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Mechanisms of Graft Rejection after Lung Transplantation

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Abstract

Purpose of review—To date, outcomes after lung transplantation are far worse than after transplantation of other solid organs. New insights into mechanisms that contribute to graft rejection and tolerance after lung transplantation remain of great interest. This review examines the recent literature on the role of innate and adaptive immunity in shaping the fate of lung grafts.

Recent findings—Innate and adaptive immune cells orchestrate allograft rejection after transplantation. Innate immune cells such as neutrophils are recruited to the lung graft early after reperfusion and subsequently promote allograft rejection. While it is widely recognized that $CD4^+$ T lymphocytes in concert with $CD8^+$ T cells promote graft rejection, regulatory $Foxp3^+$ $CD4^+$ T, central memory $CD8^+$ T cells and natural killer cells can facilitate tolerance.

Summary—This review highlights interactions between innate and adaptive immune pathways and how they contribute to lung allograft rejection. These findings lay a foundation for the design of new therapeutic strategies that target both innate and adaptive immune responses.

Keywords

Ischemia reperfusion injury; alloimmunity; rejection; tolerance

Introduction

Lung transplantation (LTx) is a live-saving treatment for patients with end-stage pulmonary disease. Advances in surgical technique and postoperative management have resulted in dramatic improvements in short-term outcomes [1]. However, long-term survival after LTx has not significantly changed over time and outcomes remain relatively disappointing [2]. According to the International Society for Heart and Lung Transplantation registry report,

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Conflicts of interest

The authors have no conflicts of interest to declare.

the median survival after primary LTx is 5.7 years with a survival rate of 31% at 10 years [1]. These suboptimal outcomes are largely related to the development of chronic lung allograft dysfunction (CLAD), a condition for which no effective medical treatment exists [3].

Acute rejection (AR) represents one of the most common complications after LTx and has been recognized as a major risk factor for the development of CLAD [4,5]. AR is the result of an adaptive immune process related to an MHC mismatch and T cell allorecognition [6]. According to the data on long-term graft survival, currently employed immunosuppression does not protect lung allografts to the same extent as other solid organ allografts [2]. Acute rejection of lungs may differ from other solid organ transplants [7]. To this end, the lung is constantly exposed to the external environment and may exhibit more complex immunologic features [8,9]. Moreover, the combination of recently developed small animal models and advances in intravital imaging techniques have added new insights into the cellular framework that contributes to acute and chronic lung rejection [10].

Here we will review mechanisms underlying lung allograft rejection, explore the impact of early graft injury and innate immune activation, and discuss how adaptive immune responses lead to allograft rejection.

Early graft inflammation and alloimmunity

It has been recognized that early inflammatory events occurring in response to graft injury may enhance adaptive responses (Figure 1) [11–13].

Ischemia-reperfusion injury and activation of TLRs

Early graft injury after organ transplantation is largely dependent on ischemia-reperfusion injury (IRI) [14]. IRI induces alterations in cellular metabolism that lead to the generation of reactive oxygen species and promote cell damage and death resulting in the release of endogenous proinflammatory mediators [14]. An early increase in the cell death biomarker M30 was recently demonstrated by Hashimoto in a population of LTx patients, who developed primary graft dysfunction (PGD) [15]. Higher plasma levels of this biomarker were associated with worse clinical outcomes suggesting a link between early graft cell death and LTx prognosis[15].

One of the most well-characterized endogenous proinflammatory mediators related to cell damage and death is the high-mobility group box1 (HMGB1). HMGB1 is a non-histone DNA binding protein actively secreted or passively released by cells undergoing necrosis [16–18]. The proinflammatory effects of HMGB1 are mostly related to the stimulation of pattern recognition receptors (PRRs), such as the toll-like receptors (TLRs) and the receptor for advanced glycation end-products (RAGE) [11]. Intragraft accumulation of pro-inflammatory mediators, also exacerbated by an impaired drainage function of the damaged lymphatic vessels [19], leads to leukocyte activation, which may result in graft rejection (Figure 1). An early increase in plasma levels of the soluble RAGE (sRAGE) after LTx has been associated with longer durations of mechanical ventilation, longer intensive care unit lengths of stay and development of CLAD [20]. In addition, transcriptome analysis of bronchoalveolar lavage fluid and lung tissue from LTx recipients shows an overall up-

