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Review Article

Analysis of the Application of Regulatory Dendritic Cells in Kidney Transplantation

Haiyan Xu and Xiaozhou He*

Department of Urology, Third Affiliated Hospital of Soochow University, China

***Corresponding author:** Xiaozhou He, Department of Urology, Third Affiliated Hospital of Soochow University, No.185, Juqian Street, Changzhou 213003, China.

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Abstract

Kidney transplantation (KT_x) is the optimum therapy for end-stage renal diseases. However, long-term usage of immunosuppressive agents results in various toxicities and side effects, which has been a major obstacle for recipients. How to reduce the dosages of immunosuppressive agents has become a problem that desperately needs to be solved. Among potential methods, cell therapy has great potential, and regulatory dendritic cells (DC_{reg}) have attracted special attention for their tolerogenic ability. Currently, some DC-based clinical trials are ongoing or have been completed at several research centers, including an immune tolerance trial in KT_x named "The One Study", in which autologous peripheral blood mononuclear cells were isolated and stimulated with low doses of GM-CSF or immunosuppressive agents. DC_{reg} generated with different induction methods or from different cell sources may function in different ways in different organs. After surgery, kidney allografts become the focus of attacks by the immune system and form a specific immune microenvironment. Can DC_{reg} successfully induce immune tolerance in KT_x recipients? In the present manuscript, we comprehensively analyzed the potential of DC_{reg} in KT_x from the perspective of kidney immunology.

Keywords: Regulatory dendritic cells (DCreg); Kidney transplantation; Cell therapy

Abbreviations: DCs: Dendritic Cells; DCreg: Regulatory Dendritic Cells; KTx: Kidney Transplantation; HLA-G: Human Leukocyte Differentiation Antigen; PD-L: Programmed Death-Ligand; mDCs: Myeloid DCs; PDCs: Plasmacytoid DCs

Introduction

After kidney transplantation (KT_x), recipients need to take immunosuppressive agents to prevent rejection. However, the toxicities and side effects of long-term usage of immunosuppressive agents should not be overlooked. How to reduce the dosages of immunoinhibitory agents has become a major problem that desperately needs to be solved. Currently, new immunosuppressive strategies, new immunosuppressive reagents and cell therapies are all being researched and developed [1]. Cell therapy has drawn increasing attention, and further investigation will not only provide potential targets of immunosuppressive reagents but also have very important clinical value. Dendritic cells (DC_s) are heterogenous professional antigen-presenting cells that play central roles in innate immunity and adoptive immunity, including roles in immune tolerance induction and immune stabilization [2]. A group of DCs with the capability of immune tolerance induction was named tolerogenic DC_s [3] or regulatory DC_s (DC_{reg}). DC_{reg} have been applied as a cell therapy-based alternative to immunosuppressive agents. In addition, phase II clinical trials assessing the treatment of diabetes and autoimmune diseases with DC_{reg} have been carried out [4]. The kidneys, which have a special structure and function, are an important organ for ensuring a stable internal environment and normal metabolism. Before and after KT_x, does DC_{reg} infusion function to induce immune tolerance as expected? This is the focus of DC_{reg}-based cell therapy. In this manuscript, we review the application of DC_{reg} in KT_x recipients in regard to kidney immunology.

Discussion

Characteristics of DC_{reg}

There are few natural DC_{reg} in vivo, and these cells are small and round [5] and greatly differ from DC_{reg} obtained in vitro. DC_{reg} induced in vitro are always smaller than normal mature DCs, with few short

dendrites, and DC_{reg} cell phenotypes are also different from mature DC phenotypes [6]. Without inflammatory stimulation, immature DC_s participate in peripheral immune tolerance induction, showing a DC_{reg} phenotype and functional characteristics. Under normal conditions, DC_{reg} express low levels of major histocompatibility complex II molecules and costimulatory molecules such as CD80 and CD86 [7]. Nevertheless, the expression of inhibitory molecules, such as human leukocyte differentiation antigen-G (HLA-G) [8], programmed death-ligand (PD-L)-1 and 2 [9], and galectin [10], increases. An increased PD-L1/CD86 ratio and enhanced IL-10 secretion are thought to be characteristics of DC_{reg} [11]. DC_{reg} may have relatively specific phenotypes in different tissues and organs; for instance, DC_{reg} are likely to have a CD141+CD14+ phenotype in the skin [12], and DCreg may be DC-10 in the blood [13,14]. At present, genetic modification, drug intervention, cytokine exposure and so on are used to induce DC_{reg}, and precursor cells can be isolated from bone marrow cells, peripheral blood mononuclear cells or lymph node cells [15-17]. DC_{reg} can produce TGF-β1 [18,19], IL-10 [20,21], 2,3-IDO [22-24], IFN-γ and the Epstein-Barr virus (EBV) induction gene [25] or induce regulatory T cells (Tregs) [26,27] to exert their immune tolerance induction function.

