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Review

Lung transplantation: Chronic allograft dysfunction and establishing immune tolerance

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ABSTRACT

Despite significant medical advances since the advent of lung transplantation, improvements in long-term survival have been largely unrealized. Chronic lung allograft dysfunction, in particular obliterative bronchiolitis, is the primary limiting factor. The predominant etiology of obliterative bronchiolitis involves the recipient's innate and adaptive immune response to the transplanted allograft. Current therapeutic strategies have failed to provide a definitive treatment paradigm to improve long-term outcomes. Inducing immune tolerance is an emerging therapeutic strategy that abrogates allograft rejection, avoids immunosuppression, and improves long-term graft function. The aim of this review is to discuss the key immunologic components of obliterative bronchiolitis, describe the state of establishing immune tolerance in transplantation, and highlight those strategies being evaluated in lung transplantation.

Contents

1. Introduction

Lung transplant remains the only definitive treatment available for many end-stage pulmonary disorders including chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, idiopathic pulmonary arterial hypertension, and cystic fibrosis [1]. The utility of lung transplantation as a treatment modality is reflected by the number of transplants performed, which has increased from 5 in 1985 to 3640 worldwide in 2011 [1]. However, despite dramatic improvements in surgical technique, immunosuppressive regimens, and coordinated patient care, the median 5 year survival among recipients is 50%, lower than any other solid organ allograft (Fig. 1) [1,2]. Chronic lung allograft dysfunction

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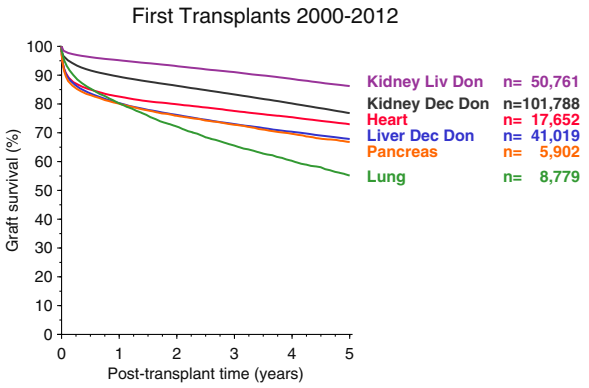

Fig. 1. Graft survival: collaborative transplant study data comparing graft survival for solid organ allografts. Used with permission.

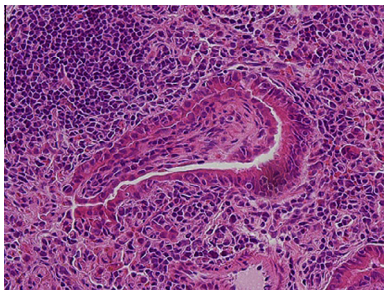

Fig. 2. Obliterative bronchiolitis histologic specimen: lung specimen demonstrating characteristic occlusion of the bronchiolar lumen in obliterative bronchiolitis.

(CLAD), in general, and obliterative bronchiolitis/bronchiolitis obliterans syndrome (OB/BOS) in particular, are the predominant factor limiting long-term survival after lung transplant. CLAD, previously known as chronic rejection, can be represented by different histologic patterns with OB being the most common. OB occurs in the small conducting airways, sparing the more distal respiratory bronchioles. As seen in Fig. 2, partial or complete airway occlusion arises as a result of proliferation of connective tissue, which may include microvascular-rich granulation in the context of abnormal tissue repair and remodeling [3]. BOS is the clinical correlate of OB and is diagnosed on the basis of forced expiratory volume in 1 s (FEV_1) [4]. Within 5 years of transplant nearly 49% of recipients have BOS, a number that increases to 76% at 10 years and represents the most common cause of death among recipients following the first post-transplant year [1]. At present, once initiated there is no effective treatment to reverse the obliterative process. The aim of this review is to describe the immunopathophysiology of OB and outline the current state of establishing immune tolerance in transplantation, particularly in the setting of lung allografts.

2. Immunopathophysiology of obliterative bronchiolitis

The pathogenesis of OB has not been fully characterized but is known to be multifactorial and includes components of cellular and humoral alloimmunity, innate immunity, and both cellular and humoral autoimmunity. The cellular immune response to allo- and autoantigens is dependent on the migration of antigen presenting cells (APCs) to secondary lymphoid organs, including the spleen and lung's regional lymph nodes where reactive T cells are activated [5]. T cells may also be stimulated directly by dendritic cells within the lung [6]. As depicted in Fig. 3, T cell receptors can recognize intact allogeneic major histocompatibility complex (MHC) on donor cells (direct pathway), peptide fragments of allogeneic MHC presented by recipient MHC molecules (indirect pathway), or possibly the semidirect pathway that involves intact donor derived MHC-peptide complexes presented by recipient antigen presenting cells to recipient T cells [6,7]. However, unlike other solid organ transplants, there is little evidence of the semidirect pathway involved in lung transplant rejection. Following the recognition of MHC antigen, T cells require secondary costimulatory signals, which result in a cascade of secondary signaling leading to proliferation and differentiation. The primary T cell type responsible for ongoing immune reactivity includes Th1 and Th17, which are key sources of interferon-γ and IL-17, respectively, which facilitate further the immune response [8].

The role of humoral alloimmunity has been suggested by clinical findings where MHC antibodies that develop after transplant have been demonstrated to confer an increased risk of BOS and decreased survival [9]. The allogeneic antibody targets include MHC and minor histocompatibility antigens. Following transplant, T cell dependent donor specific B cells develop resulting in anti-donor antibody production by plasma cells. Antibodies bind their donor antigenic target, as well as complement factor C1q, resulting in activation of the complement cascade [10]. The involvement of antibody mediated rejection in OB has been suggested by findings that donor specific antibodies precede the onset of BOS and are strongly associated with its development [11]. Furthermore, it is mechanistically supported by studies demonstrating anti-HLA antibodies induce fibrogenic growth factor production, proliferative changes, and apoptotic death in airway epithelial cells [12]. However, unlike OB that occurs in graft versus host disease post hematopoietic stem cell transplants, there is no direct evidence that alloantibodies, alone, induce OB post lung transplantation [13].

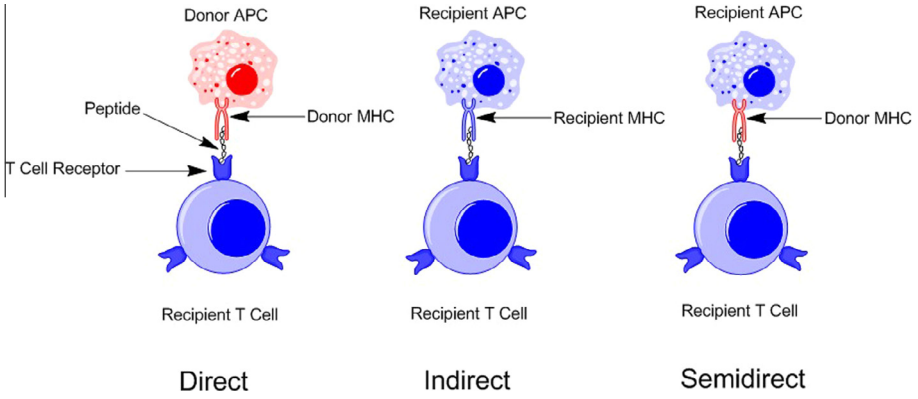

Fig. 3. Alloantigen recognition: direct recognition of antigen presented by allogeneic MHC on donor APC, indirect recognition of antigen presented by recipient MHC on recipient APC, and semidirect recognition of antigen presented by allogeneic MHC on recipient APC.