regulation of TLRs [21]. Using a mouse model of lung IRI, Altemeier demonstrated reduced inflammation in murine lungs deficient in the TLR signaling protein Myd88 [22]. Additionally, Zhang recently showed reduced signs of lung IRI in TLR3-deficient mice, which signals through the TRIF/TICAM-1 adaptor molecule in Myd88-independent fashion [23]. TLR activation triggers proinflammatory effects that promote adhesion molecule expression, cytokine release from innate immune cells, and also enhance leukocyte trafficking through endothelial cell activation. In particular, TLR2 and TLR4 signaling have been shown to enhance post-ischemic vascular permeability and leukocyte migration after IRI [24]. TLR2 and TLR4 activation can be driven by low molecular weight hyaluronan, which is released in response to IRI. Low molecular weight hyaluronan promotes neutrophilia and abrogates lung allograft tolerance in a TLR2/4 and MyD88-dependent manner [25].

Leukocyte trafficking into the injured graft

Despite advances in the understanding of the molecular signaling pathways that drive early graft inflammation, only recently have we gained insight into the *in vivo* mechanisms of intragraft leukocyte trafficking by using modern imaging techniques [26–28]. Using intravital two-photon imaging and a mouse LTx model of IRI we discovered that neutrophils (PMNs) are not only rapidly recruited into the injured graft, but also tend to aggregate in dynamic clusters with intragraft monocytes. Monocytes appear to be critical in driving PMN transendothelial migration [26]. Subsequent investigations found that a $CCR2^+$ recipient-derived subset of proinflammatory monocytes promotes PGD [27]. Additionally, graft-infiltrating recipient monocytes can also differentiate into dendritic cells (DC), acquire donor MHC molecules, and contribute to both indirect and direct allorecognition within the lung allograft [29]. PMN recruitment into injured lungs can also be promoted by donor-derived immune cells such as alveolar macrophages [30]. We have shown that the membrane-associated protein DAP12, expressed by donor alveolar macrophages, regulates the release of PMN chemoattractants such as CXCL1 and CXCL2 after IRI (Figure 1) [28].

Intragraft granulocytes and alloimmunity

Infiltrating PMNs in damaged airways are a clear hallmark of lung IRI. Thus, the role of PMNs in promoting allograft injury has been extensively investigated in the past few years [31]. Besides their well-known effector functions, PMNs can also recruit activated $CD8^+$ T cells through Fas ligand expression [32]. PMNs also facilitate antigen presenting cell (APC) activity, which is critical to T cell activation and differentiation, through the expression of MHC class II and co-stimulatory molecules [33]. In addition, PMNs enhance adaptive immunity after LTx [34]. Using a mouse model of orthotopic LTx we showed prolonged interactions between recipient-derived PMNs and donor DCs within lung allografts; this contact-dependent mechanism promotes IL-12 production by DCs and expansion of IFN-γ^+ T cells [34]. In addition, our group demonstrated that graft-infiltrating neutrophils upregulate co-stimulatory molecules CD80 and CD86 during respiratory bacterial infections, which promotes the activation of T cells and triggers lung allograft rejection [35].

In addition to the role that PMNs play in LTx alloimmunity, some conflicting observations come from studies investigating the putative role of mast cells (MC) in this process [36–38]. In

