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The Role of Antibodies in Transplantation

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Abstract

For the past forty years T-cells have been considered the primary threat to the survival of allografts. However antibodies can induce severe vascular disease of organ transplants and this disease, particularly “antibody-mediated” rejection, has become a major clinical challenge. Not only do antibodies cause rejection, the rejection caused by antibodies resists treatment by conventional drug regimens. On the other hand, antibodies can induce a condition in which grafts seemingly resist antibody-mediated injury, which is accommodation. In this communication we discuss the role of antibodies in the diagnosis and pathogenesis of rejection and accommodation, and suggest what we consider the major gaps in knowledge and directions research into this subject might productively take.

To what extent and by which mechanisms antibodies determine the fate of transplants has been unsettled for decades. Early experiments in tissue transplantation sought to link destruction of allografts with the production of antibodies in the recipient directed against the donor (1). Gorer (2,3) did connect the fate of tumor grafts with the production of allospecific antibodies but these antibodies were never shown to actually cause injury. Antibodies were clearly implicated in the destruction of transfused erythrocytes of incompatible blood groups; however, anti-blood group antibodies had no apparent impact on the fate of skin allografts in which incompatible blood groups were expressed (4,5). Because antibodies could not be shown to destroy allografts some questioned whether destruction of allografts had an immunological basis. Medawar and Gibson (6) found that skin transplants repeated from the same donor to the same recipient fail to engraft and they took the hastened loss of viability to indicate that immunity caused graft injury, but subsequent efforts to identify antibodies responsible for graft destruction failed. Later, Mitchison (7) found that cells rather than antibodies caused the destruction of allografts and immunologists focused on cellular immunity as the primary threat to graft survival. The development of drugs and regimens that are able to successfully suppress cellular immunity has led to a renewed interest in the problems in organ allografts that are caused by antibodies and now that subject is at the forefront of clinical transplantation (7). Below we explain why antibodies have little or no impact on the fate of cell and tissue grafts but profoundly influence the fate of organ grafts.

Transplant type and susceptibility to antibody-mediated injury

Transplanted foreign tissues and organs engender both cellular and humoral immune responses of similar quality and intensity; the impact of those responses on a transplant depends to the greatest extent on whether the transplant consists of cells, tissues or organs (8). All types of

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transplants are susceptible to cellular rejection. Transplants differ profoundly, however, in susceptibility to humoral rejection. The differential susceptibility to humoral rejection reflects in large part the way in which the transplant receives its vascular supply (Figure 1). Isolated cells, such as hepatocytes, derive their vascular supply entirely from the host (9). Antibodies of the recipient do not bind to blood vessels of such cellular grafts and antibodies may penetrate poorly through the blood vessels feeding the grafts. Free tissues, such as skin and pancreatic islets, derive their vascular supply both by the in growth of host blood vessels and the spontaneous anastomosis of graft and host capillaries. Antibodies of the recipient may bind to donor segments of these vessels but not to segments derived fully from the recipient. Organ grafts such as heart, kidney, liver and lung receive blood flow from the surgical anastomosis of donor and recipient vessels and the graft is fed entirely through a foreign vascular system. Antibodies of the recipient can bind to these foreign vessels. Thus, antibody-mediated injury is observed in organ grafts to a much greater extent than in cell or tissue grafts. Furthermore, because immunoglobulins are largely confined to vascular spaces, alloreactive antibodies have minimal direct impact on parenchymal cells (9,10).

Figure 2 lists the various types of vascular disease and conditions caused by antibodies in relation to when they occur after organ transplantation. Below we discuss the various conditions caused by alloreactive antibodies after organ transplantation.

Hyperacute rejection

Hyperacute rejection of clinical organ transplants was first described by Kissmeyer-Nielson et al. (11). Hyperacute rejection occurs within 24 hours of reperfusion and is characterized by immediate or near immediate loss of graft function and by a pathologic picture of interstitial hemorrhage, microthrombosis and, to a varying extent, inflammation. Hyperacute rejection is thought to be triggered when anti-donor antibodies bind to blood vessels and activate the complement system in a newly transplanted organ.

