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Interplay between immune responses to HLA and non-HLA self-antigens in allograft rejection

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ABSTRACT

Recent studies strongly suggest an increasing role for immune responses against self-antigens (Ags) which are not encoded by the major histocompatibility complex in the immunopathogenesis of allograft rejection. Although, improved surgical techniques coupled with improved methods to detect and avoid sensitization against donor human leukocyte antigen (HLA) have improved the immediate and short term function of transplanted organs. However, acute and chronic rejection still remains a vexing problem for the long term function of the transplanted organ. Immediately following organ transplantation, several factors both immune and non immune mechanisms lead to the development of local inflammatory *milieu* which sets the stage for allograft rejection. Traditionally, development of antibodies (Abs) against mismatched donor HLA have been implicated in the development of Ab mediated rejection. However, recent studies from our laboratory and others have demonstrated that development of humoral and cellular immune responses against non-HLA self-Ags may contribute in the pathogenesis of allograft rejection. There are reports demonstrating that immune responses to self-Ags especially Abs to the self-Ags as well as cellular immune responses especially through IL17 has significant pro-fibrotic properties leading to chronic allograft failure. This review summarizes recent studies demonstrating the role for immune responses to self-Ags in allograft immunity leading to rejection as well as present recent evidence suggesting there is interplay between allo- and autoimmunity leading to allograft dysfunction.

1. Introduction

Vascularized solid organ transplantation (Tx) following end-stage organ failure is a viable treatment option providing significant improvement in the quality of life. The ever increasing numbers of solid organ Tx (kidney, lung, heart, liver, pancreas etc.) demonstrates the success of this strategy. The research leading to progress in donor organ preservation, improvements in surgical techniques and management of recipients with immunosuppression following Tx have contributed to the success. However, despite advances in these key areas, acute and chronic rejection (CR) following Tx remains the most important problem for sustaining continued long-term function of the transplanted organs. Recent statistics from the Registry of Transplant Recipients 2013 shows an active waiting list of more than 75,000 patients, while there were only 30,000 transplantable organs [1]. The incidence of CR is a major hazard especially given the limitations with donor availability and re-transplantation (Table 1). This is compounded by the fact that once set-in, there are no viable treatment options to reverse CR.

Regardless of transplanted organ, CR is characterized by enhanced inflammatory cellular infiltration around vessels and tubular structures, fibrosis of the graft parenchyma that develops

Abbreviations: Ab, antibody; AEC, airway epithelial cells; Ag, antigen; AGTR1, angiotensin II type 1 receptor; AMR, antibody mediated rejection; APC, antigen presenting cell; BOS, bronchiolitis obliterans syndrome; CAN, chronic allograft nephropathy; CAV, cardiac allograft vasculopathy; CR, chronic rejection; ColV, collagen V; CMV, cytomegalovirus; DC, dendritic cells; DSA, donor specific antibodies; HCV, hepatitis C virus; HIF-1α, hypoxia inducible factor; HLA, human leukocyte antigen; iNKT, invariant natural killer T cells; IRI, schemia/reperfusion injury; Kα1T, Kα1 tubulin; MHC, major histocompatibility complex; MICA, MHC class I related chain A; mTOR, mammalian target of rapamycin; NHBE, human bronchial epithelial; OAD, obliterative airway disease; OLT, orthotopic liver transplantation; PGD, primary graft dysfunction; TG, transplant glomerulopathy; TRALI, transfusion-related lung injury; Tx, transplantation.

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Table 1
Incidence of acute and chronic rejection in various solid organ transplants; (#) one year incidence, (*) five year incidence.

Organ	Acute rejection# (%)	Refs.	Chronic rejection* (%)	Refs.
Lung	30–60	[79,80]	40–70	[81,82]
Heart	10–25	[83,84]	25–60	[85,86]
Kidney	10–20	[87,88,40]	40–50	[89]
Liver	7–22	[90]	4–12	[91]

anywhere from days to years after Tx. The primary targets of the recipient immune response against the allograft are the donor major histocompatibility complex (MHC) antigens (Ags). Immune recognition of mismatched donor HLA (human leukocyte antigens) results in both cellular and humoral immune activation which leads to allograft rejection. In this review we will present evidence that self-Ags play an important role in allograft rejection and often there is interplay between allo-and autoimmunity which culminates in organ failure due to rejection.

1.1. Immune responses following solid organ transplantation

The primary targets of the recipient immune response against the allograft are the donor MHC Ags present on the allogeneic tissue. Immune recognition of mismatched donor histocompatibility Ags results in both cellular and humoral immune mechanisms which leads to allograft rejection [2,3]. Allorecognition has been proposed to occur through two unique but not mutually exclusive pathways: the direct and indirect pathways of Ag presentation. The direct pathway involves recognition of intact donor MHC molecules on the cell surface, usually by antigen presenting cells (APC). Both CD8+ and CD4+ T cells can directly recognize donor MHC molecules, MHC class I and II respectively. In contrast, the indirect pathway involves presentation of processed donor Ags by recipient APC to recipient T cells. A 'semi-direct' pathway has also been recently described which involves recipient APCs that acquire donor MHC through cell-to-cell contact and activate host T cell responses which may contributes to CR [4–7].