various animal models of lung IRI, MCs have been shown not only to be recruited into injured lungs, but also to actively contribute to the proinflammatory microenvironment through the release of thromboxane B2, leukotriene B4, PGD_2, TNF-α and IL-6 (Figure 1) [36,37]. However, using adoptively transferred MCs in a stringent MC-deficient mouse model, Greenland recently showed a minor contribution for MCs in IRI [38]. Moreover, evidence stemming from a skin transplant model has even suggested a beneficial role for MCs in inducing peripheral tolerance through a mechanism involving an IL-9-dependent interplay with $CD4^+CD25^+Foxp3^+$ regulatory T cells (Treg) [39]. Conflicting evidence regarding the role of MCs following LTx may be reconciled by recent reports suggesting that MCs can exhibit a "phenotypic switch" after solid organ transplantation [40,41]. Banga recently showed a time-dependent transition from a $tryptase^+$ to a $tryptase^+$, $chymase^+$ MC phenotype; this phenotypic switch was associated with a progressive decline in allograft function [40]. These observations suggest that MCs are recruited into lung allografts and may play an important, albeit uncertain, role in modulating the early inflammatory events and adaptive immune responses that bring about allograft dysfunction.

Mechanisms of allorecognition

Allorecognition is a process where donor antigens are presented to recipient immune cells, resulting in the activation of an adaptive alloimmune response. Recent investigations suggest that T cell allorecognition is accomplished by at least two different mechanisms, termed "direct" and "indirect" pathways [42]. The direct pathway involves recognition of allogeneic MHC molecules on donor APCs by recipient T cells. Meanwhile, T cells recognize processed alloantigens on recipient-derived APCs in the indirect pathway. For many years, it was believed that allorecognition was initiated only in recipient secondary lymphoid organs; this hypothesis was supported by a landmark study demonstrating that rejection of skin grafts could be prevented when the afferent lymphatic drainage was surgically disrupted [43]. Similarly, Lakkis demonstrated that the survival of skin and heart grafts was extended in recipient mice lacking secondary lymphoid tissues[44]. However, this notion has been challenged by recent findings suggesting that the lung can be a site for the priming of adaptive responses. In a mouse model of viral infection, Moyron-Quiroz demonstrated that mice lacking secondary lymphoid organs are still able to mount a strong adaptive immune response and clear viral lung infections [9]. Constant suggested that activated APCs could locally promote T cell differentiation towards a Th2 subtype in lung tissue, and that T cell priming in secondary lymphoid organs is not required [45]. Using a mouse model of orthotopic LTx, we demonstrated that graft-infiltrating naïve T cells are activated locally in allogeneic lung grafts early after transplantation [46]. Moreover, pulmonary allografts are rejected in non-immunosuppressed recipients that lack secondary lymphoid organs, supporting the notion that allogeneic immune responses are generated within lung grafts (Figure 1).

Role of T cells in acute cellular rejection

Recently, research has focused on the role of Th17 cells, characterized by the secretion of interleukin (IL)-17A and the expression of a transcription factor RORγT, in lung allograft rejection. In mice and humans, Th17 cells may play an important role in the development of CLAD [47–49]. Mechanistically, Th17 cells downregulate complement-regulatory proteins on

airway epithelial cells, which results in robust complement activation that damages the donor graft [48]. Lendermon demonstrated that a robust induction of IL-17 production in $CD8^+$ T cells triggers obliterative airway inflammation in t-bet-deficient hosts that are treated with CD154 blockade [50]. This finding extends previous reports which suggested that $CD8^+$ T cells are sufficient to trigger allograft rejection in lungs, challenging the notion that allograft rejection is dependent on $CD4^+$ T cells [51]. In addition to Th17 cells and IL17-producing $CD8^+$ T cells, IL-17-producing γδT lymphocytes may also play a role in triggering alloimmune responses that lead to graft rejection (Figure 1) [50]. Finally, development of acute rejection and inflammation can be blunted by neutralization of IL-17 [49,52]. These findings suggest that IL-17 is a key player of allograft rejection, and may be a suitable therapeutic target.

Regulatory $Foxp3^+$ Tregs and Allograft Tolerance

Regulatory $CD4^+$ $Foxp3^+$ T cells (Tregs) have emerged as key regulators in allograft tolerance (Figure 1) [53]. Tregs modulate immune responses through: 1) production of immunosuppressive cytokines (TGF-β and IL-10), 2) suppression of effector cells (i.e. Th1 and Th17 cells), and 3) regulation of DC maturation and function [54], all of which were shown to mediate transplant tolerance [53,55].

