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Accommodation in ABO-incompatible organ transplants

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Abstract

Accommodation refers to a condition in which a transplant (or any tissue) appears to resist immune-mediated injury and loss of function. Accommodation was discovered and has been explored most thoroughly in ABO-incompatible kidney transplantation. In this setting, kidney transplants bearing blood group A or B antigens often are found to function normally in recipients who lack and hence produce antibodies directed against the corresponding antigens. Whether accommodation is owed to changes in anti-blood group antibodies, changes in antigen or a change in the response of the transplant to antibody binding are critically reviewed and a new working model that allows for the kinetics of development of accommodation is put forth. Regardless of how accommodation develops, observations on the fate of ABO-incompatible transplants offer lessons applicable more broadly in transplantation and in other fields.

KEYWORDS
ABO-incompatible transplant, accommodation, blood group, blood type, kidney transplant, rejection

1 | INTRODUCTION

Those who first engaged in the practice of clinical organ transplantation believed that kidney donors and recipients should be compatible for ABO blood groups;[1-4] that is, kidneys from blood group A and/or B donors should not be transplanted into recipients lacking the corresponding antigens. Soon, however, anecdotal experience suggested that ABO-incompatible kidney transplants could be safely performed,[5-7] until shortly thereafter experience suggested otherwise.[8-10] Thus, ~35% of ABO-incompatible kidney transplants never functioned compared with 5% of ABO-compatible transplants. The immediate failure of ABO-incompatible transplants could be caused by ischemia-reperfusion injury or anti-blood group antibodies or anti-HLA antibodies, any combination of which might generate what later would be called hyperacute rejection (Figure 1). Of the ABO-incompatible transplants that did evidence function, at least one half lost function within 3 months (vs <25% of ABO-compatible transplants). These first ABO-incompatible transplants probably suffered early acute, antibody-mediated, or accelerated cellular rejection of both. Figure 2 shows the course of an ABO-incompatible transplant performed in the early 1960s that was probably destroyed by early acute rejection. Approximately 25% of ABO-incompatible transplants performed in that era continued to function however and those were functioning at 3 months survived thereafter as well as did ABO-compatible transplants.[10a] The decades since these early reports have brought significant improvement in the preparation (eg, antibody depletion, screening for anti-HLA), care, and overall outcome of ABO-incompatible kidney transplants; however, results of some surveys still reveal increased susceptibility to early acute rejection followed by a course approaching that of ABO-compatible transplants thereafter.[11-13] Why are some ABO-incompatible kidney transplants suffer devastating and lethal injury during the early weeks after transplantation and what allows ABO-incompatible transplants to avoid ongoing susceptibility to antibody-mediated injury? Below we offer our perspectives on these questions.

2 | AN IMMUNOLOGIST'S VIEW OF ABO-INCOMPATIBLE TRANSPLANTATION

The classic principles of immunology, established by investigation of the interaction of anti-blood group antibodies with target cells bearing the corresponding antigens, would suggest that the outcome of ABO-incompatible transplants should be uniformly poor. Figure 3

