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Autoantibody Formation in Human and Rat Studies of Chronic Rejection and Primary Graft Dysfunction

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Abstract

Lung transplantation is considered a definitive treatment for many lung diseases. However, rejection and other pathologic entities are major causes of morbidity and mortality for lung transplant recipients. Primary graft dysfunction (PGD) and obliterative bronchiolitis (OB) are the leading causes of early and late mortality, respectively. While the immune basis of PGD has not been clearly defined, evidence is emerging about roles for autoantibodies in this process. Similarly, the pathogenesis of OB has been linked recently to autoimmunity. This review will highlight the current understanding of autoantibodies in PGD and OB post lung transplantation.

Keywords

Lung transplantation; autoimmunity; IL-17; antibody mediated rejection; obliterative bronchiolitis; primary graft dysfunction

1. Introduction and Overview

Lung transplantation is the only therapeutic modality for the treatment of many end stage lung diseases. However, the lung is rejected more commonly than other solid organ allografts. Chronic allograft dysfunction refers to a group of pathologic entities that contribute to long term graft failure and mortality in the lung transplant patient. The pathologic condition, obliterative bronchiolitis- OB, or its clinical correlate, bronchiolitis obliterans syndrome – BOS, both contribute to chronic allograft dysfunction and are the key reasons why the five year survival of lung transplant recipients is only 50% (1). OB/BOS is highly prevalent post lung transplantation and occurs to some degree in at least 75% of individual who survive seven years post transplant (2, 3). In most cases, the pathology of OB is characterized by extensive peribronchiolar connective tissue deposition, loss of bronchiolar epithelium, and progressive scarring which ultimately obliterates the small airways. While there is some debate, proliferative forms of bronchiolitis obliterans have also been considered as part of the spectrum of chronic allograft dysfunction. These lesions differ from classic OB in that the histopathology may reveal proliferating fibrous plugs of granulation tissue that protrude into and may ultimately obliterate small airways (2, 3). Either pathologic entity leads to progressive and irreversible airways obstruction which is the hallmark of BOS. Notable to OB/BOS is that the immunology and pathophysiology is

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focused on airway and not vascular injury in the donor lung. This distinction is important since varying degrees of vascular injury are the key features of acute rejection in the lung transplant recipient (1).

While OB and BOS are part of a spectrum of chronic allograft dysfunction, they are not the only causes of mortality post lung transplantation. Primary graft dysfunction – PGD, an entity that is characterized by varying degrees of non-cardiogenic pulmonary edema and impaired systemic oxygenation occurring within 72 hour post transplantation, is the leading cause of early mortality in lung transplant recipients (4, 5). PGD had been considered a vascular injury pattern, not unlike ischemia reperfusion injury (IRI) that occurred in other solid organ allografts. However, seminal studies from Dr. Keshavjee's group were first to report that the airway epithelium, and not vascular endothelium that is the target of IRI in other solid organ allografts, is the primary target in what is now known as PGD (6). Therefore, similar to OB/BOS, the airway is also the target of injury in PGD.

The pathophysiology of OB/BOS are incompletely understood but there is a clear role for immune responses to donor antigens (anti-HLA), and more recently, immune responses to autoantigens (7-13). While the anti-donor responses can involve direct and indirect allorecognition pathways (14, 15), the recently described autoimmune basis for OB/BOS is mediated by the indirect pathway. A potential immune basis for PGD has been debated for several years. Recent studies show that interstitial lung disease, of which idiopathic pulmonary fibrosis comprises the vast majority of this group is a major risk factor for PGD (16). Reports from a number of investigators, including our group, have shown the presence of autoimmunity in IPF pathophysiology (9, 17). Since PGD is a risk factor for OB/BOS (1), then the autoimmune status of the recipient prior to transplantation could greatly impact chronic allograft dysfunction post lung transplantation. However, the emerging role of autoimmunity in OB/BOS and PGD is just now becoming recognized as a key part of these disease processes.

