by PD-L1 were capable of recruiting Foxp3+ Tregs [50].

In addition to focusing on the mechanism of MDSC induction, some studies have also examined the possibility of increasing the induction of MDSCs, which may indicate a possible direction for immune therapy in transplantation. Mammalian target of rapamycin (mTOR) inhibitors are the main immunosuppressive drugs for organ transplant recipients. Nevertheless, the mechanisms by which mTOR inhibitors induce immunosuppression are not fully understood. Interestingly, in a murine cardiac transplantation model, rapamycin treatment led to the recruitment of MDSCs and increased their expression of iNOS [51]. Adoptive transcoronary arterial transfer of MDSCs from rapamycin-treated recipients prolonged allograft survival. Co-administration of rapamycin and the mitogen-activated protein kinase (MEK) inhibitor trametinib reversed rapamycin-mediated MDSC recruitment. Thus, the author concluded that the mTOR and Raf/MEK/extracellular signal regulated kinase (ERK) signaling pathways appeared to play an important role in MDSC expansion [51]. IL-33, which is thought to be able to facilitate Th2 responses, significantly increased CD11b+Gr1int M-MDSCs in a chronic cardiac rejection model, reduced antibody-mediated rejection and ultimately prolonged allograft survival [52, 53]. These findings support IL-33-based MDSC therapy in cardiac transplantation. The induction of other molecules, such as IL-6 [54, 55] and IFN-γ [56], has also been tightly associated with MDSCs in cardiac transplant protection.

**Skin transplantation**

Skin transplantation is a convenient animal model for the study of rejection and tolerance. In 2008, a study conducted by Zhang et al. demonstrated the expansion of MDSCs by immunoglobulin-like transcript 2 receptor and its ligands [57]. Moreover, the immunosuppressive function of MDSCs was enhanced by this specific kind of receptor, which led to a better survival rate of allografts after transplantation. Other studies have illustrated that MDSCs induced by IL-2C or neupogen [58], IL-33...
IL-13 inhibits GVHD lethality with more efficacy. Indeed, arginase-1 up-regulation. Compared to MDSCs, MDSC-IL-13 is more potently suppressive and results in which was produced by exogenous IL-13 (MDSC-IL-13). The suppression was attributed to l-arginine depletion by arginase-1 activity. More recently, Highfill et al. in 2010. The suppression was attributed to the over-activation of donor-specific T cells in the spleen [62]. Furthermore, in order to assess the effect of MDSCs in immunosuppressive treatments, Carretero-Iglesia et al. directly compared the function of three regulatory myeloid cell types in a skin transplant model, including autologous tolerogenic dendritic cells, suppressor macrophages (suppMφs) and MDSCs [63]. They found that these three types of cells perform their roles in T cell inhibition in three different ways. Autologous tolerogenic dendritic cells mainly regulate the activation, proliferation and reactivation process of T cells, while suppMφs are thought to be responsible for inducing and expanding Treg cells. However, MDSCs appear to exert their immunosuppressive function through Treg expansion as well as induction of T cell death.

Bone marrow transplantation (BMT)
The discovery of MDSCs can be attributed to BMT. In 1984, MDSCs were first reported in patients who received BMT [64]. At that time, these cells were called “natural suppressor cells,” and it was indicated in the study that MDSC expansion was actually induced by radiation. Because of the application of various pro-inflammatory cytokines, such as IFN-γ, granulocyte-colony stimulating factor (G-CSF), and IL-1β [65], some animal models have emerged in recent years in which MDSCs accumulate and are activated without radiation [66, 67].

The efficacy of BMT can be limited by graft-versus-host disease (GVHD), and the first use of MDSCs in vitro to suppress major-mismatch driven GVHD was reported by Highfill et al. in 2010. The suppression was attributed to l-arginine depletion by arginase-1 activity. More importantly, Highfill et al. found a new subset of MDSC which was produced by exogenous IL-13 (MDSC-IL-13). MDSC-IL-13 is more potently suppressive and results in arginase-1 up-regulation. Compared to MDSCs, MDSC-IL-13 inhibits GVHD lethality with more efficacy. Indeed, MDSC-IL-13 express high levels of PDL1 which regulates tolerance by PD1-PDL1 interactions [68]. It is known that tumor relapse is a common but severe threat to BMT recipients. In a BMT model, Wang et al. revealed that the additional accumulation of MDSCs (both in the spleen and in peripheral blood) after allogeneic BMT was stimulated by tumor relapse [69]. Thus, MDSCs may also serve as a predictor for tumor relapse after BMT. Consistent with this finding, another clinical investigation observed that MDSC subsets in patients who received a hematopoietic stem cell transplant were positively correlated with T, B, and double-negative T cell numbers after transplantation [70]. This study supports the previous findings in animal models and further analyzed the kinetics of MDSC subsets in clinical work. Koehn et al. summarized recent advances in investigation of MDSC and allogeneic hematopoietic cell transplantation [71].