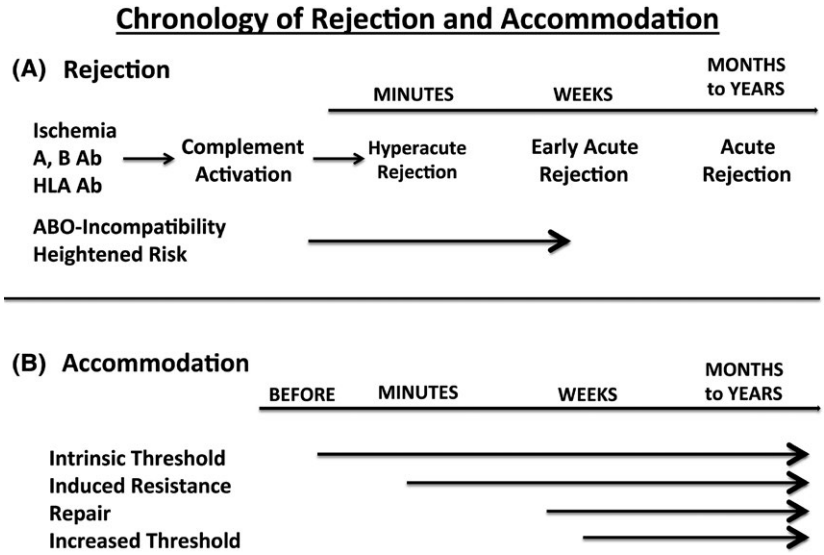

FIGURE 1 Chronology of rejection and accommodation of ABO-incompatible kidney transplants. A, Rejection of ABO-incompatible kidney transplants. Ischemia-reperfusion injury and antibodies directed against donor blood group and possibly against HLA antigens activate the complement system. If complement activation from this combination of factors is robust and fast, hyperacute rejection may ensue within minutes to hours of the time reperfusion. Today, hyperacute rejection is rare because of cross matching and depletion of anti-blood group antibodies. However, lower levels of these antibodies can induce early acute vascular rejection. After several weeks, however, the risk of rejection of an ABO-incompatible graft is no higher than that of an ABO-compatible graft. One explanation for the decrease in the risk of rejection may be "accommodation" of the graft to ongoing presence of anti-blood group antibodies in the recipient. B, Accommodation of ABO-incompatible kidney transplants. ABO-incompatible kidney transplants exhibit heightened risk of antibody-mediated rejection during the first several weeks up to approximately 1 mo after transplantation. This risk reflects the ongoing production of antibodies specific for blood group antigens in the graft. Susceptibility to early rejection (and ischemia-reperfusion injury) is mitigated by intrinsic resistance of nucleated cells and tissues to complement mediated injury and by the immediate response to complement activation on cell surfaces. Over a period of weeks, grafts acquire a higher level of resistance to injury by antibodies and complement. This heightened resistance reflects in part the repair of damage already inflicted and in part changes at the cellular and tissue level that reduce susceptibility to injury. The condition in which a tissue or organ resists otherwise lethal injury by complement or other factors is called "accommodation."

illustrates experiments showing that the concentration of anti-blood group antibodies and the concentration of human complement determine the extent of lysis of human erythrocytes exposed to these factors in vitro. If labeled erythrocytes with anti-blood group antibodies bound to the corresponding antigens are introduced into the circulation, the erythrocytes are rapidly and reliably cleared (Figure 3). Even those with the lowest concentrations of IgM in blood specific for foreign blood group antigens activate complement to a sufficient extent to induce complement-mediated clearance of the erythrocytes.[14,15] If the fate of ABO-incompatible transplants was faithfully modeled by experiments testing interaction of antibodies and complement with ABO-incompatible erythrocytes then one might expect that ABO-incompatible kidney transplants in recipients with appreciable levels of anti-blood group antibodies would exhibit notable complement-mediated changes, if not "lysis."

The targets of anti-blood group antibodies in ABO-incompatible transplants are endothelial cells, and endothelial cells are not faithfully modeled by erythrocytes. One limitation of erythrocytes is the small surface area, particularly as investigated in vivo. The considerably greater surface area of endothelium of a transplant might absorb much or all anti-blood group antibody from blood but, as a result, deposit a lower density of the antibody on surface of each endothelial cell. However, under optimal conditions, a single molecule of IgM bound to the surface of an erythrocyte can initiate activation of complement to a sufficient extent to lyse the erythrocyte[16] and in ABO-incompatibility, the impact of IgM predominates. In this system, 800 IgG molecules must be bound to generate lysis.[17] In an homologous in vivo system, attachment of one molecule of IgM to an erythrocyte could still effect complement-dependent clearance while at least 2000 molecules of IgG had to attach to initiate complement activation.[18] Thus, the greater surface area of endothelium in a kidney cannot by itself explain why ABO-incompatible kidney transplants are not severely injured or rapidly destroyed immediately upon reperfusion by the recipient.

Another explanation for absence of lysis in ABO-incompatible kidney transplants is intrinsic resistance of the transplant and cellular elements of the transplant to complement-mediated injury. Endothelial cells and indeed all nucleated cells are not inert targets for attack by antibodies and complement. Rather, endothelial cells resist complement-mediated injury through various properties of cell membrane and cell metabolism that are less available or unavailable in erythrocytes. The surface of endothelial cells is decorated by acidic saccharides, such as heparan sulfate, and by complement regulatory proteins that slow and potentially block activation of complement.[19] Further, nucleated cells actively dispose of the products of complement activation, profoundly modifying the kinetics