Most studies have shown the cellular immune basis (T cell mediated) for autoimmunity post transplantation, including the lung. The role of humoral immunity, either to alloantigens or autoantigens in solid organ allografts, other than the lung, is becoming widely accepted. This is in part due to fairly specific histologic patterns plus evidence of complement product deposition at sites of presumed humoral immunity (18-22). However, the role of humoral immunity in lung allograft pathology such as OB/BOS or PGD is yet to be fully understood both clinically and in terms of basic science mechanisms. This is due to a non-specific histopathology ascribed to humoral immunity in the transplanted lung, as well as, the lack of biomarkers that are indicative of humoral responses, either alloantibody or autoantibody-mediated injury (22-24). For example, the presence of complement-derived C4d deposits in kidney or heart allografts with the appropriate histopathology is highly suggestive of antibody mediated rejection in those organs. Why is the lung different in this regard? The immune response to alloantigens and autoantigens is believed to occur in the regional lymph nodes with trafficking of effector cells/molecules back to the allograft where they mediate pathology. However, the lung is able to mount its own immune responses, in situ, without secondary lymphoid tissues, and these responses are sufficient to induce graft destruction (25, 26). This is due to the development of inducible bronchus associated lymphoid tissue known as iBALT which contains a full complement of antigen presenting cells, B and T cells, that are able to induce local humoral and cellular immunity (27-29). As such, the lung may function as a "lymph node with alveoli" (10). In addition, many immune cells in the lung are phenotypically and functionally distinct relative to those associated with other solid organs. Specifically, the function and subtypes of dendritic cells, key initiators of immune responses, and T cells are somewhat unique (30). In general, these reports suggest that the

types of cellular and humoral immune responses that occur in other organ allografts may not be applicable to the lung.

Despite a lack of many reports, recent studies have identified a link of humoral autoimmunity in the pathogenesis of OB/BOS, as well as PGD (8, 31). The current article will discuss the human studies and animal models of OB/BOS and PGD as well as the contribution of autoantibodies in disease pathogenesis.

2. Induction of Autoimmune Responses

2.1. Interleukin 17 - IL-17

Although the paradigm of Th1 and Th2 cells were introduced by Mosmann and Coffman, it has been long recognized that not all immune responses fit into these groupings (32). In organ transplantation, Th1 cells, those that produced primarily $\text{IFN}\gamma$, were associated with rejection whereas Th2 cells, major sources of IL-4 and/or IL-10, were considered to be protective (33). However, multiple studies using mice genetically deficient in Th1 or Th2 cytokines revealed that rejection could occur though the tempo of the alloimmune response may have varied, rejection still occurred (33). Data reported in non-transplant studies revealed that another group of Th cells were involved in a variety of diseases. Known as Th17 cells and defined by production of IL-17A – reviewed in (34), these cells are not only important for host defense but also play a role in the pathogenesis of organ transplantation, and have major roles in induction of autoimmune diseases (reviewed in (35)). IL-17, also called IL-17A, is the original member of what is now the IL-17 family of six isoforms and other cytokines characterized by disulfide-linked homodimeric glycoproteins (36). Secreted primarily by CD4^+ T cells, many other cellular sources have been reported for IL17 and include $\gamma\delta$ T cells, NK cells, CD8^+ T cells, NK T cells and neutrophils. Indeed, a very recent study implicated IL-17 derived from $\gamma\delta$ T cells as having a critical role in ischemia reperfusion injury, a condition that could be linked to PGD (37).

2.2 IL-17, Lung Transplantation, OB/BOS and PGD

IL-17 and Th17-associated cytokines have been linked to the development of acute and chronic rejection after lung transplantation in both animal models and humans (8, 11, 12, 31). Verleden and colleagues found that increased IL-17 in bronchoalveolar lavage (BAL) was associated with an increase in BAL lymphocytes and neutrophils during acute rejection on transbronchial biopsies from lung transplant patients (38). The levels of IL-17 also correlated with increased severity of rejection (38), whereas a report from Shell et al did not find a correlation of IL-17 positive cells in endobronchial biopsies post lung transplantation (39)..

