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Mechanisms of chronic rejection in cardiothoracic transplantation

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1. ABSTRACT

Despite significant improvements in early post-transplantation survival rates, long-term patient and graft survival have remained poor, due in large part to the vexing problem of chronic allograft rejection. Attempts to combat this problem with intensification of immunosuppression have led to concomitant increases in the rates of fatal malignancies and infections. In cardiac transplantation, chronic rejection is manifested primarily by a disease entity known as cardiac allograft vasculopathy, an occlusive narrowing of the coronary vessels. In lung transplantation, chronic rejection is typified by obliterative bronchiolitis, an airflow limiting narrowing of the bronchioles. From an immunologic standpoint, chronic rejection is believed to be the end result of repeated immune and non-immune insults to the graft. This review examines the pathophysiology of heart and lung chronic, with emphasis on both immune and non-immune causes.

2. INTRODUCTION

With the advent of modern immunosuppression, early post-transplantation graft and patient survival rates have improved dramatically over the last quarter of a century. However, long-term graft survival remains poor, with overall graft half-lives currently being 9.9 years for hearts, and 5 years for lungs (1,2). The majority of post-transplant deaths can be attributed to either chronic rejection (CR) or malignancy. The clinical impact of CR is most evident in the field of cardiothoracic transplantation, where re-transplantation for failed grafts is usually not possible because of the relatively small donor pool. Data from the International Society for Heart and Lung Transplantation (ISHLT) demonstrate a linear decrement in both patient and allograft survival for recipients of cardiothoracic organs after the first post-transplant year, which continues for at least 15 years. By the fifth post-transplant year, cardiac allograft vasculopathy (CAV) and

subsequent graft failure account for 30% of deaths in heart transplant recipients (1). For lungs, the bronchiolitis obliterans syndrome (BOS) is the predominant cause of death after the first post-transplant year (2). Mortality not withstanding, the morbidity of those that survive with BOS is considerable. Given the clear toll that CR takes on heart and lung graft recipients, research is currently underway to understand the pathogenesis of CR in the hope of developing both preventive and therapeutic strategies. This chapter examines the pathophysiology of heart and lung CR, with emphasis on both immune and non-immune causes.

3. HISTOLOGY AND PATHOPHYSIOLOGY OF CHRONIC REJECTION

The diagnosis of CR has historically relied on invasive procedures to obtain graft biopsies for histological evaluation. Regardless of the type of vascularized allograft, organs undergoing CR manifest similar pathological findings: obliterative vasculopathy, infiltration of leukocytes, luminal occlusion, and a marked fibrotic response. These histologic findings are the final result of a complex, multi-stage process of repeated immune- and non-immune-mediated cellular injury and inflammation. Repetitive insults exhaust the recipient's natural repair mechanisms and result in fibrotic replacement and organ failure. The fibrosis appears to preferentially narrow and obliterate the endothelial- and epithelial-lined tubular structures in the graft.

In heart allografts, the principal histological and clinical manifestations of CR consist of concentric vasculopathy with smooth muscle cell proliferation, together known as cardiac CAV. These intimal changes can be detected by intravascular ultrasound, which is becoming the gold standard for early diagnosis (3). As the disease progresses, myointimal proliferation eventually occludes coronary vessels, resulting in infarction and ischemic cardiomyopathy. Although it is believed that antigen-independent (4) and autoimmune (5,6) factors can contribute to CAV, CAV is predominately incited by an antigen-dependent stimulus (4,7).

In the lung, CR leads to histologic lesions of obliterative bronchiolitis (OB), which presents clinically as BOS. OB is a concentric fibrosis of the membranous and respiratory bronchioles that results in an obstructive defect to airflow. The histopathologic features of OB include inflammation of the epithelial cells and subepithelial structures, believed to result from aberrant tissue repair (8). In severe chronically rejecting lung allografts, fibrosis can extend into the interstitium and may involve the pulmonary vasculature in a process similar to CAV.

4. ALLOIMMUNITY

Most investigators currently believe that that immune-mediated injuries to the graft are the fundamental cause of CR (9). The immune response to an allograft is initiated by T cells, which, when activated, can orchestrate a cytotoxic cellular response, as well as providing help for antibody production by B cells. Understanding antigen targets and mechanisms by which T cells respond to allogeneic material is crucial to the elucidation of the pathogenesis of solid-organ CR.