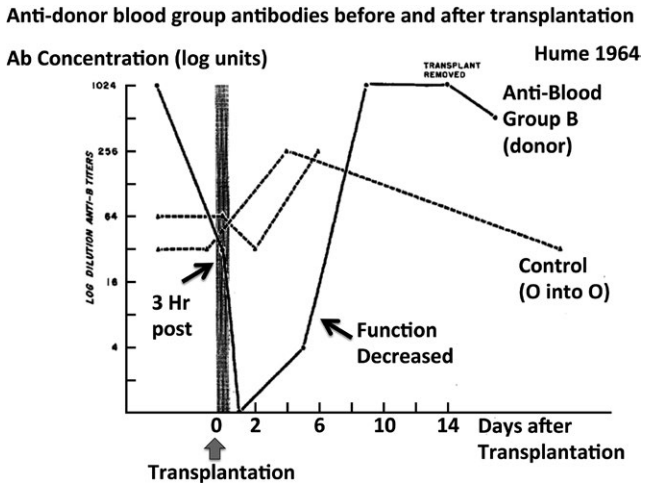

FIGURE 2 Concentration of anti-blood group antibodies in the blood before and after kidney transplantation. Originally published by Hume et al (*Annals of the NY Academy of Sciences* 120: 578, 1964) with permission of the publisher (John Wiley & Sons). The figure (modified for clarity) depicts the concentration of anti-blood group B antibodies (1/titer determined using twofold dilutions, ie, the reciprocal $\log_2$) in a patient of blood group A before and after transplantation of a kidney from a donor of blood group B (solid line). Also shown are the concentrations of anti-blood group B antibodies in two controls, patients of blood group O who received kidney transplants from donors of blood group O (dashed lines). The figure shows that immediately after transplantation, antibodies against donor blood group B are depleted from the blood (arrow; from 1:1024 to ~1:25) and within 12 h are undetectable. The figure also shows that anti-donor blood group antibodies are detected again 5 d after transplantation, likely the time that function deteriorates from rejection. On day 7, urinary output decreased, presumably from rejection. In two controls (blood type O kidneys in blood type O recipients), the levels of anti-blood group B antibodies do not change notably after transplantation. The figure shows that a functioning transplant depletes all or nearly all anti-blood group antibody from a recipient

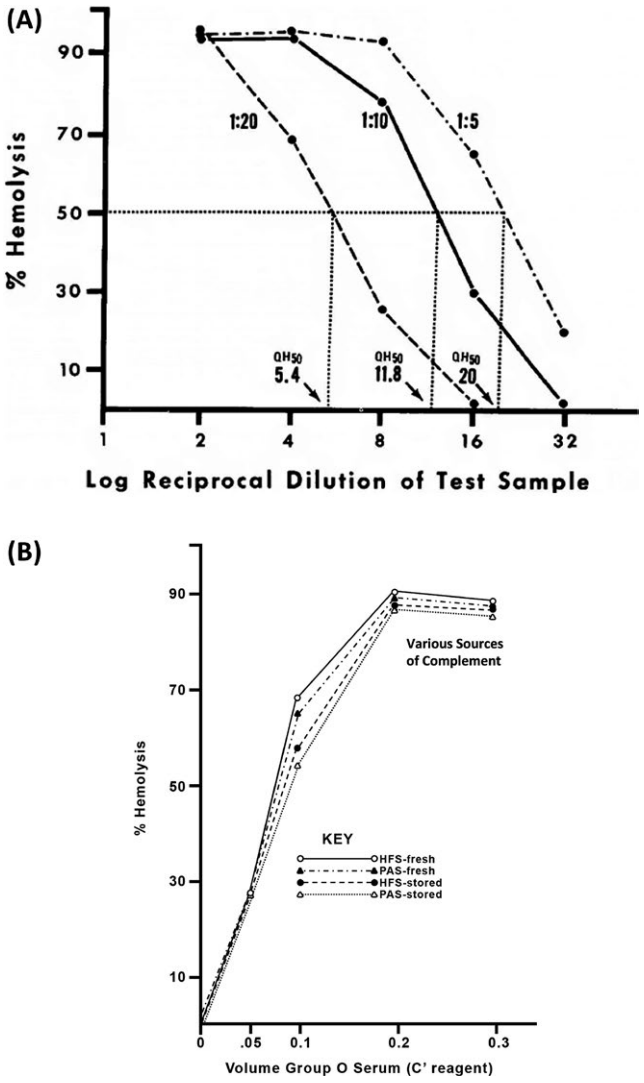

FIGURE 3 Lysis of human erythrocytes by blood group-incompatible serum is a direct function of the concentration of anti-blood group antibodies and concentration of complement. The illustrations are from the US Army Medical Research Laboratory Report #818[90] and are presented with permission of the US Army Medical Research and Material Command. A, Lysis of human erythrocytes is a function of the concentration of anti-blood group antibodies used to activate human complement. Three dilutions of a reference serum, used as a source of anti-blood group A antibodies, were used to determine the QH50, the dilution of a serum that lyses 50% of a standard red cell suspension (QH50) in the presence of excess complement. The QH50 for the three dilutions (shown at the bottom) indicate that lysis is a direct and predictable function of the concentration of anti-A antibodies. B, Assay of various sources of human complement for ability to lyse erythrocytes when combined with serial dilutions of serum from an individual of blood group O. A standard volume (0.1 mL) of serum containing anti-A or anti-B antibodies is combined with various volumes of absorbed human serum lacking anti-A or -B antibodies (ie human complement) and added to a standard preparation of washed A- or B-type erythrocytes. The figure shows that lysis is a function of the amount of human complement added