While the direct pathway is more important for acute allograft rejection, the indirect pathway plays a dominant role in CR [8,9]. Experiments have demonstrated that inhibition of acute rejection by depleting passenger APC significantly delays but does not prevent development of CR [10]. It has been observed that the frequency of direct alloreactive T cells exceeds indirect alloreactive T cells in the early post-Tx period [11]. The frequency of direct alloreactive T cells declines with time following Tx while the continuous influx of the processed donor Ags by the recipient APC through the indirect pathways increases the number of indirect alloreactive T cells that are themselves more resistant to currently used immunosuppression [12,13]. In addition to the above two pathways, transfer of intact MHC molecules between cells has been observed [14]. Dendritic cells (DC) have been shown to acquire intact MHC class I and II molecules from exosomes secreted by other DC and prime both naïve $CD8^+$ and $CD4^+$ T cells [15]. Reports from Lechler's group proposed that this represents a third mode of allorecognition, which has been termed "semi-direct" pathway [16]. Through this pathway, DC present intact MHC molecules to directly alloreactive $CD8^+$ T cells as well as internalized and processed donor MHC peptides to indirect alloreactive $CD4^+$ T cells [17].

CR, the immunopathogenesis of which is not fully characterized, still remains the leading cause of long-term allograft failure in Tx recipients with no viable treatment options (Fig. 1). Several risk factors have been proposed to play a role in CR, including recurrent/refractory acute rejections, cytomegalovirus (CMV) and other viral infections, HLA mismatches, organ ischemia etc. [18,19]. Several non-specific risk factors such as donor and recipient age, graft ischemic time, and bacterial/fungal/non-CMV viral infection have also been associated with decreased long term survival of the graft [19–21]. We propose a possible unifying hypothesis that all the above mentioned inflammatory risk factors potentially lead to tissue remodeling which facilitates the induction of immune responses against self-Ags, and development of autoimmunity in CR. Further, recent evidence has demonstrated an important role of T-helper immune responses specifically Th17 responses against self-Ags along with augmentation of humoral immune responses to the self-Ags as a mechanism leading to CR. Initial studies have demonstrated prolongation of murine cardiac allograft survival following blockade of IL-17 suggesting a primary role for IL-17 in the rejection of allografts [22]. Since then, studies in the Th17 subset has been expanded considerably and current evidence demonstrate that Th17 cells are key players in developing and sustaining immune responses to self-Ags (autoimmunity) [23]. In this review, we will present evidences for cross-talk between alloimmune and autoimmune responses to self-Ags and their role as well as proposed mechanisms leading to allograft rejection.

1.2. Lung transplantation

CR after lung Tx is clinically diagnosed as bronchiolitis obliterans syndrome (BOS) and is characterized by obliteration of terminal airways within the lungs. The development of BOS following lung Tx is multifactorial and several risk factors including viral infection, primary graft dysfunction (PGD), alloimmunity and recently autoimmunity have been implicated. The development of immune responses against mismatched HLA involving both cell-mediated and humoral immunity against the mismatched donor HLA have been identified in patients diagnosed with BOS [24]. An important risk factor of interest is the transfusion of blood products. It has been well documented that transfusion-related lung injury (TRALI) can result in an acute respiratory disease syndrome (ARDS-like) picture similar to that seen with PGD following human LTx [25]. Recent multicenter studies have shown an independent association between blood product administration and increased risk for PGD, but the relationship between the two needs to be studied further [26]. The ischemia/reperfusion injury (IRI) can be an initiating event that activates inflammatory cascade leading to injury seen with TRALI [27]. Conversely, the lung injury induced by TRALI could accentuate any underlying IRI, resulting in PGD. Further, increased frequency of alloreactive CD4+ T cells against mismatched donor MHC class I and II molecules (indirect antigen presentation) has been detected in a human lung allograft recipient years after Tx and are associated with BOS [28]. Intrapulmonary lymphoid tissue has also been implicated in the pathogenesis of CR as it serves as a reservoir for effector memory T cells in high endothelial venules which can contribute to a local immune response in small airways leading to BOS [29].

Several studies have demonstrated that development of Abs to mismatched donor -HLA class I is associated with the development of CR [30–32]. Based on the reports by us [33] and others [34,35] the presence of 'shed' donor HLA Ags in the bronchoalveolar lavage fluids following lung Tx, provide the substrate for Ag presentation to T helper cells and induction of alloimmunity. These T helper cells, which are engaged in indirect recognition pathways, can produce lymphokines required for the growth and maturation of alloantibody producing B cells. In addition, recent reports also demonstrated that there is strong correlation between *de novo* development of Abs to self-Ags in the absence of demonstrable Abs to HLA to development of BOS following human lung Tx [36–38]. Strong correlation between the development of Abs and Th17 responses to a self-protein, K-α1 tubulin (Kα1T), as well as Collagen V (ColV) with BOS have been identified in lung Tx patient