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Accommodation in Renal Transplantation: unanswered questions

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Abstract

Purpose of review—Accommodation, an acquired resistance of an organ to immune-mediated damage, has been recognized as an outcome of renal transplantation for more than 20 years. Accommodation was originally identified in blood group-incompatible kidney transplants that survived and functioned normally in recipients with high titers of anti-blood group antibodies directed against antigens in the grafts. The most compelling questions today include how often and by which mechanisms accommodation occurs, and what might be the biological implications of accommodation. This communication summarizes recent advances in addressing these questions.

Recent findings—Because its diagnosis has depended on identification of anti-donor antibodies in serum, the prevalence of accommodation has been considered low. Recent research in animal models and in clinical subjects may challenge that view. This research also suggests that sublethal graft injury of various types induces accommodation and that accommodation may be a dynamic condition, eventuating into tolerance on the one hand and chronic graft injury on the other.

Summary—Burgeoning lines of investigation into accommodation now portray a condition of greater prevalence than once thought, exposing pathways that may contribute to the understanding of a range of responses to transplantation.

Keywords

accommodation; rejection; tolerance; renal transplant

Introduction

The condition of accommodation was first described in ABO-incompatible renal transplants which were found unexpectedly to survive and function after anti-blood group-A or –B antibodies were temporarily removed from the circulation of graft recipients [1,2]. The term “accommodation” was first applied to organ xenografts that appeared, like ABO-incompatible organ grafts, to resist hyperacute and acute vascular rejection [3]. The resistance to injury continued even after anti-ABO antibody in human kidney transplant recipients or xenoreactive antibody in experimental xenotransplantation returned in the recipient’s blood [3]. Most surprisingly, biopsies of functionally healthy grafts showed

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persistence of ABO antigens on endothelial surfaces [2]. The seemingly paradoxical coexistence of antibody and target antigen without evidence of rejection or graft injury encouraged the idea that a novel type of graft-recipient interaction might exist.

The immune response to transplantation and outcome of transplants can be viewed as combinations of two dichotomies – immunity versus no immunity and injury versus no injury. Absence of immunity can be ascribed to immunological ignorance, tolerance, and immunosuppression. Injury in the absence of immunity can be manifest as ischemia-reperfusion in the short term and chronic rejection in the long term. Injury associated with immunity is usually ascribed to rejection, although one cannot exclude the possibility that injury might be from a non-immune source with immunity being incidental. Absence of injury in the face of immunity is typical of accommodation and enhancement. We recently discussed the functional and structural basis for these distinctions, as well as the significance of accommodation in avoiding rejection [4]. Accommodation differs from tolerance in that the immune system retains the capability to reject fresh tissue from the same donor, but accommodated donor tissue remains protected even if re-transplanted into a new recipient [5].

The origins of the field of accommodation lie in ABO-incompatible kidney grafts, which by their very nature were exceptional and experimental. Starzl and colleagues initially reported that ABO incompatibility did not preclude renal allotransplantation, but then abandoned the idea after suffering a number of graft losses through hyperacute rejection [6]. The field remained relatively dormant until the late 1980s, when Alexandre published his series of live-donor ABO-incompatible recipients [7]. These patients all received preoperative splenectomy and plasmapheresis, and in a cautionary note, the same group described rapid graft loss in three individuals who did not undergo splenectomy [8].

Splenectomy remained a cornerstone of crossing ABO barriers for several years, but was gradually superseded by more selective immunosuppressive measures. As described in a recent outline of the Johns Hopkins experience in desensitization protocols [9], splenectomy was first replaced with Rituximab (anti-CD20) monoclonal antibody B-cell depletion [10]. In time, B-cell depletion was dropped altogether, and only plasmapheresis and IVIG therapy were retained for a transient reduction of circulating isoagglutinins [11]. As these studies have shown, the once formidable barrier of ABO-incompatibility can now be crossed, with accommodation being a central feature of graft survival in the face of anti-donor antibodies. A lateral application of desensitization, where accommodation has been demonstrated, is the desensitization of individuals with high titers of donor-specific (anti-HLA) antibody. The previously well-accepted requirement for a negative crossmatch between donor and recipient was overcome using techniques directly drawn from the ABO-incompatible experience [12].