of injury and introducing the potential for repair.[20-23] Perhaps it is not surprising then that the pathology of hyperacute rejection is not characterized by "lysis" of endothelial cells but rather by ultrastructural changes in plasma membranes (and by "regional" changes such as aggregation of platelets and variable attachment of neutrophils) that reflect fewer membrane attack complexes than are needed for lysis of endothelial cells.[24-27] Thus, activation of complement in an organ transplant sparks a race between the generation and disposal of terminal complexes and the development of hyperacute rejection requires either the rapid and quantitative generation of membrane attack complexes on endothelial cells or the compromise of endothelial cell defenses. The lower density of IgM binding in newly reperfused ABO-incompatible transplants usually cannot overcome endothelial defenses (xenogeneic organ grafts in contrast have intrinsically defective control of heterologous

complement and hence the same levels of anti-endothelial antibodies reliably induce hyperacute rejection).[28] Consistent with this concept, most ABO-incompatible transplants performed before methods for antibody depletion were used did not undergo hyperacute rejection.[10,29]

Most ABO-incompatible transplants performed in the era before antibody removal was performed underwent early acute rejection. Early acute rejection (antibody-mediated and/or accelerated cellular rejection) requires far less complement activation (~10% of level required for hyperacute rejection).[30-34] The activation of smaller amounts of complement on endothelial cells triggers endothelial cell "activation," characterized by changes in blood vessel physiology from hindering to promoting coagulation, inflammation, and vasoconstriction.[31,33]

Classical studies on the fate of erythrocytes with bound antibodies might not faithfully represent organ transplants but they do provide a further explanation for the scarcity of hyperacute rejection of ABO-incompatible transplants compared to the frequency that would be expected in recipients with IgG antibodies against donor HLA. After human erythrocytes are exposed to IgM anti-blood group antibodies in vitro and infused in human subjects, the erythrocytes are rapidly cleared (Figure 4) and potentially destroyed.[14] However, while practically all erythrocytes are removed from the circulation, under some condition erythrocytes with bound anti-blood group antibody are not destroyed and indeed reenter the circulation, surviving as long as control erythrocytes (to which antibody was not bound).[35] In this setting, activation of complement by IgM actually protects the erythrocytes by generating C3d that blocks further covalent attachment of C3 or C4 to the surface. Blocking of reactive sites on endothelium with C3d or C4d might limit the number of membrane attack complexes present at a given time and contribute the low frequency of hyperacute rejection in ABO-incompatible transplantation. However, this mechanism should not prevent development of acute rejection because far less activation of complement is needed to generate that condition.

Given these considerations, why does hyperacute rejection of ABO-incompatible transplants ever occur? Comparison of outcomes of donated left versus right kidneys indicates that kidney donors vary considerably in susceptibility of their kidneys to acute injury.[36-38] The nature of this variation is poorly understood but much of the variation is manifest early after transplantation, especially in susceptibility to ischemia-reperfusion injury. Occasionally, preservation or ischemia-reperfusion injury or concurrent donor-specific anti-HLA antibodies in combination with anti-donor blood group antibodies could increase the activation of complement to an extent to cause hyperacute rejection. Such a concept is consistent with descriptions of the clinical course and pathology of transplants performed in the era before antibody depletion was performed. For instance, in one series of 12 subjects, none of four transplants of kidneys from living ABO-incompatible donors exhibited immediate failure and pathology consistent with hyperacute rejection, whereas 3 of 8 ABO-incompatible transplants from deceased donors in recipients not depleted of antibodies exhibited immediate non-function and inflammation consistent with hyperacute rejection.[29]

As ABO-incompatible transplants are susceptible to early antibody-mediated rejection, it is not surprising that the level of anti-donor blood group antibodies in the recipient at the time of kidney transplantation or before the antibodies are depleted predicts the early outcome of transplants.[11,12,39-43] Consistent with the concepts regarding differential susceptibility to hyperacute and acute antibody-mediated rejection are observations on the transplantation of kidneys from donors of blood group A2. Blood group A2 binds less anti-blood group antibody than blood group A1 and kidneys of blood group A2 rarely undergo hyperacute rejection,[39,44-46] but do sometimes exhibit early acute antibody-mediated rejection and graft loss.[11,47,48]

3 | DEFIANCE OF IMMUNOLOGY IN ABO-INCOMPATIBLE TRANSPLANTATION

In striking contrast to the linear relationship between concentration of antibodies against foreign blood groups and lysis of target cells in vitro, practically no relationship can exist between the levels of antibodies against donor blood groups in the blood of the recipient and the function of an ABO-incompatible kidney transplant (Figure 5), especially after the period of risk of early acute injury has passed. Once an ABO-incompatible transplant is successfully perfused by the blood of the recipient, and function is established for some period, the antibodies implicated in the immediate demise of ABO-incompatible transplants can return to the circulation without harming the transplant. Abrupt increases in the levels of anti-donor blood group antibodies are sometimes observed coincident with rejection, for reasons we later discuss, but, high levels do not foreclose the fate of a graft. One of us first observed this paradox in the 1980s.[49] An individual of blood group O received a kidney from a donor of blood group A. The recipient was depleted of antibodies by plasma exchange before and immediately after transplantation. Over days, however, antibodies specific for donor blood group returned to the circulation and neither the presence nor the level in the blood correlated with the function of the incompatible graft (Figure 5). Others observed a similar phenomenon,[50-53] but no explanation had been offered.