Effects of the internal environment on DCs in KT_x recipients

Under normal conditions, KT_x recipients receive immune induction therapy before surgery and routine immunosuppressant administration after surgery to suppress potential immune rejection. Specific and nonspecific immunosuppressants severely weaken recipient immune function, and DC_s are significantly affected. Studies have shown that immunosuppressive agents have different effects on different DC subsets. After KT_x, the numbers of recipient myeloid DC_s (mDC_s) and plasmacytoid DC_s (pDCs) are dramatically decreased, and the number of mDC_s does not recover within 3 months after surgery [28]. If recipients receive immunosuppressive therapy in addition to conventional immunosuppressive therapy, DC numbers, including the numbers of mDC_s and pDC_s, decline more significantly early post operation; CD62L expression significantly increases on mDC_s, but CD86 expression significantly decreases [29]. CD62L, an adhesion molecule, can mediate the initial retention related to DC rolling on endothelial cells. If recipients have taken immunosuppressive agents for over 1 year, the number of peripheral blood DC_s (mDC1, mDC2 and pDC_s) is decreased [30,31]. In other words, immunosuppressive agents result in maturation arrest in peripheral m DC_s [32]. Some studies have reported that DC_{reg} numbers increase after usage of immunosuppressive agents. Rapamycin application can induce the production of ILT3highILT4high DC_s [33], which have the ability to induce immune tolerance. Specific anti-CD52 monoclonal antibody (alemtuzumab, also called Campath-1H) induction therapy dramatically decreases the number of peripheral blood DC_s, and after one month, mDC_s will transform into pDC_s (the mDC_s/pDC_s ratio declines) [34]. CTLA-4-Ig (belatacept) application can induce DC_s to express HLA-G [35], which interferes with the activation of T cells. In recipients treated with belatacept, the numbers of regulatory cells (Tregs/regulatory B cells (Bregs)/plasmacytoid dendritic cells (pDC_s)) markedly increase in renal allograft tissues, but the proportions of apoptotic cells and aged cells significantly decrease, and proliferation marker expression increases [36]. All of the published research indicates that immunosuppressive agents can interfere with DC growth and differentiation or the induction of DC_{reg}, and the results also emphasize the key role of DC_{reg} in inhibiting alloantigen-mediated rejection. The effects of different immunosuppressive agents may overlap. Thus, the following aspects, including DC_{reg} preparation, infusion frequency, pathways and cell numbers, all need to be considered to evaluate the similar and unique effects of immunosuppressive agents when DC_{reg} are applied as a cell therapy.

Specific microenvironment of renal allograft tissue

CX3CR1+ DC_s can be found in the renal mesenchyme and glomerular mesangium by confocal laser scanning microscopy. These DC_s highly express CD11c, F4/80, MHCII, FcR and inhibitory costimulatory molecules. Among these cells, at least one subgroup has the ability to perform phagocytosis, which means that the cells in this subgroup are tissue-resident immature DC_s, and this subgroup forms a monitoring network for the microenvironment [37]. During the process of removal from the donor, transfer into an organ-preservation fluid, and implantation into the recipient, a renal allograft will undergo ischemia-reperfusion injury, which causes the release of endogenous molecules. Pattern recognition receptors can recognize these molecules as danger signals and induce inflammatory cell recruitment and mediator activation. As one of the sentinels in the kidneys, DC_s will mature in the microenvironment and drain into the lymph nodes, presenting and activating T cells. Under this condition, T cells can differentiate into Th1 and Th17 effector cells or Th2 cells and Tregs [38,39]. Animal experiment results suggest that donor DC_s in renal allograft tissue are rapidly replaced by recipient DC_s after the donor kidney is implanted into the recipient [40]. Infiltrated recipient DC_s and T cells in tissues are associated with shortened graft survival [41]. Clearance of recipient DC_s can reduce the proliferation and survival of infiltrating T cells in a graft and inhibit effector T cell-mediated rejection [40,42]. Renal tubular epithelial cells are thought to be the main cell type that attracts white blood cells during the inflammatory response in the kidneys. They release MIP3α/CCL20, attracting immature DCs [43]. Renal tubular epithelial cells produce GM-CSF, inducing pDC_s to perform phagocytosis and enhancing the alloantigen responsiveness of CD4+ and CD8+ T cells, which may act in the indirect alloantigen-presentation process [44]. Studies also showed the importance of pDC_s in the induction of tolerance via the special mechanisms [45]. A recent study indicated that Tregs could also induce DC_{reg} generation, which was probably due to the contents of extracellular vesicles (such as miR-150-5p and miR-142-3p) released by Tregs, and that these DC_{reg} could secrete increased amounts of IL-10 and decreased amounts of IL-6 when stimulated with LPS [46].