Hyperacute rejection of clinical allografts is most often caused by anti-HLA antibodies. Hyperacute rejection is observed in up to 80% of the kidneys transplanted into recipients with cytotoxic antibodies detected by cytotoxic cross match (12) and known to be directed predominantly toward HLA. The risk of hyperacute rejection when these antibodies are present, as defined by complement-dependent cross-matching, is significantly higher than the risk of hyperacute rejection of ABO-incompatible grafts (12). The risk of hyperacute rejection from anti-HLA antibodies may appear less today because assays such as fluorescence-activated cell sorting (FACS) cross-detect lower levels of these antibodies and are better able to detect antibodies that fix complement less effectively (9). Although the relative risk of hyperacute rejection depends on the cross match assay used and the titer of antibodies, a positive cross-match is generally viewed as a contraindication to transplantation.

Hyperacute rejection can also be caused by antibodies directed at allogeneic blood groups A and B. Gleason et al. (13) found that 46% of ABO-incompatible allografts never gained function and at twelve months only 1 of 24 ABO-incompatible renal transplants continued to function, whereas only 9% of a large group of ABO-compatible grafts did not show early function. However, many of these transplants do not suffer hyperacute rejection but rather succumb to acute humoral rejection.

Whether anti-blood group antibodies cause hyperacute rejection depends on such factors as the antibody levels, affinity of particular antibodies and the susceptibility of the graft to injury. For example, the A2 antigen interacts less well with anti-A antibodies; hence, organs expressing A2 transplanted into recipients of blood group O are far less susceptible to destruction by humoral responses (14).

ABO incompatible organs vary in susceptibility to hyperacute rejection. ABO-incompatible liver transplants are less susceptible to hyperacute rejection than ABO-incompatible kidney or heart transplants (15). Gordon et al. (16) retrospectively examined liver transplant recipients and found that the three year graft survival rate for ABO-compatible grafts and ABO-incompatible grafts was remarkably similar, 39% and 36% respectively. We surmise that differences in the size of the vascular beds may explain the varying susceptibility, as a given amount of antibody and complement would be deposited less densely in the liver than in a smaller organ such as the kidney. The liver also intrinsically resists injury by complement (17,18).

Hyperacute rejection may occur in some recipients appearing to lack anti-donor antibodies. In some cases antibody capable of binding to and injuring the graft may be present but is not detected by assays in which leukocytes are used as the target. For example, antibodies specific for major-histocompatibility-complex class I-related chain A antigens, which are not expressed on leukocytes (10) but are expressed on endothelial cells, have been found to be cytotoxic in the presence of serum complement (19). As another example, antiendothelial cell antibodies have also been linked to rejection in HLA- identical sibling transplants (20). In other cases the recipient may truly lack anti-donor antibodies and complement may be activated by the alternative and/or lectin pathways without the involvement of antibody.

Pathogenesis of hyperacute rejection

The pathogenesis of hyperacute rejection depends absolutely on the activation of complement (21). In fact, a substance or drug that impairs the activation of complement prevents hyperacute rejection. Brauer et al. (22) found that hyperacute rejection does not occur when discordant cardiac xenografts are transplanted into complement-deficient rats, while hyperacute rejection always occurs when transplanted into wild-type recipients. Cobra venom factor, which consumes complement by activating the alternative pathway, prevents hyperacute rejection in rodents, canines, and non-human primates (23). Soluble CR1, a recombinant protein that causes the dissociation of C3 convertase complexes leading to the inhibition of the classical and alternative pathways prevents hyperacute rejection in rodents and non-human primates (24). Expression of very low levels of complement regulatory proteins likewise can prevent hyperacute rejection (25). Although cobra venom factor and sCR1 are quite effective, they are not used in the clinical setting because they prevent complement from contributing to host defense.

Complement activated through any pathway (classical, alternative, or lectin) can initiate hyperacute rejection. In some combinations of xenogeneic species, such as guinea pig transplants into rats, complement is activated by the alternative pathway without involvement of antibodies (26). In clinically relevant settings, swine grafts into non-human primates and human allografts, complement is activated through the classical pathway by antibodies directed against donor cells (27). Bound IgM or IgG fixes C1q and the C1r and C1s subunits are activated. Activated C1s cleaves C4 and C2. C4b and C2a associate to generate C4b2a or C3 convertase which ultimately cleaves C3 and leads to terminal complement activation. Some antibodies can activate complement through the alternative pathway (they may do so in part by impairing the ability of factor H to regulate C3b) (28,29); the relevance of this mechanism for clinical transplantation has not been explored. Hyperacute rejection can occur independent of anti-donor antibodies and these cases may reflect activation of the alternative or lectin pathways as might occur with ischemic injury (30,31). Thus, prolonged preservation and high perfusion pressures in allografts can cause lesions that are pathologically similar to those found in hyperacute rejection (32,33).