4 | CHANGES IN ANTIBODY IN ABO-INCOMPATIBLE TRANSPLANTATION

Thinking as immunologists, we (and others) believed the most likely explanation for the happy coexistence of the transplant with antibodies directed against donor antigens was that either the antibodies or the antigen had changed in ways that precluded the antibody-antigen interactions observed in vitro or upon reperfusion of the transplant. At the time of transplantation, antibodies specific for blood groups of the donor are clearly capable of recognizing and

(A) RESULTS FOLLOWING THE INJECTION OF GROUP-A OR -B INCOMPATIBLE CELLS

Recipient		*Donor's phenotype*	*Reactions of recipient's serum in vitro*		*Volume of cells injected (ml.)*	*Percentage of injected ^{51}Cr 3 minutes after injection*	
Case No.	*Phenotype*		*Agglutinin titre*	*Haemolysin titre*		*Cells*	*Plasma*
1	A	B	256	12	0.12	<1	99
2	O	A_1	32	nil	0.42	nil	49
		A_2	64*	nil	0.64	3	37

* 18 days after injection of A_1 cells.

(B)

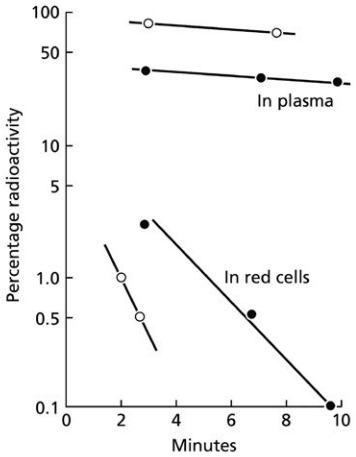

Fig 10.3 Intravascular haemolysis of ^{51}Cr-labelled ABO-incompatible red cells. ○, B cells injected into a group A recipient. ●, A_2 cells injected into a group O recipient (Cutbush and Mollison 1958).

(C)

Elapsed Time		Hemoglobin			Bilirubin T/D (mg./100 ml.)	Anti-A Titer	Haptoglobin (mg./100 ml.)
Hours	Days	Urine (mg.*)	Plasma (mg./100 ml.)	C_{Hb} ml./min.			
zero			?	—	2.1/1.0	1 : 512	8
0.5			123	3.76		1 : 16	
3.0		1025	134	5.63	30.0/6.2	1 : 16	
4.5		377	109	0.5	11.1/6.6	1 : 32	
9.5		158	74	0.1	7.5/4.8	1 : 8	0
19.5		32	51.7		2.5/1.0	1 : 32	

FIGURE 4 Intravascular hemolysis of blood group A- and blood group B-incompatible erythrocytes in human subjects. This figure depicts classic experiments performed to ascertain the mechanism of clearance of blood group A and blood group B erythrocytes administered to human subjects with the corresponding anti-blood group antibodies. Depending on the isotype and concentration of anti-A or -B blood group antibodies and the antigen density and the number of cells administered, clearance might be generated by immediate complement-mediated lysis (intravascular hemolysis) or by sequestration in spleen, liver, or blood. In the examples shown, erythrocytes are labeled in vitro with ^{51}Cr and then a small volume (<1 mL) is given intravenously. A, Intravascular hemolysis of ^{51}Cr-labeled blood group A and blood group B erythrocytes within minutes after administration to subjects with anti-A and anti-B antibodies. Hemolysis occurs even in subjects whose antibody titers are too low to generate hemolysis in vitro. The table is from M. Cutbush and P. L. Mollison, *Brit J Haemat* 4: 115, 1965 with permission of the publisher (John Wiley & Sons). B, Intravascular hemolysis ^{51}Cr-labeled erythrocytes of blood group B administered to a subject of blood group (open circles) and ^{51}Cr-labeled blood group A2 erythrocytes into a subject of blood group O (solid circles). Erythrocytes of blood group A2 have less antigen but intravascular hemolysis still occurs to the same extent (>99%), if slightly less quickly. From Mollison's Blood Transfusion in Clinical Medicine eleventh ed., H. G. Klein and D.J. Anstee (2005), Chapter 10, fig 10.3. C, Laboratory findings after transfusion of 140 mL of blood group A2 erythrocytes into a patient of blood group O. Although the density of blood group A2 antigen is low, sufficient antibody is bound to decrease the concentration 32-fold (1:512 to 1:16) and to cause activation of complement and intravascular hemolysis, indicated by the presence of hemoglobin in plasma and urine. Some erythrocytes were cleared by phagocytosis indicated by the increase in bilirubin. The table is from C. P. Duvall et al *Transfusion* 14: 382, 1974, with permission of the publisher, John Wiley & Sons