Tregs have been shown to inhibit Th17 responses. An imbalance of the Th17:Treg ratio has been linked to graft rejection after LTx [56]. Additionally, administration of inducible Tregs can induce lung allograft tolerance through the suppression Th17-mediated responses [56]. In human lung grafts the number of $Foxp3^+$ Tregs correlates with a better prognosis, fewer episodes of AR, and better pulmonary function after transplantation [57–59]. The quantity of Tregs in transbronchial biopsies positively correlates with the degree of AR after lung transplantation, suggesting that Tregs are actively recruited to sites of AR and may play a role in downregulating inflammation [57,58]. Interestingly, the recruitment of Tregs occurs in concert with the upregulation of the chemokine CCL22 in the graft, suggesting that naïve Tregs may be primed in secondary lymphoid organs prior to their entry into the lung graft in response to CCL22 [60].

Our group has reported that Tregs are critical in maintaining lung allograft acceptance [61]. Dodd-o further demonstrated that CD154/CD40 signaling blockade blunts lung allograft rejection, in part by enhancing $CD4^+$ Treg expansion [62]. It is widely believed that alloantigen-specific Treg expansion predominantly takes place in secondary lymphoid organs [63]. Treg trafficking to donor graft tissue from recipients appears to be a dynamic, yet crucial process for immune tolerance. Furthermore, migration of Tregs from allograft tissue to draining lymph nodes is required for optimal immune suppression and allograft tolerance [64]. However, evidence has emerged suggesting that Tregs can be activated locally within the allograft itself. The discovery of Foxp3-rich ectopic lymphoid aggregates within renal and pulmonary allografts, also called tertiary lymphoid organs (TLOs), supports this notion [61,65].

Central Memory CD8+ T cells and Allograft Tolerance

The activation of alloreactive $CD8^+$ T cells has been linked to allograft rejection in both experimental and clinical settings. Alloreactive memory $CD8^+$ T cells infiltrate heart and kidney grafts early after transplantation and can facilitate rejection [66–70]. Memory $CD8^+$ T cells are rather resilient to immunosuppression and represent a barrier to tolerance induction [71]. Depleting $CD8^+$ T cells in mouse heart and skin transplant models prolongs long-term graft survival [72,73]. By contrast, our group demonstrated that central memory $CD8^+$ T cell, characterized by high surface expression of CD62 ligand (CD62L) and CD44, promote lung allograft tolerance induction (Figure 1) [74]. This finding may represent a challenge for currently employed immunosuppressive regimens, which target T cells nonselectively potentially depleting beneficial T cell populations. In addition to central memory $CD8^+$ T cells, natural killer (NK) cells may also play a crucial role in tolerance induction [75]. Jungraithmayr demonstrated that lung allograft infiltration with NK cells is associated with tolerance. These NK cells recognize and destroy donor-derived DCs, which would otherwise activate T-cell-dependent alloimmune responses (Figure 1).

Concluding Remarks

Due to unique immunological features, the lung represents a challenge in designing effective immunosuppressive therapies. Rejection after LTx may start with the activation of innate immune pathways in response to early graft injury. The resulting proinflammatory microenvironment is capable of shaping the adaptive immune response. Targeting innate immune pathways in the peri-operative period may blunt graft rejection. Furthermore, indiscriminately targeting T cells at the time of LTx should be reconsidered since beneficial cell populations may be depleted. These findings present a more complex framework for lung allograft injury, allorecognition, and tolerance induction than previously recognized. Additional translational research is needed to examine the impact of the above mentioned findings on human lung transplant patients.

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Key points

- Ischemia reperfusion injury drives innate immune activation, which plays a critical role in enhancing adaptive immune responses.
- Lungs provide a suitable environment for either promoting allograft rejection or tolerance.
- IL-17^{+} T lymphocytes drive rejection while CD4^{+}Foxp3^{+} Tregs, CD8^{+} central memory T cells and NK cells may promote tolerance after lung transplantation.