Here, we will expand on these data from ABO- and HLA- incompatible transplants to discuss recent advances in understanding accommodation as it pertains to renal transplantation. Although accommodation clearly occurs in other types of solid organ transplants [13], and the concept can be usefully extended beyond transplantation [14,15], accommodation remains most studied as a response to renal transplantation. This reflects not only historical bias, but also the recent surge of interest in ‘desensitization,’ or transplanting recipients with high levels of preformed antibodies to either HLA or ABO donor antigens [16] who are more likely to respond vigorously to allogeneic tissue. Renal transplant recipients and experimental systems have been used in tandem to determine the frequency of accommodation after allo- or xeno-transplantation, the cellular and molecular mechanism of accommodation and the durability and consequences of accommodation for the graft and recipient.

Frequency of accommodation

The prevalence of accommodation after renal transplantation is perhaps the key question awaiting answer. Defined by the presence of anti-donor antibodies in the circulation of recipients of organ transplants, accommodation is seen with some frequency after ABO-incompatible transplantation. Stegall's group [17], found variable recovery of anti-blood group titers after ABO-incompatible transplantation with desensitization protocols. Similarly, data from the Japanese experience with ABO-incompatible grafts show a rise in both IgM and IgG2 subtype anti-blood group antibodies, regardless of graft rejection [18].

When classically defined, accommodation appears less prevalent in ABO-compatible grafts where the main target for alloreactive antibodies is HLA. Montgomery and colleagues recently published the results of serial protocol biopsies and serum antibody measurement in their crossmatch positive recipient cohort [19]. They found C4d staining in 20–30% of their recipients, with detectable donor-specific antibody (DSA) in recipient serum in each of these individuals. The presence of DSA and C4d staining were not strictly predictive of subclinical rejection, however, and renal function among histologically-different groups was unchanged. These data are highly suggestive for accommodation being crucial to successful engraftment in the crossmatch-positive population.

Because ABO-incompatible grafts are still experimental and because anti-HLA antibodies are not often seen in ABO-compatible recipients of fully functioning grafts, accommodation has received little attention, and remains controversial. At the 10th Banff Conference on Allograft Pathology, Haas presented an ABO-incompatible renal transplant series where 21 out of 37 patients had C4d deposition without further histologic evidence of rejection [20].

We have stated that limiting the definition of accommodation to the presence of anti-donor antibodies in the circulation of the recipient, as it was originally laid out [3], may greatly underestimate its prevalence. Functioning grafts can absorb large amounts of anti-donor antibody; in fact we have used foreign organs as a way of clearing allo-reactive and xeno-reactive antibodies from the blood [21]. In these experimental studies, donor reactive antibodies were detected in the circulation after and not before injury to the graft occurred. If these experimental studies apply to the clinical setting, then detectable donor-reactive antibodies are a late sign of humoral injury, and most subjects may produce these antibodies only to have them fully absorbed to a graft.

Given that accommodation occurs in response to carbohydrate (ABO, Galα1-3Gal glycans) and protein (HLA) antigens, there is no theoretical reason why it should not play a part in recipient-graft interactions in ABO-matched, crossmatch-negative renal transplantation. In order to demonstrate accommodation, however, one must show evidence of recipient reactivity without graft injury. A recent summary of the Roman experience with 100 consecutive renal transplants demonstrated that recipients with no preoperative DSA, but with detectable anti-HLA antibodies, had significantly greater rates of antibody-mediated rejection (AMR) than did those without preformed antibody [22]. In analyzing this cohort, the authors found positive postoperative flow cytometric crossmatches in all four individuals who experienced AMR. Interestingly, four patients without AMR also had positive crossmatches. This discrepancy between the incidence of DSA and AMR provides evidence for accommodation in what would be considered 'standard' donor-recipient pairs.