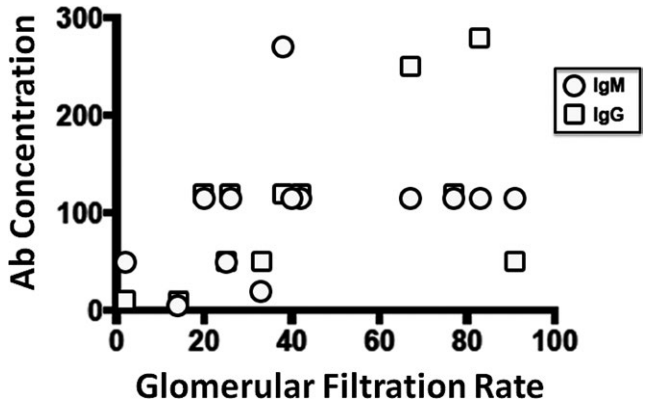

FIGURE 5 Relationship or lack thereof between the concentrations of IgM and IgG specific for blood group A in a kidney transplant and function of the transplant. A patient of blood group O received a kidney transplant from a donor of blood group A, and the levels of IgM and IgG in the recipient specific for blood group A and the serum creatinine (an inverse measure of renal function) were measured at various times after transplantation. Repeated biopsies confirmed the continued expression of blood group A on donor endothelium (not shown). The figure depicts these values at times other than those immediately following antibody depletion. The results reveal absolutely no relationship between the levels of antibodies directed against donor blood groups and the function of the transplant in contrast to the impact of anti-blood group antibodies on erythrocytes depicted in Figures2-4

binding to antigens expressed in the graft as the levels of donor-specific anti-blood group antibodies decrease drastically after reperfusion of transplants. Figure 2 illustrates this phenomenon in one of the first reports of deliberate ABO-incompatible transplantation in a recipient from whom antibody was not depleted (we do not illustrate our recipient because plasmapheresis was performed immediately after transplantation). During the days that follow, anti-blood group antibodies often return to the circulation of recipients regardless of whether antibodies had been depleted at the time of transplantation. The levels in some recipients are below or at the baseline levels before transplantation and the levels in some others "rebound" to exceed the baseline.[42,50,52-54] In some series, the rebound to higher levels is associated with early antibody-mediated rejection. Investigation of levels of antibodies against donor blood groups and B-cell responses has suggested that decreased production of donor-specific anti-blood group antibodies can be detected in graft recipients and the suggestion has been made that perhaps this decrease explains the well-being of ABO-incompatible kidney transplants.[55,56] However, the general experience has been that at least some recipients of ABO-incompatible kidney transplants produce substantial amounts of antibody against the donor antigen and the preponderance of ABO-incompatible transplants contain deposits of C4d, in the absence of impaired function and consistent with ongoing binding of anti-donor antibodies.[57-59] Even more to the point, the extent of antibody rebound after the first weeks appears to have little or no impact on the long-term outcome (Figure 5).[60,61]

One problem that confounds investigation of the levels of antibodies against donor-blood groups in ABO-incompatible transplantation is that at a given point in time the transplant can absorb a substantial amount of antibody against donor blood group antigens (Figure 2). In experimental models, donor-specific antibodies have been quantitatively depleted by perfusion of kidneys expressing antigens of interest.[25,62,63] The absorption of substantial amounts donor-specific antibodies, whether those directed against xenogeneic antigens or blood groups or HLA antigens leaves behind in the blood antibodies of lower avidity for donor antigens or antibodies directed antigens of lower abundance and conceivably removes the antibodies of pathogenic significance. We shall discuss this problem below.

