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Accommodation in Organ Transplantation

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Abstract

Purpose of review—We review recent insights into the mechanisms and prevalence of accommodation. Accommodation refers to an acquired resistance of an organ graft to humoral injury and rejection.

Recent findings—Accommodation has been postulated to reflect changes in antibodies, control of complement and/or acquired resistance to injury by antibodies, complement or other factors. We discuss the importance of these mechanisms, highlighting new conclusions.

Summary—Accommodation may be a common, perhaps the most common outcome of organ transplantation, and in some systems a predictable outcome of organ xenotransplantation. Further understanding of how accommodation is induced and by what mechanisms it is manifest and maintained could have a profound impact on transplantation in general and perhaps on other fields.

Keywords

Xenotransplantation; allotransplantation; antibodies; complement; endothelial cells; accommodation

Introduction

In the 1980s, we [1] and a few others [2] studied kidneys transplanted across blood group A or blood group B barriers in humans. Although the prospect of ABO-incompatible transplants was then considered poor, the others and we found that if anti-donor antibodies were removed from the circulation at the time of transplantation the transplanted kidneys might survive and function for extended periods of time. These observations suggested that compatibility of blood groups need not pose a profound barrier to transplantation, and prompted us to question of how these kidneys survived. It had been shown that although some recipients had antibodies specific for donor blood groups, the transplanted kidneys continued to express donor antigen without incurring rejection [3]. Based on these findings, we reasoned that some condition heretofore unrecognized allowed the survival of the kidneys across a humoral barrier that otherwise should have been nearly insurmountable. We subsequently called this condition “accommodation” and reasoned that induction of accommodation, whatever it may be, might allow the clinical application of xenotransplantation [4].

ABO-incompatible transplantation has been proposed as a model for xenotransplantation [5–8], and during the ensuing decade, the occurrence of accommodation was linked to one or more phenomena (Figure 1). These phenomena are still considered as potential mechanisms of accommodation, as a review of recent literature will show.

Potential Mechanisms of Accommodation

Because we consider accommodation a fundamental biological process [9] and because one may want to induce accommodation deliberately or in advance of transplanting an organ, we have emphasized the importance of understanding the mechanisms that bring about accommodation [10]. Below we discuss and summarize recent insights into mechanisms of accommodation.

Change in antibodies

Accommodation might result from a change in the effector properties of antibodies directed against the donor; such a change might limit the damage to the graft those antibodies cause [4,11]. Yu et al. [12] found that human IgG2 specific for Gal α 1-3Gal blocks activation of complement on target cells by blocking the binding of complement-fixing IgM and other IgG. Mohiuddin et al. [13] found that a transition from complement fixing to non-complement-fixing isotypes occur in the context of transplantation, and speculated that this change might explain accommodation. Conceivably, this transition could be sparked by immune deviation toward a Th2 phenotype after xenotransplantation [14].

Recent work suggests this mechanism might indeed mitigate graft injury. Galili [15] reviewed work in his laboratory that had suggested that stimulation of B cells in the absence of T cell help might generate antibodies which bind but do not injure grafts. This conclusion was reached using a model system in which mice deficient of α -1,3-galactosyl transferase (such mice, in contrast to wild type mice, do not make Gal α 1-3Gal and do make anti-Gal α 1-3Gal antibodies) [16] are transplanted with pig kidney membranes to stimulate immunity and then with hearts from wild type mice.

As interesting as the evolution of effector properties of immunoglobulin may be as a means by which tissue injury is limited, we no longer consider this phenomenon a primary mechanism of accommodation [17]. If a change in effector properties of an immune response occurs, we would prefer to think such a change reflects a type of immune regulation and is best understood in that context, allowing us to consider accommodation as a distinct entity better described as acquired resistance of a graft to injury [9]. Moreover, studies of clinical allografts, including ABO-incompatible transplants [18] and swine-to-primate xenografts by us [19,20] and by others [21], have not revealed a shift in the effector properties of antibodies directed against the graft in conjunction with accommodation. Indeed, careful analysis reveals these grafts contain C4d, indicating that antibody binding and initial steps in complement activation have occurred [18,22].

