Molecular Mechanisms of Antibody-Mediated Rejection and Accommodation in Organ Transplantation

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Keywords

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Abstract

Antibody-mediated rejection (ABMR) in organ transplantation has been recognized as the main cause of graft rejection. Binding of donor-specific HLA antibody (DSA) and A/B blood type antibody on graft endothelial cells causes complement-dependent tissue damage. C4d, a product of the complement cascade, has long been an indicator of graft tissue damage in graft endothelial cells. By contrast, recent evidences indicated histological findings of ABMR without C4d deposition in many cases and Banff classification criteria included a category of C4d-negative ABMR. Several mechanisms have been proposed for complement-independent tissue injury in the presence of DSA. It is well known that activated monocytes and macrophages infiltrate into graft tissues. The inflammatory environment triggered by the binding of DSA to endothelial cells alone can induce an allo-reaction of CD4 T-cells via graft endothelial cell HLA-class II. Accommodation is a condition that no rejections occur even

in the presence of an antibody against donor organs and becomes attracting considerable attention as a therapeutic strategy to acquire long-term survival of the transplanted organs. Several recent publications have suggested some mechanistic insights about graft accommodation, including the upregulation of antioxidant, anti-apoptotic, and complement regulatory proteins genes via activation of PI3K/AKT survival signal or inactivation of extracellular signal-regulated protein kinase pro-inflammatory signals after DSA and anti-A/B antibody ligation on endothelial cells.

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The Diagnosis of Antibody-Mediated Rejection in Organ Transplantation

Antibody-mediated rejection (ABMR) is a major cause of graft dysfunction and leads to graft failure in solid organ transplantation. According to the 2017 Banff Classification, both pathological and clinical criteria are required for the diagnosis of ABMR [1]. The complement system has been considered part of the innate immune system because of its enhancement of antibody abilities and phagocytosis to clear pathogens and damaged cells,

as well as promotion of inflammation and the membrane attack complex [2]. Because the degradation product C4d of the complement factor C4 participates in both classical and lectin pathways and keeps binding to the endothelium for several days or weeks, C4d staining in peritubular capillaries (PTCs) has long been one of the well-established features of ABMR [3]. However, recent efforts have identified C4d-positive samples without ABMR or C4d-negative samples with ABMR [4]. To understand how donor specific HLA antibody (DSA) and ABO blood carbohydrate antibody cause graft injury and accelerate acute and chronic rejection becomes more important for the management of sensitized recipients.

Macrophages and Natural Killer Cells

Fc receptor proteins are found on the surface of several cells such as B lymphocytes, natural killer (NK) cells, and macrophages, and they contribute to prevention of pathogens via phagocytosis in an antibody-dependent fashion [5]. It was demonstrated that Fc-gamma receptor polymorphism was the marker to predict the incidence of urinary tract infection in kidney transplant recipients [6] and infectious complications after liver transplantation [7]. Intravascular CD68-positive macrophages have appeared to be associated with ABMR and sometimes provided a more sensitive histological marker compared with C4d [8]. NK cells have long been considered the primary effector cells of rejection after MHC-mismatched bone marrow transplantation [9], but increasing evidence has shown that NK cells are involved in solid organ transplantation as well. The inhibition of NK cells resulted in long-term allograft survival, in which ABMR at chronic stages was delayed [10]. Taken together, although Fc SNP, macrophage staining, and NK cells are not currently included in the Banff criteria, these clinical observations shed light on the central role of the innate immune response in graft injury via donor-specific antibodies.

Complement-Independent Antibody-Mediated Endothelial Cell Activation

ABMR has been implicated to be primarily driven by the effector functions of the Fc fragment of DSA, whereas experimental evidence indicates antibody-independent promotion of endothelial cell activation and proliferations. Anti-HLA-class I antibodies promote focal adhesion kinase, matrix metalloproteinase-2, and neutral

sphingomyelinase-2-dependent proliferation and migration of smooth muscle cells [11, 12]. In addition, it was demonstrated that anti-HLA-class I cross-linking activated Rho kinase, myosin light chain kinase, and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) in a calcium-independent manner to stimulate stress fiber formation [13]. Anti-HLA-class I antibody ligation activated the transcription factor cAMP response element binding protein, which was involved in adhesion molecule and chemokine expression by microvascular endothelium, which drove monocyte adhesion [14]. Recently it was suggested that anti-HLA-class II antibody ligation also increased endothelial-to-mesenchymal transition without C4d deposition [15], and promote endothelial activation via ERK and mTOR signaling pathways [16]. Taken together, although further investigation will be needed, recent progresses have indicated the antibody ligation itself trigger intracellular signaling pathway that is important in the regulation of cell survival of grafts.