5 | CHANGES IN ANTIGEN IN ABO-INCOMPATIBLE TRANSPLANTS

Could the antigen in the graft change in ways that hinder antibody binding? Based on binding of lectins and monoclonal antibodies specific for human blood groups, we concluded that antigens in the graft did not change.[49,64] Using labeled blood group antigens as probes, we also found that at least some antibodies deposited in the kidney transplants were specific for blood group of the donor[64] (previously, anti-blood group antibodies had been eluted from an ABO-incompatible kidney transplant that was undergoing rejection).[65] On the other hand, the group in Göteborg, which had been conducting numerous ABO-incompatible transplants, also conducted elegant biochemical and immunochemical analysis of neutral glycolipid extracts from transplants.[45,47,53] This work suggested that kidneys from donors of blood group A2, which could be safely transplanted into recipients with anti-A antibodies, contained A2 antigen that was less reactive with anti-A2 antibodies.[45] More pertinent perhaps was the observation that blood group substances could change qualitatively and quantitatively after transplantation, and perhaps these changes could explain the better than expected outcomes.[47,66] We know of no work since then that would dispute the possibility that blood group antigen in transplants changes or decreases over time and that less antibody binds to graft as a result. Nevertheless, our subsequent work would tend to limit the impact of changes in antigen. First, using a foot printing approach to identify carbohydrate epitopes actually bound by antibodies in a related system (antibody binding to Galα1-3Gal on swine cells), we found that even under the most optimal conditions only a small fraction of epitopes are likely occupied by antibody.[67,68] Second, we found that steric hindrance in part limited antibody binding. And, third, and probably most important we found that while antibody binding was likely the limiting event in immediate (hyperacute) rejection, the pathogenesis of which depends on rapid assembly of complement membrane attack complexes, antibody binding does not limit the molecular events that generate acute vascular (antibody-mediated) rejection caused by activation of endothelial cells in the graft.[30,31,69] Antibody and complement induced activation of endothelial cells requires <10%

as much antibody binding as the endothelial changes that underlie hyperacute rejection; therefore, loss of antigen is unlikely to explain absence of antibody-mediated rejection.[70] Thus, neither changes in the antibodies directed against donor blood groups nor in the blood groups expressed in kidney transplants persuasively explained the success of ABO-incompatible transplantation.

6 | ACQUIRED RESISTANCE TO INJURY BY ANTIBODY AND COMPLEMENT

When fundamental principles of immunology failed to explain the success of ABO-incompatible transplantation, we turned to a new biological paradigm—that success might reflect the accommodation of the graft to a hostile environment. The observations in ABO-incompatible transplants in patients appeared to be recapitulated in experimental efforts to prolong the survival of porcine organs transplanted into non-human primates. The xenotransplantation model had the advantage that rejection always occurred if the recipient was not depleted of xenoreactive antibodies but when those antibodies were removed a graft might function for a period of time after antibodies returned to the circulation of the recipient.[63,71] The model allowed us to study the antibodies in serum and the antibodies deposited in functioning grafts.[28,63] This work confirmed the idea that a transplant could undergo changes unrelated to antigen expression that would enable the transplant to resist otherwise devastating immune-mediated injury. We named this change "accommodation".[28]

Accommodation has been observed frequently during the past 25 years. If one applies the definition of accommodation we first used—continued function of an organ transplant despite the presence in the recipient of antibodies against donor antigens expressed in the graft—accommodation is likely to be found in most ABO-incompatible transplants and is likely the most common outcome of such transplants, at least for a time. Accommodation also occurs, although less often, in ABO-compatible transplants when recipients are found to have antibodies specific for donor-HLA.[72-74] The most pressing questions are what generates and what maintains accommodation.

7 | MECHANISM(S) OF ACCOMMODATION

Although antibodies directed against blood group antigens of the donor clearly could initiate severe vascular rejection, what changes could make a graft inured to the presence of such antibodies in a recipient was unknown when ABO-incompatible transplantation was pursued in the 1980s. Two possibilities considered at the outset were as follows: (i) that transplantation inflicts injury that renders a kidney highly susceptible to antibody and complement but repair of this injury engenders resistance; and (ii) that sublethal injury would induce a condition of increased resistance to cytotoxicity.[28] We think both concepts are correct at least during the initial hours and days after transplantation. Thus, protective factors are essential to overcoming the ischemic injury inevitably suffered during transplantation. Moreover, the cytoprotective factors, such as HO-1 expression [75] and AKT activation,[76] must be induced or activated if the new transplant is to survive (Figure 1). However, while cytoprotection is essential for accommodation to occur, cytoprotection is not the process that sustains the function of transplants under persistent assault by antibodies and complement or other noxious factors. Nor do heightened expression cytoprotective genes and proteins determine the ultimate outcome of transplants.[54,77,78]

Rather, we have explored and will soon report other processes and changes we think sustain the functional integrity of transplants in the face of ongoing attack by complement and noxious substances and hence represent accommodation manifest in ABO-incompatible transplants, as listed in Figure 1. This new model of accommodation springs from clinical observations of ABO-incompatible transplants suggesting that a period of vulnerability countered by transient induced cytoprotection is followed by ongoing loss of vulnerability reflecting persistent cellular and biochemical changes. We believe this model might have broader application as discussed below. This model, actually a working hypothesis, shown in Figure 1 accounts for molecular and physiologic changes that would prevent or reverse: (i) the immediate or hyperacute rejection; (ii) the "early" irreversible rejection observed within the first weeks after transplantation; and (iii) processes that confer ongoing repair and a new higher threshold for injury lethal injury from complement and phagocyte activation. The delayed onset of increased capacity for repair may reflect in part changes in the biosynthesis of antibody engendered by earlier interaction of antibodies and complement and phagocytes with antigen targets.[79] The increased threshold for injury may reflect in part remodeling of blood vessels and supporting structures.[80]

8 | SOME LESSONS FROM ACCOMMODATION OF ABO-INCOMPATIBLE TRANSPLANTS

The discovery and investigation of accommodation in ABO-incompatible transplantation have brought insights and lessons potentially applicable more broadly in transplantation and in other fields. We shall discuss a few of these in closing.