Change in antigen

Accommodation might reflect a change in the properties or expression of antigen targeted by anti-graft antibodies. Ulfvin et al. [23] reported that kidney allografts undergo a change in glycolipid metabolism over time. Yuzawa et al. [24] showed that glycoprotein and glycolipid antigens can undergo modulation following antibody binding; they speculated these changes might explain accommodation. We found that antibody binding to Gal α 1-3Gal depends on the positioning of that saccharide among the components of the cell membrane and glycocalyx [25,26]. However, past [27] and recent studies in xenotransplantation suggest that accommodated organs can bind antibody to at least the same extent as normal organs [28]. Hence, modulation of antigen or change in antigen

synthesis, while occurring in some settings, does not explain accommodation in clinically relevant models of xenotransplantation.

Modified control of complement

Accommodation might reflect modification of the complement cascade such that its effector functions cause little or no injury to graft endothelium. Incubation of cells with complement in sub-toxic amounts has long been known to modify cells in ways that cause the cells to resist subsequent exposure to higher concentrations of complement [29,30]. Resistance to complement is caused by some combination of: (i) shedding and internalization of terminal complement complexes [29]; modification of cellular metabolism such that cells intrinsically resist lysis [31]; and increased expression of complement regulatory proteins such as decay accelerating membrane co-factor protein or CD59 [32]. Dalmaso et al. [33,34] found that binding of antibodies or a lectin to Gal α 1-3Gal increases resistance of the cells to lysis, and this resistance is mediated at least in part by heightened expression of CD59 on endothelial cells [35]. Dorling et al. [36] found that binding of xenoreactive IgG to porcine cells increases resistance to lysis.

Consistent with these concepts, Ding et al. [28] recently reported that infusion of anti-Gal α 1-3Gal IgG1 into mice that are immunodeficient, lacking of α -1,3-galactosyl transferase (such mice, in contrast to wild type mice, do not make Gal α 1-3Gal and do make anti-Gal α 1-3Gal antibodies, as described above), and bearing rat cardiac xenografts (which express Gal α 1-3Gal) causes the grafts to increase expression of decay accelerating factor, Crry and CD59. These grafts resisted destruction when the recipients were administered a bolus of IgG1. Although other mechanisms were not excluded, the results suggested that heightened expression of complement regulatory proteins might have contributed to accommodation. Williams et al. [37] found that accommodated swine-to-baboon cardiac xenografts exhibit heightened control of complement at the level of C3, at least partly independent of the level of expression of known regulatory proteins. Wang et al. [38] reported that administration of anti-C5 antibodies in pre-sensitized allograft recipients in conjunction with immunosuppression prevented rejection and allowed accommodation to occur.

Although heightened control of complement activation provides a compelling explanation for accommodation, it cannot stand alone as a mechanism. Saadi et al. [39] showed that repair of endothelium following complement-mediated damage requires insertion of the membrane attack complex. McCurry et al. [40] and Cozzi et al. [41] among others showed that heightened expression of human complement regulatory proteins as the product of transgenes or administration of soluble forms of these receptors (which are potent inhibitors of complement) [42] does not by itself bring about accommodation; indeed, organs expressing those proteins undergo acute vascular rejection. Rather, manipulation of antibodies is still apparently needed to generate accommodation [43,44]. And, in human subjects and in some model systems, manipulation of antibodies suffices to allow accommodation to ensue [4,45]. We think that complement regulation is essential for survival of transplants over time and thus for accommodation to be manifest; however, regulation of complement *per se* does not appear to us to explain accommodation.

Acquired resistance to injury

Accommodation might reflect an acquired resistance of an organ or tissue to injury by complement or other noxious factors (independent of modifications in control of complement). Obviously, such protection could only be appreciated if some antibodies bind to a graft and some complement is activated. Acquired resistance to injury does not exclude other mechanisms or vice versa; however, if some other mechanism were fully manifest, an

acquired resistance to injury would not be needed for accommodation, nor could it be proved.