Alloantigens are able to activate T cells via two pathways. "Direct allorecognition" refers to the process by which intact donor major histocompatibility complex (MHC)-peptide complexes are recognized on donor antigen presenting cells (APCs) by host T cells. This type of recognition is unique to transplantation. Alternatively, the "indirect allorecognition" pathway occurs when donor MHC molecules or minor antigens are processed into peptides and presented to host T cells by host APCs. Many scientists believe that early acute rejection is predominantly mediated by the direct pathway. As time passes, the donor-derived passenger APCs that were transplanted with the graft are depleted and indirect allorecognition predominates. Swine studies have demonstrated that pre-transplant immunization with donor-derived MHC peptides accelerates rejection in both heart (10) and lung allografts (13). Furthermore, the immunodominance of various donor antigens changes over time during the rejection process, as has been shown in human recipients (11-13). These findings emphasize that indirect allorecognition likely plays a critical role in the development of CR.

4.1. HLA matching

The degree of immune disparity between the host and donor is the dominant predictor of the incidence and vigor of CR. Early clinical observations have now been confirmed in experimental studies that show that isografts remain free of CR, while recipients intentionally sensitized to donor antigen develop accelerated chronic and acute rejection (14). In renal transplantation, organ allocation is partially driven by human leukocyte antigen (HLA) matching because of the significantly improved graft survival seen with higher degrees of HLA matching (15,16). In contrast, allocation based on HLA matching for thoracic organs has been problematic due to shorter permissible ischemic times and a relatively smaller donor pool. Nonetheless, retrospective data has emerged that demonstrates a significant improvement in cardiac graft survival when recipients are HLA matched. Hosenpud and colleagues performed a retrospective review of the United Network for Organ Sharing (UNOS)/ISHLT registry and demonstrated that HLA matching would be beneficial in cardiac transplantation (17). Opelz and colleagues showed that the extent of HLA compatibility influences graft survival, independent of other variables (18). Kaczmarek and colleagues found that HLA-DR matching improves survival after heart transplantation by as much as 25% within 3 years (19). Finally, data from the ISHLT registry indicate that, in addition to HLA-DR, mismatches at the HLA-B locus predict reduced survival, as measured 10 years following transplantation (1). These findings, coupled with the advent of more precise and rapid tissue typing techniques, may soon refine the way in which cardiac allografts are allocated.

For lung allografts, there is currently insufficient data to draw definitive conclusions on HLA matching.

Some studies report no association (20,21). However, three studies initially suggested a significant positive association exists between mismatching at the HLA-A locus and the development of BOS (22-24). More recently, HLA matching was shown to independently impact survival in single-lung transplantation (17). The most recent report from the registry of the ISHLT clearly demonstrates a detrimental effect of mismatches at the HLA-A and HLA-B loci (2). More information regarding HLA typing for lung transplantation should be forthcoming, as the total number of lung transplants performed with known HLA haplotypes increases.

4.2. Acute cellular rejection

Acute rejection (AR) has been clearly demonstrated to be a harbinger of future CR in most solid organ transplants. For lung transplantation, it is widely accepted that AR is a risk factor for both OB and BOS, and this relationship is believed to be causal (25). Several studies have identified severe AR, recurrent episodes of rejection, the cumulative burden of AR, and late AR as risk factors for BOS (20,24,26-29). More recently, a single episode of mild AR was found to be an independent risk factor for the development of BOS (30).

The association between AR and CR in cardiac transplantation was debated for years because early studies had relatively low statistical power and produced equivocal findings (31). However, in recent years, the link between AR and CAV has been further defined for AR episodes both within the first postoperative year (32-34) and later years (35,36). Jimenez and colleagues showed that the biopsy rejection score correlated with the rate of CAV progression as measured by intravascular ultrasound (33). The mechanism is likely one of inflammation and failed repair, but whether it is the frequency and/or the severity of the AR episodes that influences the development of CAV remains to be determined.

4.3. Humoral alloimmunity

The role of B cells and alloantibody formation in the rejection of allografts has been underappreciated. Emerging evidence suggests that alloreactive B cells and anti-HLA antibodies are seminal components of the rejection process (37). Importantly, memory alloreactive B cells can persist for years after the initial immunizing event and therefore have the potential to initiate CR at any time, even years after the initial inciting event. In heart grafts, the development of anti-HLA antibodies is known to correlate with CAV development (38). B cells have been identified in lung tissue during rejection episodes, and anti-HLA antibodies also correlate with the development of OB (39,40). However, the mechanism by which humoral alloimmunity leads to CR is not well understood, and whether the presence of antibody is an initiating event or merely a response to tissue damage remains to be determined. However, the principal target of humoral immunity appears to be the graft endothelium, which can be activated and injured by alloreactive antibodies.