One lesson, mentioned above, concerns the possibility that antibodies, or absence thereof, in the blood of a transplant recipient might misrepresent the state of immunity to the donor and the presence or absence of accommodation. As shown above in Figure 2 and in many experimental settings, ABO-incompatible transplants can absorb donor-specific antibodies from the circulation. Therefore, the level of donor-specific antibodies in the blood does not necessarily reflect the level of antibody produced or the amount bound to the graft. At an extreme, a recipient with no detectable donor-specific antibodies in blood might nonetheless produce antibodies that bind to and act on the graft. To test the possibility, we examined donor-specific B-cell responses in a series of (ABO-compatible)

kidney transplant recipients that had no appreciable donor-specific antibodies in their blood.[81] All of these subjects (and nearly all others examined since) had donor-specific B-cell responses characterized by secretion of donor specific IgM and sometimes donor-specific IgG during the first several months after transplantation. Absence of these antibodies in the blood probably reflected absorption to the transplant and accommodation to the bound antibody. Consistent with this possibility is the low titer of donor-specific blood group antibodies in many recipients of ABO-incompatible kidney transplants and the high frequency of C4d deposits in ABO-incompatible transplants with unimpaired function,[57-60] the combination of which suggests accommodation.

As another lesson, the studies on C4d in ABO-incompatible transplantation and the classical work on the fate of erythrocytes with bound anti-blood group IgM[35] should remind us that C4d is not pathogenic. Every site with covalently bound C4d is unavailable for reaction with C3 and C4 and hence protected.[82] If C4d sometimes marks the presence underlying disease, it also marks accommodation and mechanistically the inert property of C4d is more in keeping with accommodation.

Another lesson emerging from investigation of ABO-incompatible transplantation and later from investigation of xenotransplantation concerns the appreciation that the processes involved in rejection and accommodation also function in the broader context of host defense. The responses of blood vessels to activation of complement (and/or interaction with activated phagocytes) characteristic of rejection reflect initial physiologic responses to foreign agents and noxious conditions.[19,80,83] At sites where an infectious agent or toxin is located, the responses wall off microorganisms or toxins, preventing systemic spread (the problem in transplantation is that the assault and the response is diffuse in the grafted organ). The processes we think reflect accommodation, then, are likewise orchestrated to reverse the physiology introduced by the initial defenses once the organism or toxin is destroyed. The "delay" of days or even weeks in the onset of accommodation is consistent with that concept. Viewed in this way, accommodation is not merely the resistance to injury we first imagined but is better envisioned as a process that repairs injury and regenerates tissue functions. Understood in this way, one can see how accommodation enables cancer cells to not only survive but also to expand and progress in hostile microenvironments and in the face of immune surveillance.[84-86]

As one final "lesson" or hypothesis, we would suggest that if ABO-incompatible transplants are accommodated to ongoing production of anti-blood group antibodies, then one cause of rejection could be the loss or diminution of accommodation, as might occur with intercurrent illness or infection. How would rejection owed to diminution of accommodation be manifest? We think one manifestation would be loss of ability to absorb and metabolize donor-specific antibodies leading to the reappearance or to an increase in the level of donor-specific antibodies in blood. If this concept is correct then graft injury or disease would precede rather than follow increases in the level of antibodies specific for donor blood groups. Such an order of events—graft injury followed by increases in donor-specific antibodies—has been observed in the clinical setting for donor-specific anti-HLA antibodies[87,88] and in the setting of experimental organ xenografts for anti-Gala1-3Gal antibodies.[34,89] Conversely, restoration of accommodation would be marked by a decrease in anti-donor antibody levels in blood. From this perspective, donor-specific antibodies in blood could mark existing graft injury and represent a late and not an early indication of antibody-mediated injury. Because ABO-incompatible transplantation crosses a barrier comprised by well-defined antigens and antibody responses to those antigens in immune competent recipients, that setting should be ideal for testing hypotheses such as this one regarding accommodation. Although relatively infrequent, these transplants might thus shed light on avenues, besides immunosuppression, for treatment of autoimmunity and transplant rejection and new opportunities for targeting cancer and chronic infection.

ENDNOTE

[a]The outcomes were extrapolated from The Kidney Transplant Registry report of 1967[10] for living donor transplants; the results of deceased donor transplants were so poor, little sense could be distilled.

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