Further evidence for graft resistance to DSA-mediated injury comes from the work of Aubert and colleagues, who used solid-phase assay measurements of preoperative anti-HLA antibody and DSA in 113 renal transplants [23]. They found anti-HLA antibodies in 49% and DSA in 9.7% of their recipients. With standard induction and maintenance immunosuppression regimens, the authors reported 11 instances of acute rejection and one

instance of AMR. While the AMR case did occur in a pre-transplant DSA-positive patient, there was no increased risk for either cellular or antibody-mediated rejection in this group when compared to the remainder of the cohort. These data strongly support the presence of some occult graft-recipient interplay, such as accommodation, by which preformed antibody's deleterious effects are ameliorated.

A trend in these data is that as antibody-detection techniques become more sophisticated, the number of antibody-positive, rejection-negative patients rises. Both the Italian data, as well as a much larger report by Opelz and his collaborators in the Collaborative Transplant Study [22,24], found that reactivity to different classes of HLA carries different prognoses. In the Collaborative Transplant Study report, the authors found a two year graft survival of 76.5% in those patients with anti-Class I and Class II antibodies, as compared to 87.5% in patients without reactivity to either group. While not statistically significant, there was a lower graft survival in patients with only anti-Class I reactivity (82.7%) than anti-Class II reactivity (86.1%). One obvious explanation for these discrepancies is that the differential effect of antibody binding, whether it be to induce accommodation or rejection, is dose-dependent. The restricted expression of Class II antigens may create a similar response to plasmapheresis and IVIG in desensitization protocols; enough binding occurs to initiate an adaptive response in the graft without activating the immune system enough to precipitate acute rejection. This concept appears both plausible and relatively simple at face value but, as we will discuss, elucidating the mechanism by which it occurs has proven more difficult than might be expected.

Mechanism of Accommodation

We originally proposed that accommodation might reflect one or more of three processes: a change in antigen so that less antibody would bind, a change in antibodies so that they would be less cytotoxic, or a change in the graft so that it resisted humoral injury [3]. We recently discussed these in depth [25]. Among these possibilities, changes to antigen profiles do not appear to play a significant role, given that accommodated organs can bind antibody to the same degree as those at baseline [26]. We also found that donor-reactive antibodies can become less cytotoxic [27] but we have found no confirmation that this occurs in the clinical setting. On the other hand, much evidence supports the concept that organ transplants can become resistant to humoral injury. One hallmark of accommodated organs is C4d deposition without other signs or symptoms of rejection. Complement fixation suggests that antibody binding is intact in accommodated organs, while the lack of lysis implicates some form of regulatory pathway as the basis for graft survival in accommodation.

Defining the pathway by which cells resist lysis has long been an area of interest in accommodation. Previous work at the University of Minnesota had shown that low-dose immunoglobulin can induce accommodation in a hamster-to-rat model [28], and Ding and colleagues recently showed a similar effect with rat-to-mouse heart transplantation [29]. Iwasaki, et al, recently reported that binding of monoclonal anti-HLA class I antibody to cultured human aortic endothelial cells protects the cells against later complement-mediated lysis through induction of antioxidant gene transcription, including heme oxygenase and ferritin H [30]. These changes proceeded through induction of PI3K/AKT and expression of excess Nrf2. These findings suggest that what we call accommodation may not be peculiar to transplantation, but may occur more broadly in response to cell stressors such as hypoxia. This in turn provides an explanation of why *in vitro* accommodation-type changes are cross-protective, as was shown by Reiter with multiple membrane damaging proteins, including complement, streptolysin O, and mellitin [31].

Some changes in accommodation do not reflect resistance to injury so much as resistance to complement activation. Grubbs, et al, first showed that binding of antibody to endothelial cells and activation of complement induces CD59 [32], a protein that regulated complement at the level of C9. Iwasaki, by contrast, found no link between the PI3K/AKT pathway and changes in CD55 or CD59 expression [30]. In contrast, disruption of the terminal complement cascade through C5-neutralizing antibody resulted in long-term renal allograft survival in a mouse model of antibody-mediated rejection [5]. Rother, et al, pre-sensitized mice with skin grafts, then performed renal allotransplantation with grafts from the same strain. This model showed normal binding of graft by alloantibody and early complement components, but substantially less deposition of C5 even after withdrawal of monoclonal antibody therapy.