Other transplantations

Corneal transplantation
Even though the acceptance rates of penetrating keratoplasty are relatively high [72, 73], either inflammation or neovascularization can induce corneal graft rejection and failure [74]. When retroorbitally injected into the recipients immediately after keratoplasty surgery, both iMDSCs and tMDSCs had a suppressive effect on CD4+ T cell proliferation, and they improved the histological condition and decreased neovascularization of corneal grafts. However, a supplementary injection of iMDSCs did not cause graft improvements at later stages [75]. This result was partly consistent with a study in which CD11b+ cells were induced by lipopolysaccharide (LPS) [76].

Islet transplantation
Type 1 diabetes accompanied by diabetic complications usually occurs when patients lose insulin-producing pancreatic β cells. The routine therapy for this disease is the administration of exogenous insulin. However, insulin may not fulfill the function of normal β cells. Pancreas transplantation has been considered to address this situation, but deleterious side effects are unavoidable [77–79]. In recent years, islet transplantation in optimal situations has appeared as an alternative to pancreas transplantation [80, 81]. As a type of cell transplant, islet grafts have promising prospects, and the induction of tolerance to remove the dependency on immunosuppressive drugs is challenging and necessary. Considering the significance of MDSCs in transplantation, Arakawa et al. co-transplanted MDSCs (generated from bone marrow cells cultured with hepatic stellate cells and GM-CSF with islet grafts in diabetic recipient mice [82]. The results showed that the co-transplantation of these two types of cells significantly promoted allograft survival. As expected,
MDSCs exerted their inhibitory function on T cells in an iNOS-dependent manner. MDSCs from inos-deficient mice failed to protect islet allografts [82], which indicated the key role of iNOS in MDSC-induced tolerance in islet transplantation. The conclusion agreed with a previous study in which MDSCs expressing a high level of arginase-1 enhanced antigen-specific Tregs in the B7H1 pathway [83].

What is the impact of immunosuppressive agents on MDSCs?
To date, complete tolerance induction has not been achieved in the clinic, so we must consider the influence of immunosuppressive agents on MDSCs. Several studies have recently reported on the influence of immunosuppressants on myeloid cells in transplant models. Cyclosporine (CsA), a typical type of calcineurin inhibitor, is extensively used to prevent anti-allograft rejection in clinical settings [84]. CsA was previously reported to stimulate the accumulation and suppressive function of MDSCs. In a skin transplantation study, CsA treatment upregulated the allograft infiltration of CD11b<sup>+</sup>Gr1<sup>+</sup> cells [85]. However, the increase in CD11b<sup>+</sup>Gr1<sup>+</sup> MDSCs was not attributed to their proliferation but rather to their migration induced by CsA. Moreover, it was CD11b<sup>+</sup>Gr1<sup>+</sup> MDSCs that were critical for CsA prolongation of allograft survival. The authors demonstrated that CsA-induced MDSCs exerted their function in ameliorating the allograft immune response through the calcineurin-NFAT-IDO signaling pathway, and these MDSCs were able to regulate T cell differentiation from Th1 to Th2 and also CD8<sup>+</sup> T cell differentiation.

Rapamycin, as an mTOR inhibitor, is another immunosuppressive agent. In a cardiac transplant model, rapamycin treatment at a dosage of 3 mg/kg at different times after transplantation promoted the recruitment of MDSCs and enhanced the activity of arginase-1 and iNOS in MDSCs [51]. The results also showed that the MEK inhibitor trametinib could reverse MDSC induction, which indicated that the ERK signaling pathway was important in the expansion of MDSCs. Our group further investigated whether the mTOR signaling pathway regulates MDSC differentiation and immunosuppressive function [86]. We found that inhibiting mTOR signaling by rapamycin regulated the induction of MDSC towards the CD11b<sup>+</sup>Ly6G<sup>+</sup>Ly6Chigh G-MDSC subset. The ability to suppress T-cell proliferation of both bone marrow-derived CD11b<sup>+</sup>Ly6G<sup>+</sup>Ly6Chigh G-MDSCs and CD11b<sup>+</sup>Ly6G<sup>-</sup>Ly6Chigh M-MDSCs was enhanced by mTOR signal inhibition via upregulation of arginase-1 and iNOS expression. However, the impact of rapamycin on MDSCs is still controversial. In a skin transplant model, Wu et al. reported that rapamycin significantly delayed alloskin graft rejection by decreasing the number of M-MDSCs and directly inhibited M-MDSC differentiation in vitro [87]. The reason for these different results might be due to the use of different disease models and will require further investigation.