Regardless of how complement is activated, it is the terminus of the complement cascade that triggers the pathological processes leading to hyperacute rejection (21,34). Consistent with this concept, Brauer et al. (22) found that rats lacking C6, needed for formation of terminal complement complexes but not for activation of complement, do not hyperacutely reject xenografts.

Terminal complement complexes injure tissues through several mechanisms. When produced rapidly and in large numbers, terminal complement complexes can cause lysis of cells. In the case of endothelial cells, lysis would presumably trigger massive loss of blood into interstitium and the aggregation and adhesion of platelets to the underlying matrix. Although lysis of some endothelial cells undoubtedly occurs, the ultrastructure of hyperacute rejection usually reveals largely intact endothelial cells (35). Our studies of endothelial cells in culture suggest an alternative mechanism. Insertion of terminal complement complexes in sublytic amounts causes endothelial cells to retract from each other, exposing the underlying matrix to elements of the blood (34). As a consequence, platelets can adhere and blood elements exit the vascular space. Formation of platelet thrombi and attenuation of blood flow presumably ensue. Consistent with this mechanism, tissue with hyperacute rejection often show evidence of ischemia rather than “lysis” as the predominant injury (32).

Antibody-mediated rejection

The most vexing clinical condition caused by antibodies in organ transplants is “antibody-mediated rejection” (7,36). Antibody-mediated rejection was previously known as “humoral rejection” and before that as “acute vascular rejection.” Most cases appear to be caused by antibodies and therefore the term antibody-mediated rejection is used. However, the term antibody-mediated rejection may be misleading as this type of rejection can occur in the absence of anti-donor antibodies and in some cases this condition may arise without the involvement of ‘humoral’ factors (37).

Anti-donor antibodies such as those directed at major histocompatibility antigens likely trigger antibody-mediated rejection. The time when antibody-mediated rejection occurs after transplantation depends mainly on the time when anti-donor antibodies are produced (29). In the absence of immunosuppression, antibody-mediated rejection can begin within twenty four hours of transplantation and proceed over days if the recipient is sensitized to donor antigen. In immunosuppressed recipients antibody-mediated rejection usually appears weeks or months after reperfusion.

Evidence of antibody-mediated rejection can be found in 20–30% of episodes of acute rejection (38), but the diagnosis of antibody-mediated rejection is sometimes challenging. Although antibodies specific for the donor are sometimes found in the circulation, such antibodies are not often found, at least not at high levels. The absence of anti-donor antibodies can not be taken to exclude antibody-mediated rejection because an organ graft can absorb tremendous amounts of antibody leaving little or none left in the blood (39). Also, the antibodies found in the blood may be of lower affinity and thus may not represent the antibodies bound to the graft and those that cause tissue injury. Further, as mentioned above, some antigens may be poorly expressed on the peripheral leukocytes typically used to detect anti-donor antibodies.

Because of the limited value of measuring anti-donor antibodies, pathologists have turned to the detection of C4d as diagnostic evidence of antibody-mediated rejection (40). Collins et al. (41) demonstrated that C4d deposition in peritubular capillaries was present in biopsies from human transplant recipients with circulating donor-specific antibodies, strongly suggesting that C4d is a specific and reliable indication of antibody-mediated rejection following kidney transplantation. Formed by cleavage of C4b covalently bound to target cells, C4d is functionally inert and hence, a relatively enduring footprint of complement activation. Since

C4 can be activated during activation of the classical pathway, the presence of C4d on the endothelium of a graft is taken as evidence that anti-donor antibody may have bound to that site. However, C4d is also generated during activation of the lectin pathway; hence, it might be found in some conditions in which anti-donor antibodies do not exist. More importantly, C4d can be found in accommodation, a condition in which the graft dramatically resists injury caused by antibody and complement (42). Given these considerations, we do not consider C4d to specifically mark antibody-mediated rejection and would seek some other evidence of this condition before therapy is undertaken.

