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Review

Humoral immunity in chronic allograft rejection: Puzzle pieces come together

Olivier Thaunat *

Service de Transplantation Rénale et d'Immunologie Clinique, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France
Université Lyon 1, Villeurbanne, France
Unité 851, Institut National de la Santé et de la Recherche Médicale, Lyon, France

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ABSTRACT

Modern immunosuppressive armamentarium inadequately controls the humoral arm of recipient immune response, which in turn plays a central role in the pathogenesis of chronic rejection, a major cause of late allograft failure.

A consensus sequence has progressively emerged from the integration of both experimental and clinical data, in which the binding of circulating donor-specific antibodies to mismatched HLA molecules expressed by graft microvasculature leads to chronic inflammation and progressive tissue destruction.

Recent data suggest however that beyond their role in antibody production, B cells are also endowed with critical, yet overlooked, antibody-independent functions. Their abilities to present antigens and drive lymphoid neogenesis within rejected organ place them at the center of immune regulation with the power to enhance or inhibit antigraft immunity.

The key challenges for the next few years will be to learn how these conceptual progresses can be translated into innovative B cell-targeting therapies to improve long-term allograft outcome.

Contents

1. Introduction

Progresses achieved over the last two decades have only marginally improved the long-term outcome of transplanted organs, as demonstrated by the stagnation of graft attrition rate beyond the first year post-transplantation [1,2].

* Service de Transplantation et d'Immunologie Clinique, Hopital Edouard Herriot, 5 Place d'Arsonval, Lyon, France. Tel.: +44 7 584 222 962; fax: +44 2 072 693 393.
E-mail address: olivier.thaunatpastu@free.fr.

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Among the main cause of late allograft failure is chronic rejection, which results from the inadequate control of the recipient immune response. Indeed, unlike T cells, which have progressively come under pharmacologic control, the humoral arm of recipient immune response remains insufficiently tamed by modern immunosuppressive armamentarium. As a result, B cells and alloantibodies are increasingly acknowledged as crucial mediators of chronic allograft injury.

The present article aims at connecting the concepts that recently emerged in the field of humoral alloimmunity. Putting these puzzle pieces together, the picture of chronic rejection pathogenesis begins to come into play.

2. Alloantibodies and chronic rejection

2.1. The "humoral theory" of chronic rejection

Seminal clinical observations, made in the 1970s, have suggested a link between the presence of circulating donor-specific antibodies (DSA) and chronic rejection [3]. This hypothesis has then been substantiated by several experimental works [4,5], notably the demonstration that immunodeficient scid mice given repeated doses of anti-MHC class I alloantibody develop fibrous intimal thickening of coronary arteries in cardiac allografts [6].

Finally, a recent large-scale prospective trial, showing that transplant patients with DSA have twice the failure rate as those without, has validated the theory in the clinical setting [7]. However, while the deleterious impact of DSA on long-term allograft outcome is becoming increasingly acknowledged the precise mechanisms by which they lead to progressive graft destruction remains incompletely understood.

2.2. Natural history of chronic antibody-mediated rejection

Experimental renal transplantation in non-human primate, have provided strong evidence that chronic antibody-mediated rejection (CAMR) progresses through four defined stages [8,9].

i) The sequence starts with the detection of circulating DSA, usually IgG directed against mismatched HLA molecules between donor and recipient. The generation of such high affinity, class-switched alloantibodies requires the development of a T cell-dependent humoral immune response, which implies the expansion of CD4+ T cells with indirect allospecificity, i.e. CD4+ T cells whose TCR recognize alloantigens processed and presented in the context of MHC class II molecules expressed by recipient antigen-presenting cells. Indeed, only indirect pathway T cells can provide efficient help to allospecific B cells and trigger germinal center reaction [10,11]. The initiation of T cell-dependent humoral immune response is thought to take place within recipient's canonical secondary lymphoid organs: spleen and draining lymph nodes [12].
ii) Binding of antibodies to directly accessible allogenic targets expressed by endothelial cells of graft microvasculature triggers the classical complement pathway, as witnesses by the deposition of C4d in glomerular and peritubular capillaries.
iii) Activation of endothelial cells leads to the release of adhesion molecules and cytokines that in turn (with complement fragment C3a and C5a) recruit immune effectors, including neutrophils, monocytes, and NK cells.
iv) Chronic inflammation promotes the development of typical histological lesions, *i.e.* transplant glomerulopathy, chronic allograft arteriopathy, and lamination of the peritubular capillary basement membrane. Finally, progressive tissue destruction leads to irreversible loss of graft function, proteinuria and hypertension.