In addition to the previously referenced studies, glucocorticoid (GC) was reported to expand MDSCs both in vivo and in vitro [88–90]. As a typical synthetic GC immunosuppressant, dexamethasone was chosen to explore the potential relationship between GC and MDSCs. In alloskin transplant recipient mice after dexamethasone treatment, MDSCs prolonged graft survival and acted as functional suppressive immune modulators that resulted in fewer IFN-γ-producing Th1 cells and a greater number of IL-4-producing Th2 cells. Dexamethasone-treated MDSCs promoted reciprocal differentiation between Th1 and Th2 in vivo in a GC receptor-dependent manner [91]. In addition to transplantation, dexamethasone was demonstrated to regulate the suppressive function of MDSCs via hypoxia inducible factor (HIF)-1α as well as by GC receptor-HIF1α glycolysis in an immunological hepatic injury model [91]. High-dosage dexamethasone rescued MDSC numbers and promoted the suppressive function of MDSCs via Ets1 in immune thrombocytopenia patients [92]. Table 1 summarizes recent studies of immunosuppressive agents and MDSCs. However, the effect of other immunosuppressive agents on MDSCs, such as tacrolimus and mycophenolate mofetil, is still unknown.

| Immunosuppressive drug | Year | Disease model | Induction of MDSCs | Mechanism | Ref. |
|------------------------|------|---------------|-------------------|-----------|-----|
| Cyclosporine A         | 2014 | Skin transplantation | Yes | Calcineurin-NFAT-IDO | [85] |
| Rapamycin              | 2015 | Cardiac transplantation | Yes | iNOS/Arg-1 | [51] |
| Rapamycin              | 2017 | AKI            | Yes | iNOS/Arg-1 | [86] |
| Rapamycin              | 2015 | Skin transplantation | No | iNOS/Arg-1 | [87] |
| Dexamethasone          | 2014 | Skin transplantation | Yes | GC-GR-NO | [91] |
| Dexamethasone          | 2017 | Immunological hepatic injury | Yes | GC-GR-H1α | [92] |

AKI acute kidney injury, IDO indoleamine 2, 3-dioxygenase, Arg-1 arginase-1
Can MDSCs promote or induce immune tolerance?

Currently, no standard tolerance induction protocol is available in routine clinical practice. However, harnessing the tolerogenic potential of immune cell therapy in transplantation, including MDSC-based cell therapy, may provide an opportunity to accomplish this goal. In 2008, Dugast et al. reported an accumulation of MDSCs in the blood of a rat renal transplantation model [28]. These cells were able to inhibit proliferation but not activation of effector T cells and could induce apoptosis in a contact-dependent manner. However, adoptive transfer of MDSCs failed to induce allograft tolerance in recently transplanted recipients. Thus, researchers have focused on how to induce MDSCs that are able to induce immune tolerance. Zhao et al. found that M-CSF- and TNF-α-induced M-MDSCs have powerful immunosuppressive activity in an iNOS-dependent pathway, and that M-CSF + TNF-α-induced M-MDSCs were able to promote immune tolerance to donor antigens in a murine skin transplant model [61]. In addition to transplantation, autoimmune diseases also need antigen-specific immune suppression. In multiple sclerosis, G-MDSCs have been shown to participate in the process of tolerance induction. G-MDSCs were shown to adopt a more suppressive phenotype during peptide immunotherapy and to inhibit CD4+ T-cell proliferation in a cell-contact-dependent manner [93].