4.4. Progenitor cells and CAV

There is emerging evidence that extracardiac progenitor cells may also contribute to both beneficial and deleterious repair after graft injury. In fact, by studying sex-mismatched heart transplants, investigators now believe that as much as 0.04% of cardiomyocytes in transplanted hearts may actually be of extracardiac recipient origin (41). In addition, animal data on both aortic and cardiac allografts suggest a role for circulating progenitor cells in neointimal proliferation and CAV (42-44). The implication is that these progenitor cells migrate to areas of vascular damage and differentiate into the smooth muscle cells seen in the neointimal proliferation of CAV. However, the data on the contribution of extracardiac progenitor cells to CAV development is conflicting and remains an active area of research today.

4.5. Innate immunity

Recent studies, suggest that the adaptive immune system is not always solely responsible for CAV formation, as mice with T and B cells rendered fully unresponsive to donor antigens through the induction of neonatal tolerance or mixed chimerism still developed CAV (45). We utilized a novel system of semi-allogeneic cardiac transplants between parental donors and F1 hybrid recipients to provide the first evidence that natural killer (NK) cells, members of the innate immune system, also contribute to the generation of CAV in mice. Since NK cells are not targeted by current immunosuppressive therapy, including cyclosporine (46), these findings may explain why CAV, a primarily MHC-driven alloimmune process, still occurs in heavily immunosuppressed recipients. Indeed, the apparent resistance of NK cells to the modulating effects of conventional immunosuppression is compatible with the hypothesis that innate immunity may be an important part of the complex set of events that result in this vexing problem.

4.6. Organ procurement and implantation

A large number of clinical studies have demonstrated a deleterious effect of prolonged ischemic times on transplant outcomes, and thoracic grafts appear to be particularly sensitive to prolonged ischemia. Data from the ISHLT registry historically demonstrates that prolonged ischemic time (>7h) confers an increased risk of BOS development three years after transplantation (47), and ischemic times greater than 7 h for donor hearts increases the risk of both one- and five-year mortality (48). Prolonged ischemia time as a risk factor for decreased graft survival has also been confirmed in more recent registry data (49,50). Ischemic injury not only causes direct acute injury to the graft, but also probably increases the antigenicity of the graft by inducing inflammatory mediators (51), adhesion molecules, and MHC antigens on the graft endothelium (52). As a result, it is likely that ischemia-reperfusion can lead to chronic rejection by actually initiating an immune response. This immune response could be alloimmune or even autoimmune, as can be seen when normally cryptic antigens such as cardiac myosin or type-5 collagen become exposed (see below).

5. AUTOIMMUNITY

Itzutani and colleagues showed that chronic rejection was not abrogated by transplanting heart grafts

into syngeneic mice (53), suggesting that CR can occur in the absence of alloantigen. Just as a cellular insult to the graft could initiate an alloimmune response, emerging evidence suggests that certain injuries can expose self-antigens that the recipient's immune system does not normally encounter. Since these normally cryptic non-MHC antigens also exist in normal host tissue, this mode of graft rejection can be considered to be autoimmune mediated.

Cardiac myosin is an autologous contractile protein found in cardiac tissue that is recognized by both T and B cells during a cardiac rejection process (54). Fedoseyeva and colleagues showed that anti-cardiac myosin reactivity persists long after transplantation and hypothesized that it may play a role in CAV pathogenesis. They later supported this data with a murine study, which showed that in the absence of alloimmunity, chronic rejection was associated with a T cell response to cardiac myosin (6). Another tissue specific antigen that has been implicated in the formation of CAV is the endothelial antigen vimentin (55).

Analogous to cardiac myosin, researchers have found that immunity during lung allograft rejection involves the development of a response to collagen V (56), which is a component of the perivascular and peribronchial connective tissue. Collagen V reactive lymphocytes are known to express the pro-inflammatory cytokines IL-17 and IL-23 (57), and Wilkes and colleagues have demonstrated that oral tolerance induction to collagen V can prevent BOS development in murine models (58).

6. INFECTION

Another mechanism of tissue injury and inflammation that plays a role in the development of CR is infection. It has been suggested by several studies that viral respiratory infections, including the common community acquired infections of parainfluenza virus, respiratory syncytial virus, influenza, and adenovirus, are associated with the development of BOS (29,59,60). Cytomegalovirus (CMV) also seems to promote chronic vascular rejection of most solid organ transplants including heart and lung grafts. CMV can invade the endothelium of organs; and therefore, it is not surprising that its presence is associated with perivascular inflammation. Sequence homologies between the immediate early-2 region of CMV, and a conserved domain of HLA-DR (61) and the heavy chain of the MHC class I antigen can lead to immunologic cross-reactivity (61). Schulman and colleagues also found a clear role for CMV pneumonitis in the development of BOS, while studying HLA mismatching (62). Thankfully, the use of sensitive and quantitative assays to detect CMV antigenemia and appropriate prophylaxis with antiviral agents now seems to be reducing the impact of CMV infection in BOS development (63).