While there may be some disparity in the relationship of IL-17 to acute lung transplant rejection, a picture is emerging that IL-17 may have key roles in OB/BOS and PGD. As an example, lung transplant patients with BOS have been shown to have increased levels of IL-6 and IL-1 β in BAL which are two cytokines known to have key roles in induction of IL-production (40). Similarly, this same study detected increased transcripts for TGF- β , a known inducer of IL-17, as well as IL-17 and IL-23 (40). In addition, non-transplant studies have reported that IL-17 is fibrogenic in the lung (41). This is notable since OB is a fibrotic disease and suggests that IL-17 may have key roles in the fibrogenesis that is characteristic of OB. A very recent study revealed that IL-17 has a key role in the induction of inducible bronchus associated lymphoid tissue (27), and iBALT is readily detected in lung allografts (42). Since iBALT could be the source of local immune responses in the transplanted lung, then it is interesting to speculate that another role for IL-17 in rejection responses could be due to iBALT induction.

There are few animal models able to replicate the histology and immunology of OB. Many have been reported and include the heterotopic tracheal allograft model, as well rat and mouse orthotopic lung transplantation. Each of these models has limitations in terms of replicating the human condition of OB, but a pattern is emerging in terms of IL-17 and pre-clinical models of OB. For example, a recent report from our laboratory demonstrated a novel model of OB post orthotopic lung transplantation in mice (43). Notable in this report was the OB was dependent on minor, and not major histocompatibility antigen, differences between donor and recipient. In addition, neutralizing IL-17 abrogated the onset of OB and down regulated the severity of acute rejection (43). The finding of a causal link to IL-17 and OB may not be limited to chronic allograft dysfunction. For example, Sharma and colleagues reported that murine lung ischemia reperfusion injury, that may reproduce clinical PGD, was dependent on IL-17 production derived from natural killer T cells (37).

2.3 IL-17 and OB/BOS-related Autoimmunity

As stated previously, IL-17 (IL-17A) has been reported to have key roles in the induction of autoimmunity. This phenomenon is also applicable to autoimmunity associated with lung transplantation. For example, autoimmune responses post lung transplantation were initially reported by Ende and colleagues who demonstrated anti-lung tissue antibodies associated with human lung transplantation (44). Pre-transplant anti-epithelial cell antibodies (non-HLA antibodies) were associated with graft failure in lung allograft recipients (45). More recently, Iverson's group demonstrated the correlation of donor lung-derived transcripts and formation of autoantibodies, pre and post transplant in patients with PGD and OB/BOS (46, 47). The transcripts represented proteins involved in apoptosis and cell metabolism. Using a different approach, Magro's group reported a variety of circulating anti-endothelial antibodies in lung transplant recipients (48-50). These reports span more than three decades and suggest that the presence of autoantibodies post lung transplantation may occur in multiple settings and detected by varying techniques. However, the pathogenesis of antibody production, and ability of these antibodies to induce *in vivo* cytotoxicity were not reported in these studies.

Examining a small cohort of patients, previously unpublished studies from our laboratory determined that human lung transplant recipients developed antibodies to type V collagen [col(V)], a minor lung collagen that is intercolated within the helices of type I collagen and expressed by airway epithelial cells (51). Notable in these early studies was that these antibodies did not detect collagen types I, II, III, IV, or VI. Extending these studies into an orthotopic rat lung transplant model we reported that rat lung allografts transplanted into minor histocompatibility antigen mismatched recipients induced anti-col(V) specific T and B cells post transplantation (7). Examination of human lung allograft recipients revealed the presence of anti-col(V) CD4⁺ T cell mediated immunity in peripheral blood mononuclear cells, and this finding was strongly correlated with the onset of BOS post transplantation (8). Moreover, the anti-col(V) response was IL-17 dependent in these patients (8). These data are consistent with a prior report showing that col(V)-reactive lymphocytes that develop from immunizing rats with col(V) are Th17 type (52), and that adoptive transfer of these cells to lung isograft recipients induced OB in the transplanted lung despite the absence of any alloimmunity (8). While the presence of anti-col(V) humoral immunity was documented in human lung allograft recipients, the presence of such antibodies did not correlate with OB/BOS in that study (8)(). All antibodies studied were an IgG subtype with no evidence of IgM (unpublished data). The lack of correlation of anti-col(V) antibodies to OB/BOS could have been related to the timing of the study relative to the antibodies levels present in transplant recipients.