Attempts of MDSC-based cell therapy in transplantation

The therapeutic value of MDSCs has been recognized in patients with cancer [94, 95], inflammation [96, 97] and autoimmune disease [62, 98, 99]. In these conditions, MDSCs usually serve as biomarkers, and the program of therapy may focus on blockade of these cells. However, because of the immune suppressive function of this heterogeneous cell population, there has been growing interest in MDSC-based cell therapy in transplantation. Researchers have aimed to manipulate MDSCs to achieve immune tolerance in the context of transplantation. As mentioned previously, the adoptive transfer of MDSCs was first attempted in 2008, although it failed to induce kidney allograft tolerance [28]. Since then, several investigators have confirmed that repeated injection of MDSCs promotes allograft survival in skin [61], corneal [75] and skin-corneal combined transplantsations [25]. There have thus far been no reports concerning MDSC infusion in human transplant recipients. In BMT models, transplantation of MDSCs generated from bone marrow cells by GM-CSF/G-CSF in vitro inhibited GVHD-induced death and attenuated histologic GVHD, whereas the antitumor cytotoxicity of alloantigen-specific T cells was maintained [100]. However, the stability of MDSC immune suppressive function requires a certain microenvironment. For example, Kehn et al. reported that transferred MDSCs lost their suppressive function and their potential to inhibit GVHD lethality immediately upon entering a conditioning regimen that subjected them to GVHD inflammatory settings [101]. This indicated that in the BMT setting, the use of MDSCs as a therapeutic approach for preventing GVHD and other systemic inflammatory conditions may be more effective when combined with approaches limiting in vivo MDSC inflamasome activation.

Conclusion and perspectives

MDSCs were once thought to play a significant role in the mechanism and therapeutic treatment of tumors. Their potential diagnostic value, combined with their therapeutic value in transplantation, has now become the focus of immunologists and clinicians because MDSCs can inhibit immunoreactions. Considering this function, MDSCs may be used to induce immune tolerance and prolong allograft survival in clinical applications of the future. However, until recently, the differentiation of MDSCs has not been efficient, which has made their application difficult [102]. In addition, it is still unknown whether G-MDSCs and M-MDSCs are terminally differentiated subsets of MDSCs, or whether the phenotype and function of MDSCs subsets are stable. Macrophages, which are also differentiated from immature myeloid cells like MDSCs, consist of M1 and M2 subsets which can convert into each other in some immune microenvironments [103, 104]. We therefore cannot exclude the possibility that G-MDSCs and M-MDSCs can similarly convert into each other. As Scalea et al. pointed, it remains unknown if the type of organ transplanted (e.g. kidney versus liver) leads to MDSCs with different suppressive capacities [42].

There are many ideas on how to manipulate the differentiation and purification of MDSCs to make them more useful. In addition, the particular markers for MDSCs, the inductive pathways of MDSCs and the molecular mechanisms regulating MDSCs still need to be identified to evaluate the specific properties of MDSCs. Recent studies have been restricted to animal models or in vitro studies of the molecular mechanisms, but future investigations are expected to be conducted in humans within a safe environment. Like Tregs [105], manipulation of MDSCs in vitro and infusion MDSCs into allograft recipients as a form of cell therapy will require more animal studies before going to clinical trial (Fig. 2). The specific surface markers, stability, lifespan and molecular effector pathways/mechanisms of MDSCs need to be fully identified. Moreover, the efficiency, specificity and safety of MDSC-mediated treatment remain to be determined with experimental and preclinical studies. We believe...
that by solving the above difficulties, the application of MDSCs in transplantation will be significantly advanced in the future.

Abbreviations
MDSCs: myeloid-derived suppressor cells; CMP: common myeloid progenitor; GM-CSF: granulocyte-macrophage colony stimulating factor; TGF: transforming growth factor; Tregs: regulatory T cells; IFN: interferon; TNF: tumor necrosis factor; mTOR: mammalian target of rapamycin; MEK: mitogen-activated protein kinase; ERK: kinaseRaf/MEK/extracellular signal regulated kinase; suppMφs: suppressor macrophages; BMT: bone marrow transplantation; GVHD: graft-versus-host disease; Arg1: arginase-1; LPS: lipopolysaccharide; CsA: cyclosporine; HIF: hypoxia inducible factor.

Authors’ contributions
WZ drafted the manuscript. CY and MX conceived the proposal, revised the manuscript and provided funding support. JL collected literatures and revised the manuscript. GQ and GT helped the language editing and provided funding support. All authors read and approved the final manuscript.

Author details
1 Department of Urology, Zhongshan Hospital, Fudan University, Shanghai Key Laboratory of Organ Transplantation, 180 Fenglin Road, Shanghai 200032, China. 2 Department of Intensive Care Medicine, Zhongshan Hospital, Fudan University, Shanghai, China.

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Competing interests
The authors declare that they have no competing interests.

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