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Review

Immunological characteristics of renal transplant tolerance in humans

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ABSTRACT

Establishing allograft tolerance is a highly desirable therapeutic goal in kidney transplantation, from which recipients would greatly benefit by withdrawing or minimizing immunosuppression. Identifying biomarkers in predicting tolerance or early diagnosing rejection is essential to direct personalized management. Recent findings have revealed that multiple populations of immune cells have involved in promoting long-term graft function or inducing rejection in renal transplant recipients. Thus, roles of immune cells add another level to predict the renal tolerant state; tailoring their functional and/or phenotypic characteristics would provide insights into mechanism involved in transplant tolerance that may aid in designing new therapies. Here, we review these findings and discuss the current understanding immunological characteristics of renal transplant tolerance in humans, and their potential clinical translation to immune tolerance biomarkers.

Contents

1. Introduction 71
2. Immune cells in renal transplant tolerance 72
   2.1. B cells in renal transplant tolerance 72
   2.2. T cells in renal transplant tolerance 73
   2.3. Natural killer cells in renal transplant tolerance 74
   2.4. Dendritic cells in renal transplant tolerance 74
   2.5. Macrophages in renal transplant tolerance 75
   2.6. Myeloid-derived suppressor cells in renal transplant tolerance 75
3. Remaining questions 75
4. Conclusion 76
References 76

1. Introduction

Kidney transplantation is an optimal treatment for most patients with end-stage renal diseases (Hernandez-Fuentes and Lechler, 2010). Immune-mediated allograft damage is one of the key causes for allograft loss; thus most renal transplant patients need lifelong immunosuppressive therapy. Although advances in immunosuppressive therapy decrease acute rejection rates, long-term allograft survival remains concerned because of immunosuppressive drug toxicity such as increased risk of malignancy, infection and cardiovascular diseases (Lo et al., 2014). The crucial balance between immune-mediated graft destruction and those adverse effects of immunosuppression contributes to efficacy and durability of kidney transplantation as a therapy. Consequently, recognition of individual patients' immune status is needed to direct personalized therapy.

It is observed in some rare cases renal transplant recipients become tolerant to their graft and retain good graft function. There are two types of immune tolerance in the kidney transplant setting: spontaneous tolerance, also commonly referred to as operational tolerance, and induced tolerance. Although strategies to induce transplant tolerance in humans are rare and the mechanisms underlying tolerance development are still unknown, induction protocols for obtaining tolerance have been described in

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human kidney transplantation. Building on significant preclinical data, Kawai and his colleagues demonstrated that using hematopoietic stem cells of the intended kidney donor established a milieu where the donor and the recipient existed as a "mixed chimera", which provided earliest evidence for tolerance induction protocols in humans (Kawai et al., 2008). Later studies also confirmed that cell-based transfusion prior to the renal transplantation is the most successful protocol aimed at tolerance induction (Kawai et al., 2013; Scalea et al., 2016). Unlikely induced tolerance, "operational tolerance" does not need a tolerance induction protocol, and usually spontaneously displays a condition of tolerance when transplanted recipients have normal allograft function in the complete absence of immunosuppression. Previous work has shown that a cohort of 10 kidney recipients displayed clinical "operational tolerance" to their graft for 9.4 ± 5.2 years(Roussey-Kesler et al., 2006); a recent study demonstrated that cumulative incidences of operational tolerance and almost tolerance were estimated at 3 and 1.5 per 10 000 kidney recipients, respectively(Massart et al., 2016). Identifying immunological characteristics in these renal tolerant patients would broader clinical application of strategies to induce tolerance; thus these biomarkers could be used to access whether tolerance has been established so that it would be possible to decrease or even withdraw immunosuppressive therapy.

Emerging platforms such as Omics technology, flow cytometry, and immune cell functional assays have been used to identify immune-related biomarkers by comparing kidney transplant recipients(Gokmen and Hernandez-Fuentes, 2013). Much progress has been made over recent years in defining immunological biomarkers that mark out renal tolerance patients. Immune cells such as B cells, T cells, macrophages, dendritic cells (DCs), as well as inflammatory mediators are described to participate in promoting immune tolerance and long-term allograft survival. Here, we will review clinically specific immunological characteristics that promote renal tolerance in humans and consider the clinical potential to use these biomarkers (Fig. 1).

2. Immune cells in renal transplant tolerance

2.1. B cells in renal transplant tolerance

B cells play an important role in antibody-mediated rejection (AMR) by production of alloantibody, presentation of antigen, secretion of inflammatory mediators. The frequency of AMR is estimated to be 2–10% in renal transplant patients and increased in patients with a previously failed allograft(Kirk et al., 2010). The involvement of B cell subsets in renal transplant clinical studies include total B cells, transitional B cells, naïve B cells, plasma cells and memory B cells. These B cell subpopulations in renal transplantation can be classified two major categorization schemes following Bm1–Bm5 classification system and IgD/CD27/CD38 staining, which have been well reviewed elsewhere(Crespo et al., 2015). As described later, both protective and pathological role are found in kidney transplant on the basis of B cell subpopulations and functional properties.