Pathogenesis of antibody-mediated rejection

Antibody-mediated rejection is characterized pathologically by focal ischemia, severe injury to the endothelial cells lining blood vessels in the graft and diffuse intravascular coagulation. Antibody-mediated rejection is thought to be caused by endothelial cell activation in the graft (37,43). Normal, resting endothelial cells inhibit coagulation through expression of such anticoagulant molecules as thrombomodulin and heparan sulfate proteoglycan (44,45). The binding of anti-donor antibodies to endothelium in the graft and the activation of complement disrupt the quiescent state and causes the endothelium to become activated. Activated endothelial cells promote coagulation by shedding thrombomodulin and heparan sulfate proteoglycan and subsequently expressing tissue factor (46). Inflammation is promoted by activated endothelial cells which induce expression of cell adhesion molecules and cytokines (46–49). Complement induced coagulation and inflammation both appear to be governed by transcription and production of IL1 α and by the availability of that cytokine to act in local blood vessels (48,50,51). Coagulation and inflammation impair the flow of blood through regions of the vasculature and this impairment probably accounts for the pathological manifestations of antibody-mediated rejection, which are most consistent with ischemia.

Accommodation

Accommodation refers to an acquired resistance of an organ graft to humoral injury. It was first described and later named based on observations of the outcome of ABO-incompatible kidney transplants (21,52–54). Thus, in the mid 1980's several investigators observed that if anti-blood group antibodies were removed from the circulation at the time of transplantation, kidneys transplanted across blood group A or blood group B barriers can survive and function (55,56). This suggested that incompatibility of blood groups was not necessarily an absolute barrier to transplantation and prompted the question of how these kidneys survived. It had been shown that some recipients had antibodies specific for donor blood groups and the transplanted kidneys continued to express donor antigen; but graft injury and compromise of function did not occur (53). This observation suggested that the survival of the graft must reflect some change in the graft itself.

Based on our original definition of accommodation as a condition in which a graft recipient has antibodies directed against the graft but injury and/or dysfunction does not occur, one might conclude that accommodation is relatively infrequent (21). This conclusion may be incorrect (57). Healthy organs can absorb anti-donor antibodies in large amounts, removing those antibodies from the circulation and hence more recipients may make anti-donor antibodies than surveys of the prevalence of the antibodies would suggest. Thus, we envision that accommodation of some transplants may occur in recipients having no detectable anti-donor antibody (57), in part because the functioning graft serves as a 'sink' for that antibody (39). As an extension of this idea, we might imagine that the higher levels of antibodies typically associated with vascular rejection may represent a consequence of rejection rather than a cause. Thus, the organ damaged by antibodies and complement is less able to absorb antibodies from the blood and therefore the level of those antibodies increases.

While we named accommodation based on the idea that the condition reflects a change in the graft, we recognized that other mechanisms might contribute to graft survival across a humoral barrier (21). Thus, accommodation might reflect a change in the properties of the antibody or the antigen. Both of these mechanisms have been observed in experimental models. Under some conditions the Ig subclass of anti-donor antibodies does not efficiently fix complement (34) and may even block the binding of complement fixing antibodies (25). In other conditions carbohydrate antigen may be shed (58) or undergo biochemical change (24) and therefore might be less avidly bound (59).

While these models may apply in some cases, most studies suggest that accommodation reflects resistance to injury. Nath et al. (60) showed that exposure of an organ to heme induces heme oxygenase, which can protect the organ against lethal injury by various toxins (consistent with a heterologous mechanism). Bach et al. (61) found that xenografts and Hancock et al. (62) determined that allografts with accommodation express a number of “protective”, anti-apoptotic genes. Products of these genes may prevent cells of the graft from undergoing apoptosis that otherwise might be triggered by humoral immunity. Consistent with this concept, Delikouras et al. (63) found that exposure to xenoreactive antibodies induces expression of anti-apoptotic genes in endothelial cells. Jindra et al. (64) found that anti-HLA antibodies likewise induce such genes. On the other hand, Park et al. (65) found that cytoprotective genes may not be expressed at higher levels in ABO-incompatible allografts and Williams et al. (66) found these genes expressed at higher levels in grafts with rejection than in xenografts with accommodation. Further understanding of how accommodation is induced and by what mechanisms it is manifested and maintained could have a profound impact on transplantation in general and perhaps on other fields.