Molecular Mechanism of Accommodation

Some histological findings indicated that antibody binding to graft may not always predict graft dysfunction [17]. Accommodation is the condition in which a transplant appears to resist immune-mediated injury and loss of function even in the presence of anti-donor antibody [18]. In contrast to transplantation in the HLA-sensitized patient, this has frequently appeared in ABO-incompatible kidney transplantation, and been often associated with C4d deposition in PTCs [18]. The establishment of graft accommodation may require several weeks under the condition of anti-A/B antibody exposure without injury [19]. Upregulation of complement regulatory proteins, such as CD55 and CD59, via anti-A/B antibody-dependent inactivation of ERK1/2 and mTOR signaling pathways is advocated as one possible mechanism [20, 21]. On the contrary, small amount of anti-HLA-class I antibody enhanced the AKT survival signal [22], which is associated with HO-1 and ferritin H protein [23, 24]. Another aspect of accommodation was partly explained by the decreased production of donor-specific anti-A/B antibodies in graft recipients of ABO-incompatible kidney transplants [25]. Although infrequently observed in organ transplantation, the effort to investigate the mechanisms to acquire the accommodation might shed light on avenues for prevention of transplant rejection and new opportunities to elicit repair mechanisms from DSA-mediated injury.

Fig. 1. Molecular mechanisms of ABMR and accommodation. **a** Antibodies binding to HLA molecules or A/B carbohydrate on endothelial cells activates the complement system through classical pathway, which leads to the formation of a membrane attack complex (MAC). **b** A small amount of anti-HLA-class I antibody and anti-A/B antibody ligation has the potential to induce accommodation. Anti-HLA-class I ligation may induce cytoprotective genes, while anti-A/B ligation enhances complement regulatory molecules, such as CD55 and CD59. Antibody-dependent cell-mediated cytotoxicity by inflammatory cells, such as natural killer cells or macrophages, is performed via Fc regions (**c**), while the behavior of those cells in accommodation remains unclear (**d**).

e Anti-HLA-class I antibody binding itself induces pro-inflammatory cytokines (IL-6, IL-11, and IL-8) and adhesion molecules that enhance the cell recruitment associated with ERK and mTOR activation. **f** On the contrary, anti-A/B antibody inactivates those signaling pathways. **g** CD4 T-cell allo-immune reaction occurs through donor HLA class II expressed on graft endothelial cells, which enhanced pro-inflammatory cytokines secretion, including IL-6, IL-11, and IL-8, in the presence of anti-HLA antibody ligation. **h** Recent findings also revealed that anti-A/B antibody ligation could reduce ERK and mTOR activation, which might be involved in PD-L1 induction, resulting in reduction of CD4 T-cell allo-immune response [30].

Allo-Immune Response of Recipient CD4 T-Cells against Graft HLA-Class II

Direct allo-recognition in organ transplantation has been considered a recipient CD4 T-cell response to HLA-class II on donor antigen-presenting cells [26]. It has been believed that direct allo-recognition occurs at early phase until the disappearance of donor antigen-presenting cells in organ transplantation [27]. Emerging evidence including our current progress also suggested that recipient CD4 T-cell reacted with donor HLA-class II molecules expressed by graft cells. It was demonstrated that anti-HLA-class I

and class II antibodies activated endothelium, resulted in increasing endothelial immunogenicity, and enhanced NFκB, which in turn triggered CD4 T-cell recruitment under shear stress. The increment of allo-geneic CD4 T-cell was also reported upon co-culture with anti-HLA-class I and class II antibody-ligated endothelium [28, 29]. By contrast, our recent findings revealed that anti-A/B antibody ligation induced PD-L1 expression on endothelial cells via ERK inactivation [30]. These recent findings have attracted researchers' attention and presented many questions about the interpretations between allo-antibody and allo-reactive CD4 T-cells under physiological conditions.

Conclusions

The potential mechanisms of ABMR and accommodation discussed in this article are presented in Figure 1. Experimental evidence suggests that anti-HLA and anti-A/B antibody ligation-mediated endothelial cell modification will become more important for a better understanding of the graft microenvironment. Many questions still remain, including the physiological role of prevalent non-HLA antibodies, different types of anti-HLA antibodies (DR, DQ, and DP), IgG subclasses (IgG1–4), and graft endothelial homeostasis. Further investigation

about complement-dependent and complement-independent graft injury will be required to achieve better outcomes in organ transplantation.

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Conflict of Interest Statement

The authors have no conflicts of interest.

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