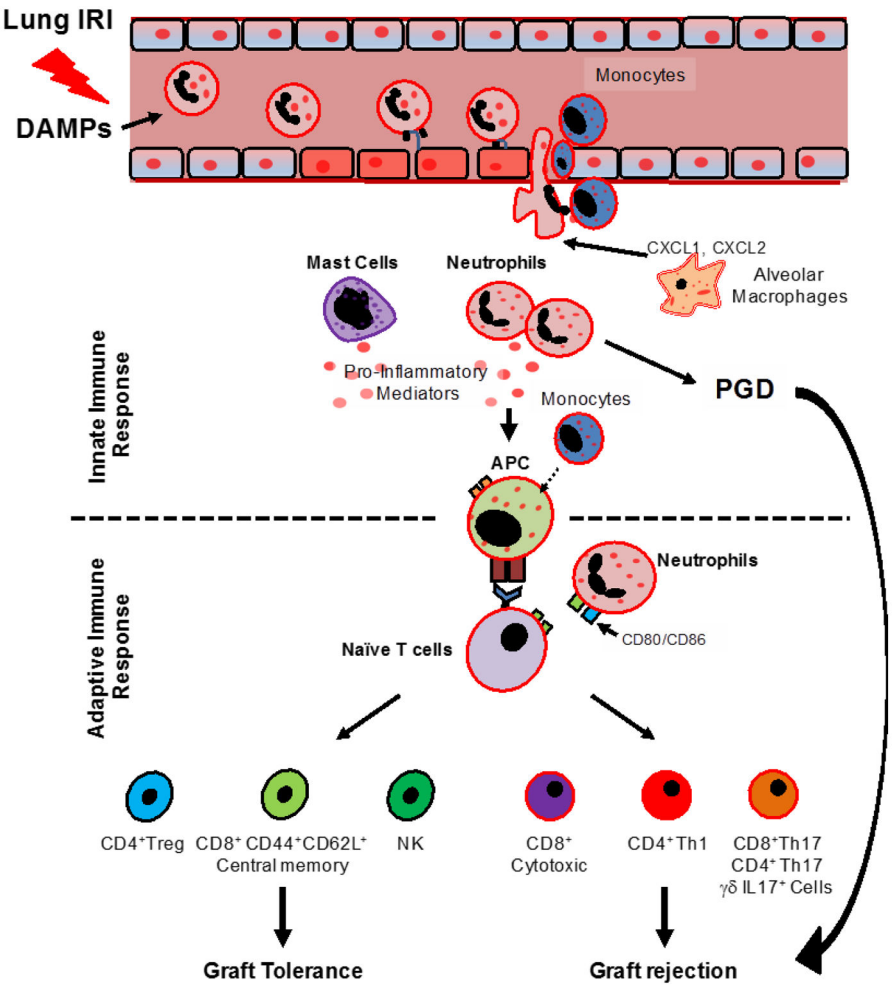

Fig. 1. Diagram depicting mechanisms mediating primary graft dysfunction, rejection and the induction of tolerance

In the context of ischemia-reperfusion injury (IRI), damage-associated molecular patterns (DAMPs) release contributes to the infiltration of neutrophils into the graft. Recipient-derived $CCR2^+$ monocytes and donor alveolar macrophages facilitate neutrophil recruitment from blood vessels to the injured lung graft. Once activated, neutrophils in concert with mast cells can produce pro-inflammatory mediators such prostaglandins (PGs), interleukin (IL)-1β and IL-6, which can promote primary graft dysfunction. Allorecognition occurs locally within lung allografts through the engagement of antigen presenting cells (APCs) and T lymphocytes. Activated neutrophils can also express co-stimulatory molecules, which further promote the activation of naïve $CD4^+$ T cells. Lymphocytes regulate outcomes after LTx. $CD4^+$Th1, $CD4^+$Th17, γδ $IL17^+$, $CD8^+$Th17 and $CD8^+$ cytotoxic T cells promote graft loss, while regulatory $CD4^+Foxp3^+$ T cells (Tregs), $CD8^+CD44^+CD62L^+$ central memory T cells and also NK cells can prevent rejection.