A large animal model used to test desensitization provides another possible mechanism [33]. Griesemer transplanted wild-type swine kidneys into Galα1-3Gal knockout swine. Depletion of anti-Gal antibodies by pheresis allowed engraftment of wild-type kidneys with histologic evidence of antibody and early complement component deposition. In an elegant demonstration of the graft-centric nature of accommodation, the transplant kidney from this recipient, along with a naive wild-type graft, were placed in a second recipient. Both organs showed antibody and C3 deposition, but only the naive kidney had terminal complement complexes on its endothelium. The authors attributed this resistance to terminal membrane attack complex formation to enhanced expression of CD59 by the accommodated graft. Finally, these findings were redemonstrated by transplanting a wild-type animal into a juvenile knockout animal without first providing plasmapheresis. Spontaneous engraftment and histologic and molecular changes consistent with the pheresed recipient were found. This finding shows that in this model, at least, donor-reactive antibody need not be temporarily reduced for accommodation to ensue. Instead, it is the absolute level of antibody that counts, in that the time needed for antibody induction postoperatively may give the organ the opportunity to engage adaptive mechanisms against injury.

Consequences of Accommodation

We, like others, would consider accommodation a “good” response to transplantation, in that it prevents acute types of humoral injury. However, accommodation may also engender problems for the graft [34]. By preventing acute injury, accommodation allows chronic processes to ensue over time. Of greater concern is the possibility that the same proteins and pathways that protect the graft acutely may injure the graft over months or years. One example of a potential mechanism for chronic change is previous data linking T_H2 T cell phenotypes to accommodated, rather than rejected, grafts [35,36], recently reviewed in [37].

Studying the outcome of renal allografts in cynomologous monkeys treated with various immunosuppressive regimens, Smith et al. [38] found that 22% of grafts surviving 50 days or more developed transplant glomerulopathy. Donor specific antibodies always preceded deposition of C4d in these grafts. This finding is in agreement with the Johns Hopkins series [19]. Furthermore, the authors report that a subset of monkeys with C4d deposition went on to develop transplant glomerulopathy, which was the penultimate step toward graft failure. These data led the authors to conclude that accommodation is an unstable state that can degenerate into chronic allograft nephropathy.

These experimental findings have mixed support from the clinical literature. ABO incompatible transplants have been found repeatedly to have outcomes comparable to ABO compatible transpants [39–41]. However, Toki et al. [42], studying the outcome of 164 ABO incompatible kidney transplants, found that recipients of blood group O had higher incidences of rejection and early graft loss than did patients with either blood group A or B.

Data with regard to the results of desensitization of recipients with antibodies against HLA antigen in kidney transplantation is similarly mixed. Mai and coauthors [43] found that recipients with high PRA and positive flow cytometric crossmatches are at increased risk for antibody-mediated and cellular rejection, but overall graft function was not different between those with and those without anti-donor HLA antibodies. Also of note with regard to this study is that the authors used antithymocyte globulin and IVIG without pheresis for desensitization. Thielke, et al, [44] and Varma et al,[45] also report that those recipients with anti-donor HLA antibodies have increased risk of rejection but comparable graft survival to recipients lacking those antibodies. As such, the question of whether accommodated organs are subject to continued immune toxicity or self-inflicted injury will likely have to wait until a large enough number of uniformly defined and treated patients are accrued for long-term analysis.

Conclusion

Accommodation remains an evolving concept in renal transplantation. As has always been the case in this field, the pressing need to expand the organ pool and maximize the longevity of grafts has driven progress on a number of fronts. Advances in the management of subjects with antibodies against ABO and HLA, may bring progress in the understanding of how frequent or infrequent is accommodation and what, if any, is the biological price paid for that condition. Clinical studies may also provide clues regarding manipulations that permit or even induce accommodation. However, as in other fields, a full understanding of accommodation and broader exploration of what may induce it may require further experimentation in cellular and animal systems.

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