Chronic rejection

Chronic rejection, more than any other condition, limits the long-term success of solid organ transplantation. Chronic rejection or chronic graft dysfunction may be caused by one or more of a number of processes, particularly repeated inflammation and injury from both immune- and non-immune-mediated causes. Here we use the term ‘chronic rejection’ to refer to chronic graft dysfunction caused by an immunological reaction and the term chronic allograft dysfunction to refer to dysfunction caused by drug toxicity, ischemia, aging or other non-immunological processes. While the clinical and biochemical signs are organ-specific, the result of chronic rejection or dysfunction is the same for all solid organ allografts. Obliterative vasculopathy, infiltration of leukocytes, luminal occlusion, and a marked fibrotic response are the hallmarks and are believed by some to lead to structural deterioration and loss of function (67).

Up to 60 % of chronic dysfunction of organ transplants is thought to be caused by anti-donor antibodies (68). Piazza et al. (69) found that circulating anti-donor HLA antibodies correlate strongly with chronic rejection. Lee et al. (70) found that de novo anti-HLA antibodies are always present prior to the loss of a graft from chronic rejection. Whether anti-donor antibodies actually cause chronic rejection or reflect a response to a damaged graft caused by other factors (and hence the antibodies simply mark dysfunction) has not been determined.

The presence of C4d deposits seen in chronic graft dysfunction has been taken to implicate humoral immunity in the loss of graft function. Lederer et al. (71) found that 64% of subjects with chronic rejection had C4d-deposits in graft biopsies. Mauiyyedi et al. (68) examined transplant recipients undergoing chronic rejection and found that all of those with donor specific antibodies at the time of biopsy also had C4d deposits and 90% of those positive for C4d also had anti-donor antibodies. C4d deposits precede and predict the development of chronic allograft glomerulopathy, a feature of chronic rejection in the kidney (72). C4d may

then have the ability to separate chronic allograft rejection from chronic injury of other etiologies. On the other hand, we speculated that C4d may mark the condition of accommodation and that this condition may allow an organ to survive long enough to suffer chronic injury from some other cause (42). Of equal concern is the possibility that accommodation might itself engender chronic changes which lead to chronic graft dysfunction marked by the presence of C4d (42,57,73).

Concluding remarks

Antibody-associated injury is now widely considered a central challenge in the field of transplantation. The perception of this challenge attests to and may even result from the successful application of therapeutics that control the cellular immune responses to transplantation. Given the impact of this challenge one is tempted to focus on the development of therapeutics that might control humoral immunity to transplantation. While we look forward to such advances, we hope investigators will continue to ask how humoral immunity injures grafts and in some cases whether humoral immunity injures grafts. We have summarized what seems like abundant information about how humoral responses induce hyperacute rejection. The importance of antibodies in this setting is beyond question (although we do suggest that exceptional circumstances may activate complement without involvement of antibodies). We also mention that some evidence connects anti-donor antibodies with what used to be called acute vascular or acute humoral rejection. For this condition we have cautioned that the involvement of antibodies is less certain and have even suggested that one might be wise to use older terminology until we know how often antibodies actually cause acute rejection.

We have urged even more caution about the conditions of accommodation and chronic rejection or chronic graft dysfunction. Since anti-donor antibodies appear to induce accommodation, at least in some cases, one might want to refrain from considering all humoral responses pathogenic. And someday we may even find chronic graft dysfunction to be a biological price paid for accommodation. These possibilities impel us to hope that investigators will focus as much energy and resources on understanding how antibodies modify the course of allotransplants as on the devising of therapeutics to impair antibody production.

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Figure 1. Mechanisms of graft vascularization

Isolated cellular grafts are vascularized entirely by in-growth of recipient blood vessels (top). Free tissue grafts are vascularized partly by the in-growth of recipient blood vessels and partly by the spontaneous anastomosis of graft and host capillaries (middle). Organ grafts are vascularized by the surgical anastomosis, the graft itself being supplied by donor vasculature (bottom).

Figure 2. The impact of antibodies on the outcome of transplantation

(a) Organ transplantation can lead to one or more of the conditions listed in this figure. The conditions are shown according to the time of occurrence after transplantation. Hyperacute rejection occurs within 24 hours of reperfusion and is caused usually by antibodies already present in the recipient at the time of transplantation. Antibody mediated rejection (also known as humoral or vascular rejection) occurs days, weeks or months after transplantation and is caused at least most of the time by antibodies produced after transplantation. Accommodation refers to acquired resistance of a transplant to humoral injury. Accommodation may be induced by anti-donor antibodies. Chronic rejection may be caused by antibodies in some cases.

(b) Tissue or cell transplants are subject to failure caused by primary non-function or by cellular rejection but usually not to injury caused by antibodies.