2.3. Molecular targets of recipient humoral immune response

The recent establishment of sensitive and specific immunoassays has allowed for detailed characterization of antibody reactivity patterns.

Highly polymorphic mismatched HLA molecules represent the most documented targets for DSA. Recent studies have reported that the presence of anti-HLA II antibodies in the serum was the most predictive for microcirculation injuries, suggesting that they might have a higher capability than anti-HLA I to trigger graft failure [13–16]. However, it should not be forgotten that antibodies detected in the blood might not represent antibodies acting on the graft. It is conceivable that instead, antibodies detected in the circulation represent those that cannot compete for binding to the graft [17].

Serological cross-reactivity analyses made in the eighties [18] have demonstrated that each HLA molecule could be seen as a unique combination of multiple epitopes, namely short sequences involving polymorphic amino acid residues in antibody-accessible positions [19]. The fact that distinct HLA antigens share some identical epitopes provides a likely explanation for the frequent detection of non-donor-specific anti-HLA antibodies (NDSA) in the circulation of graft recipients [20]. Surprisingly, this very mechanism also accounts for the presence of anti-HLA I antibodies in the sera of some normal and healthy non-alloimmunised individuals [21]. This naturally occurring anti-HLA immunization develops as a result of the shedding of β2m-free soluble HLA-E. The constant stimulation of specific auto reactive B cell clones by exposed epitopes of soluble HLA-E leads to the production of autoantibodies that cross react with other allogenic HLA molecules, which share identical epitopes [22].

Besides anti-HLA antibodies, immunoglobulins (Ig) recognizing polymorphic non-HLA alloantigens and non-polymorphic auto-antigens have also been detected in the serum of allograft recipients [23]. Using integrative genomics analysis Li et al have recently demonstrated the uneven immunogenic potential of different graft compartments by showing that serological responses to non-HLA targets were mainly directed against compartment-specific antigens from the renal pelvis and cortex after renal transplantation [24]. Although some studies suggest that "non-HLA" antibodies could participate in the development of rejection lesions [25–28] to what extent they are harmful for the graft remains currently a matter of debate.

2.4. Fc portion of alloantibodies: possible sources of heterogeneity

Ig molecule is shaped like a Y, with two identical halves, each made up of a heavy chain and a light chain. The 2 arms of the Y, each formed by the amino terminal extremity of a heavy chain and a light chain, contain the antigen-binding site. The base of the Y, composed by the carboxy terminal extremity of the constant region of the two heavy chains, is named fragment crystallizable (Fc). By binding to a specific class of receptors on immune effectors and complement proteins, Fc portion confers to Ig its effector functions.

During a T cell-dependant humoral response class switch recombination occurs in germinal center, leading to the replacement of the constant region of the Ig heavy chain. Accordingly, anti-HLA alloantibodies of a wide range of isotypes (IgG1, G2, G3, G4, Ig A1, A2, IgM,… etc.) can be eluted from explanted renal allografts [29]. Each heavy chain isotype displays different capability to bind C1q (and therefore to trigger classical complement pathway) and to recruit immune effectors. It is therefore tempting to speculate that heavy chain isotype influences the pathogenic potential of alloantibodies. In line with this hypothesis, it has been reported that patients with exclusively weak complement-activating anti-HLA DSA (i.e. IgG1 and IgG4) had a lower incidence of acute antibody-mediated rejection and experienced less early allograft loss [30,31].

Another layer of complexity arises from the carbohydrate chains that are attached to the Fc [32]. The heterogeneity of Fc glycans, which varies with age, gender, and disease status [33], modulate Ig