The renal parenchyma consists of the renal cortex and medulla. The renal cortex is rich in blood vessels, and the renal medulla shows a significant osmotic gradient. Microarray analysis suggested that the hypertonic environment of the renal medulla could induce medulla DC_s to dramatically increase the expression of transcripts with anti-inflammatory functions while reducing the expression of alloantigen-recognition transcripts, reducing the risk of local alloantigen rejection. The results indicated that the renal medulla environment might inhibit alloantigen responsiveness by regulating DC_s [47,48]. Study results for a large-sample phenotypic detection and transcriptomic analysis of three kinds of DC_s (mDC1, mDC2, and pDC_s) from mice and humans showed that the functions of DC subtypes from different lymphatic hematopoietic systems due to the cell origin rather than the microenvironment. In comparison, DC subtypes from human lungs and skin were affected by the tissue microenvironment [49]. Currently, no reports on the origin of renal DC_s have been published, but renal DC_s perhaps have relatively special phenotypes and functions in inflammatory responses and noninflamed tissue. After infusion into recipients, the ideal prognosis for DC_{reg} is the following progression: binding to endothelial cells, infiltrating allograft tissues, migrating into lymphatic vessels, traveling to secondary or primary lymphoid organs, and inducing alloantigen-responsive T cell apoptosis, clonal deletion or Treg generation, thus exerting an immunosuppressive effect. Therefore, we cannot neglect the potential role of the renal allograft microenvironment in DC_{reg} development, and we need to prepare DC_{reg} with high stability and chemotactic performance.

The origin of DC_{reg} and induction method selection

The team of Professor Li YP at Sichuan University of China conducted a meta-analysis of the effects of adoptively transferred DC_{reg} on renal allografts according to cell source, infusion route, mechanism and so on. They concluded that DC_{reg} derived from rat and mouse bone marrow precursor cells could induce immune tolerance in MHC-mismatched renal allografts and extend survival time; the effects of tolerance induction by immature DCs and genetically modified DC_{reg} were not significant [50]. The consulted references were all reports on rodent KTx, and the DC_{reg} were derived from unrelated individuals; thus, the authors did not refer to the origin of the DC_{reg}. However, the obtained results are of great significance for reference [51]. To enhance the specificity of DC_{reg}, the study gradually shifted to performing KT_x in larger animals, and bone marrow precursor cells or peripheral blood mononuclear cells were collected from donors or recipients to induce DC_{reg}.

Professor Thomas AW and his team completed a series of studies. They carried out rhesus monkey KT_x and cell therapy with DC_{reg}. In their studies, DC_{reg} were induced from donor peripheral blood mononuclear cells with vitamin D3 and IL-10 in combination with GM-CSF and IL-4. During the course of cell therapy, 8 weeks of CTLA4-Ig administration and 6 months of rapamycin treatment were continued. The results showed that DC_{reg} significantly prolonged the survival of renal allografts [52]. Further analysis indicated that the function of DC_{reg} was associated with downregulation of Emos transcript levels and upregulation of CTLA4 expression in donor responsive CD8+ memory T cells [53]. Infusion of DC_{reg} before transplantation sustained a high frequency of CD4+CTLA4hi T cells after transplantation, even if CD28 costimulatory signaling was blocked [54]. The authors obtained enhanced immunosuppressive effects with combined usage of donor antigen-loaded autologous-derived DC_{reg} and low-dose immunosuppressants [55]. Their research results indicate the great potential of DC_{reg} application in organ transplantation recipients [56-58]. Now, their team is recruiting volunteers for phase I clinical trials of a DC_{reg}-based cell therapy, and they plan to apply donor-derived DC_{reg} induced with vitamin D3 and IL-10. Another team that carried out an in-depth study of DC_{reg} is Professor Cuturi MC's team at Nantes University of France [59,60]. In the clinical trial "The One Study", they adoptively transferred autologous DC_{reg} pulsed with low-dose GM-CSF to treat living KTx recipients only once before surgery. Although no report has been published, the authors reported that no signs of rejection were observed after immunosuppressant withdrawal [61]. In these clinical trials, conventional induction methods were applied, and clinical effects remain to be reported. With developments in structural biology, pharmacology, genomics, immunology and other related disciplines, new induction methods are being developed to improve the performance and stability of DC_{reg}.

Conclusion

It has been accepted that adoptive transfer of DC_{reg} should have good clinical application prospects given capability of these DC_s to protect allografts [62]. We need to establish a treatment plan that can be referred to before clinical usage [63]. For solid organ transplantation, such as KT_x, the characteristics of kidney immunology and immunosuppressive regimens should be considered during the preparation of DC_{reg}. Furthermore, the development of sensitive, safe and effective immunosurveillance markers is also a priority.

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Conflict of Interest

None.

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