Mohanakumar's group reported that human lung transplant recipients also develop an antibody response to K- α 1 tubulin, as well as col(V), and that presence of these antibodies may be associated with OB/BOS in clinical transplantation (11, 12). Similar to col(V), K- α 1 tubulin is also expressed on airway epithelial cells and appears to be a prominent target in the immune response post lung transplantation, particularly in the pathogenesis of OB/BOS. These data again highlight the role of the airway epithelium as a key target in OB pathogenesis. In a novel murine model in which intrapulmonary instillation of anti-MHC Class I antibodies induced OB-like pathology in recipient lungs, these same mice developed antibodies to col(V) and K- α 1 tubulin (11). Moreover, the data showed that neutralizing IL-17 abrogated OB-like pathology, including air way fibrosis, and the production of autoantibodies (11). These data strongly suggest that IL-17 has key roles in not only autoantibody production but autoantibody induced fibrogenesis that may be culminate in OB.

2.4 Autoantibodies and Primary Graft Dysfunction

Autoantibodies have also been linked to PGD pathogenesis. Passive transfer of immune sera rich in anti-col(V) antibodies or purified anti-col(V) antibodies to rat lung isograft recipients reproduced the histology and pathophysiology of PGD in pre-clinical models (31). Specifically, anti-col(V) antibodies induced acute lung injury compatible with PGD, impaired systemic oxygenation, and induced complement dependent antibody cellular cytotoxicity in airway epithelial cells (31). The ability of K- α 1 tubulin antibodies to reproduce PGD in pre-clinical models has not been determined. However, de novo synthesis of anti-col(V) or K- α 1 tubulin antibodies post transplantation is likely not required for induction of lung allograft injury. Specifically, the presence of K- α 1 tubulin AND anti-col(V) antibodies pre-transplant was strongly associated with onset of PGD in clinical transplant (31, 53). In terms of col(V) reactivity pre-transplant, the anti-col(V) antibody data pre-transplant and link to PGD are consistent with our prior report showing that the presence of IL-17-dependent anti-col(V) specific CD4+ T cell immunity pre-transplant was strongly predictive of PGD onset (9). These studies noting the presence of autoimmunity pre-transplant and a subsequent link to PGD and possibly OB/BOS highlight a critical need to examine the autoimmune status of the recipient pretransplantation as a means to reduce morbidity and possibly mortality post transplantation.

Antibodies to col(V) and K- α 1 tubulin are not the only antibodies linked to PGD pathogenesis. Studies from Iverson's group, using protein array technology, identified a variety of autoantibodies linked to lung-derived transcripts that are involved in the regulation of developmental processes and cell communication (47). These antibodies were of the IgG and IgM isotype and in some cases were linked to onset of PGD. Although this report did not show the functional significance of these antibodies, this study also highlights the potential clinical significance of how autoimmunity pre-transplantation could impact lung transplantation.

3. Autoantibody Induction

Humoral responses in all forms of autoimmune disease are linked to the production of isotype class switch autoantibodies (54). Since this occurs within germinal centers, then autoantibody production post lung transplantation may occur systemically within the spleen, as is the case for organ allografts other than the lung. However, as mentioned previously, iBALT develop in the lung post transplantation and these secondary lymphoid tissues are fully capable of mounting T and B cell immunity in the absence of any other secondary lymphoid tissue. Help for autoantibody production is likely to be derived from follicular helper T cells within germinal centers which recognize the MHC class II on B cells, and via production of IL-21 known to have a key role in humoral autoimmunity (55-57). Since

iBALT has a full complement of immune cells to mount local immunity then it is likely that follicular helper T cells exist within these structures and facilitate autoantibody production. However, the presence of follicular helper T cells within iBALT has not been reported.