The most frequently studied infections related to CAV development are *C. pneumoniae* and CMV. Patients with PCR positivity and antibody formation for *C. pneumoniae* were found to have more severe CAV (64). Likewise, CMV has been associated with a 28% rate of obstructive CAV five years after heart transplantation; almost triple the rate for non-infected patients (65). More importantly, CMV prophylaxis with ganciclovir decreases the prevalence of CAV (66).

7. GASTROESOPHAGEAL REFLUX DISEASE AND BRONCHIOLITIS OBLITERANS SYNDROME

It has been suggested that GERD, as an inflammatory condition, may contribute to the development of BOS (67,68). A review of lung transplant recipients at Duke University revealed that the presence of GERD is associated with decreased survival and higher rejection rates (68). Interestingly, prophylactic anti-reflux surgery successfully reduced the incidence of allograft dysfunction. The association between GERD and lung allograft dysfunction was confirmed in a rat model by the same group (69). The hypothesis is that a non-alloimmune injury caused by the exposure of bronchial epithelium to caustic gastric fluid precipitates an alloimmune injury. Although the mechanism may only be due to direct toxicity, it may also involve stimulation of the innate and adaptive immune responses. The mechanisms responsible for GERD induced BOS remain elusive.

8. DONOR FACTORS

There is little doubt that the quality of grafted organ can influence late outcomes. This is particularly true when donor organs are relatively undersized or when older donors with co-morbidities are utilized. Some have suggested that a combination of both immune and non-immune mediated injuries to the graft prior to transplantation leads to insults in the graft that exhaust its repair capacity (70).

8.1. Brain death

Increasing data are accumulating that indicate that brain death induces the expression of inflammatory mediators in peripheral organs, eventually making these organs more susceptible to MHC-driven processes (71). Compared to controls in a rat transplant model, organs harvested from brain-dead donors seem to induce a more intense and accelerated recipient immune response (72). Implicated in this increased alloreactivity were macrophage-associated cytokines and upregulated adhesion molecules (72). More recently, a rat model was used to show that brain death induces an inflammatory response in donor lung grafts and subsequently aggravates chronic rejection (73). A similar increase in inflammatory mediators has been demonstrated in kidneys and livers from brain-dead donor rats. Anyanwu and colleagues also reported a favorable difference in CAV between living and cadaveric donors in an experimental heart transplant model (74). Segel and colleagues have shown that endothelial inflammation and dysfunction occurs as a consequence of brain death even in the absence of hemodynamic instability (75). In the clinical arena, it has been observed that pediatric lung transplant recipients of living donors had a much lower incidence

of CR than those from cadaveric donors (76). Studies are now underway evaluating the role of different forms of brain death on the development of CAV in hopes of developing pre-transplant modalities to limit brain-death induced vascular injury to allografts (77).

9. CONCLUSION

CR is a very complex problem that continues to limit the long-term success of solid organ transplantation, particularly cardiothoracic organs. This chapter highlights new findings that contribute to our current knowledge of the mechanisms of chronic rejection in cardiothoracic organs. Pathologically, CR represents the end result of repeated injury, leading to parenchymal fibrosis and luminal obliteration. The causes of CR resulting from graft tissue injury are multifactorial. Both immunologic and non-immunologic factors contribute to graft injury, which fuels the alloimmune response, predisposing the development of CR. Significant progress has occurred over the past decade to understand the mechanisms of CR development. We now know that in addition to cellular alloimmune responses, autoimmunity may play a role. Recently, the role of humoral alloimmunity has also become apparent. In addition, tissue injury from ischemia/reperfusion, infections, and brain death appears to render the graft more antigenic and susceptible to CR. Further study of all the contributing factors is crucial for understanding the mechanisms by which CR rejection develops in cardiothoracic allografts. All of these factors are potential therapeutic targets.

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Abbreviations: CR: chronic rejection; ISHLT: International Society for Heart and Lung Transplantation; CAV: cardiac allograft vasculopathy; BOS: bronchiolitis obliterans syndrome; OB: obliterative bronchiolitis; APC: antigen presenting cell; MHC: major histocompatibility complex; HLA: human leukocyte antigen; AR: acute rejection; NK: natural killer; CMV: cytomegalovirus

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