B cell signature is strongly associated with tolerant state in kidney transplant. The enrichment in B-cell-related transcripts were found across different cohorts of operationally tolerant kidney recipients(Chesneau et al., 2015; Chesneau et al., 2014; Lozano et al., 2011; Newell et al., 2010; Pallier et al., 2010; Sagoo et al., 2010). This relationship is confirmed by a recent meta-analysis, which demonstrates that a robust gene signature involving proliferation of B cells is identified in tolerant renal transplant patients (Baron et al., 2015). Costimulatory/migratory molecules of B cells were also found to be changed in these tolerant patients (Pallier et al., 2010). In a different study in humans, overexpression of miR-142-3p in B cells predicated the state of operational tolerance in kidney transplant recipients (Danger et al., 2012). These results suggested that B cells may be crucial responders to immunosuppression and graft rejection, which may uncover mechanisms underlying this clinical relevance.

Renal tolerant patients displayed an expansion of peripheral blood B lymphocytes and a redistribution of B cell subsets—an increased numbers of total and naïve B cells, a lower proportion of memory B and plasma cells, and higher proportion of transitional B cells, which are confirmed by several studies(Chesneau et al., 2015; Chesneau et al., 2014; Newell et al., 2010; Sagoo et al., 2010). These results are consistent with the fact that IRF4 and PRDM1, which are implicated in the end step of differentiation into plasma cells, are down regulated in renal tolerant patients (Chesneau et al., 2014). Additionally, terminally differentiated B cells from renal tolerant patients are shown higher cell death susceptibility in their late stage of differentiation (Chesneau et al., 2014). However, in vitro studies, B cells from renal tolerant patients activate and mature normally; this facilitates the same frequency of differentiated and nondifferentiated B cells, and no different IgM and IgG production when stimulated(Chesneau et al., 2014). These results suggest that redistribution of B cell subsets contribute to induction of immune tolerance in renal transplant.

In addition to expansion, also the functional modulation of B cell in transplant tolerance has been reported. Naïve B cells as the population of poor antigen-presenting cells, has been described to stimulate naïve T cells toward development into regulatory T cells and induce immune tolerance(Fuchs and Matzinger, 1992; Reichardt et al., 2007). Along with regulatory role of B cells in operationally tolerant patients, a preserved functional B cell compartment from operational tolerant patients with normal capacity to phosphorylate signal transducer and activator of transcription 3 (STAT3) after activation has been reported (Silva et al., 2012). Whereas, the role of regulatory cytokines that are produced by B cells in induction of allograft tolerance should be interpreted cautiously. It has demonstrated that both total B cells and transitional B cells produce high levels of immunomodulatory cytokine IL-10, and B cells from tolerant recipients produce even higher levels of IL-10 when stimulated in vitro. As transitional B cells constitute only 2–3% of total B cell, it is unlikely IL-10-expressing B cell subpopulations are contributed to the tolerance state after renal transplantation. Consequently, it is reasonable that there is no significant difference in IL-10 in total B cells with stimulated with PMA and ionomycin, or CD40 ± CpG among renal tolerance patients, or any other group in some studies (Pallier et al., 2010; Sagoo et al., 2010). These studies suggest that cytokine-mediated regulatory mechanism cannot interpret tolerance after renal transplantation. The role of cytokine-expressing B cell subsets on regulatory properties should be clearly determined.

In addition to being associated with phenotypic and function of B cell subsets, renal tolerant patients also have regulated expression of B cell differentiation and function genes, which are screened by microarray and verified by qRT-PCR. B cells from tolerant recipients exhibit clear regulated B cell differentiation genes, anti-apoptotic genes and functional genes. These significantly regulated genes include *Cd79b*, *Tcl1a*, *Sh2d1b*, *Ms4a1*, *Fcrl1*, *Fcrl2*, *Igkv1d13*, *Igkv4-1*, and *Igll1*. It should be noted that although higher proportion of transitional B cells and increased number of naïve cells is inevitable to be responsible for altered gene expression in renal tolerant patients, other B cell subsets may also contribute. Thus different gene expression levels in a per cell should be considered. For example, after correcting for total B cells or normalization for naïve and transitional B cell numbers, a difference in transcript numbers of *Igkv1d13* is remained(Newell et al., 2015).

Overall, understanding about general aspects of B cells in kidney transplantation has been gained in recent years. The mechanisms