3.1 Autoantigen Exposure within the Allograft

Although col(V) may be considered a sequestered antigen due to its location within the helices of type I collagen, it is also expressed on the apical surface of airway epithelial cells. Accordingly, this location is not “sequestered” and could be readily detected by cellular and humoral immunity. However, the bulk of col(V) is within the lung interstitium and not exposed to the immune system. Early events related to ischemia and reperfusion injury post lung transplantation result in interstitial remodeling in part due to activation of matrix metalloproteases able to cleave collagenous molecules, and thereby exposing col(V) (58). Indeed, interstitial col(V) is readily detected within four hours post lung transplantation and remains detectable for over 30 days post transplant. Although col(V) is not readily detected in the normal lung, it is over expressed highly in OB post lung transplantation (8, 59). Notably, epithelial col(V) is upregulated within hours post lung transplantation which suggests that inflammation/injury that results from the transplantation procedure is sufficient to induce or unmask col(V) (52, 58).

Similar to col(V), K- α 1 tubulin is also expressed on the surface of airway epithelial cells but under normal conditions is believed to be primarily intracellular due to its key functions such as GTP binding, GTPase activity, and microtubule-based intracellular movement (12). The detection of immune responses to intracellular antigens in lung transplant recipients leads to the question of how does K- α 1 tubulin, or other autoantigens become exposed to immune system. While there are no definite answers to this question a few theories exist. Intracellular proteins can be translocated as blebs to the cell surface during apoptosis (60, 61); and apoptosis is a feature of airway injury during PGD, acute rejection, as well as OB. Exposure of normally cryptic antigens in the presence of inflammation may lead to loss of self tolerance resulting in autoimmunity. This theory could explain why allograft damage mediated by infection or rejection could lead to de novo autoantibody production. However, this theory does not explain the presence of autoantibodies pre-transplantation, unless the specific diseases that are indications for lung transplantation may be associated with autoimmune phenomenon. Indeed, IPF, a leading indication for lung transplantation has been linked to autoimmunity as described above.

An alternative explanation for autoantibody induced injury to intracellular antigens may be related to the possibility that autoantibodies may be internalized through cell surface receptors and then trigger inflammatory cascades after binding to targets. Although these events have not been reported in lung transplantation, such pathophysiology can occur in autoimmune diseases such as systemic lupus erythematosus (62).

4. Mechanism of Autoantibody-Induced Pathology in Lung Transplantation

Complement activation is a common feature of autoantibody-induced tissue injury and pathology. Indeed, we reported that anti-col(V) antibody induced injury to airway epithelial cells was complement dependent (31). However, autoantibodies can induce apoptosis in target cells in the absence of complement activation (63). Alternatively, antibodies may mediate antibody dependent cellular cytotoxicity (ADCC) by macrophages or NK cells recognition of autoantibodies bound to their respective autoantigens. While ADCC is a putative mechanism, it has not been reported to be associated with autoantibody induced injury post lung transplantation.

Autoantibodies could also induce tissue injury by induction of signaling cascades within cells expressing the autoantigens. For example, Goers reported that binding of K- α 1 tubulin antibodies to airway epithelial cells induced strong expression of signaling proteins such as protein kinase-C (PKC), as well as vascular endothelial growth factor, TGF- β , and heparin binding epidermal growth factor-like growth factor (12). Although not all of these have been implicated in lung allograft pathology, TGF- β is likely to have key roles in fibrogenesis that is characteristic of OB. Clearly, more studies are needed to reveal the mechanism of role of autoantibody-induced pathology post lung transplantation.

5. Summary and Conclusion

The role of autoantibodies in the pathogenesis of allograft pathology post lung transplantation is an emerging field. While the presence of capillaritis in lung biopsy specimens may be suggestive of antibody mediated rejection, and possibly that due to autoantibodies, there is a critical need for biomarkers to identify the potential role of humoral immunity, in general, and autoantibodies, in particular, in lung transplant pathologies. Furthermore, additional studies are needed to understand the possible requirement for alloimmunity to precede onset of the autoantibody response, the mechanism of autoantigen exposure and autoantibody induced injury.

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Highlights

- Autoimmunity is a recently described event linked to the pathogenesis of lung transplant rejection.
- Autantibodies to type V collagen and K- α tubulin have been implicated in primary graft dysfunction and obliterative bronchiolitis.
- Autoantibodies may induce injury via complement and non-complement dependent pathways.
- IL-17 appears to have a key role in autoantibody induction,.