Before considering evidence that organs acquire resistance to injury, we should offer a few further remarks on this subject. If the acquiring of resistance to injury depends on previous sub-toxic injury, then manipulations that prevent antibody binding or complement activation would preclude the development of resistance to injury and hence accommodation. Thus, we shall be very interested to know whether resistance, such as it may be, requires prior insult. If resistance to lethal injury requires sub-toxic injury, then we should want to know whether the trigger is homologous (i.e. antibody binding impairs further antibody binding or complement activation impairs further activation of complement) or whether it is heterologous (i.e. resistance to complement as one example might be induced by sub-toxic exposure to TNF α or endotoxin) [46]. The answer has obvious implications for therapeutics – if accommodation is homologous then full inhibition of complement might be detrimental. We should also mention that since resistance to injury is acquired and not constitutive, we would think that the condition of resistance must engender something that is dys-physiologic or toxic (otherwise resistance to injury would be a constitutive state). Following on that supposition, we might speculate that some chronic conditions, perhaps chronic rejection among them, might reflect “complications” of accommodation [47]. On the other hand, the existence of accommodation might also allow a graft to survive long enough for chronic rejection to occur as a consequence of factors, such as antibody binding and complement activation that would otherwise induce acute injury to an organ. Hence, a correlation of accommodation with chronic rejection should not be taken to infer one caused the other. Finally, one must be careful about inferring that a gene product, such as heme oxygenase-1, the absence of which is associated with organ injury and hence with the absence of accommodation, must be a critical mediator of accommodation. While heme oxygenase-1 or other protective genes might be central to accommodation, they might instead simply allow an organ graft to survive independent of whether accommodation has occurred. Thus, Matsuo et al. [48] found that inhibition of the function of decay accelerating factor in an organ causes the organ to undergo severe acute vascular disease, and hence DAF is essential for the integrity of an organ under stress or even under constitutive conditions. However, that is not to say that DAF is integral to accommodation, since as we mentioned heightened expression of that protein does not prevent acute vascular rejection of xenografts (rather it appears to be one of many proteins that help maintain integrity of organs or repair).

Several models systems have revealed evidence that organs can acquire resistance to injury. Nath et al. [49] 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. [14] found that xenografts and Hancock et al. [50] that allograft with accommodation express a number of “protective genes”, that is to say genes that inhibit apoptosis and lack of heme oxygenase-1 precludes induction of accommodation. Delikouras et al. [51] found that exposure to xenoreactive antibodies induces expression of cytoprotective genes in endothelial cells. Jindra et al. [52] found that anti-HLA antibodies likewise induce such genes. On the other hand, Park et al. [53] found that cytoprotective genes may not be expressed at higher levels in ABO-incompatible allografts and Williams et al. [37] found these genes expressed at higher levels in xenografts with rejection than in xenografts with accommodation.

Other pathways may induce cytoprotection. Grehan et al. [54] and Black et al. [55] found that IL-7 and IL-13 confer resistance to lysis on endothelial cells that this resistance is owed at least in part to the PI-3 kinase/AKT pathways. Koch et al. [56] showed that the PI-3 kinase/AKT pathways makes hepatocytes naturally resist complement mediated lysis. Narayanan et al. [57] showed that anti-HLA antibodies activate the PI-3 kinase/AKT

pathway and induce production of camp, which together protect endothelial cells from complement-mediated lysis at least in part by inducing cytoprotective genes.

The Prevalence of Accommodation

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 do not occur [4], one might conclude that accommodation is relatively infrequent. Thus, the proceedings of a recent Banff conference on organ allografts, accommodation was considered an unusual phenomenon, when it was considered at all [58]. Even more focused considerations of humoral immunity and graft outcome devote far more consideration to tolerance, which is only seen with regularity in ABO-incompatible transplants in infants [59] than to accommodation, which is seen both in infants and adults [60]. We think accommodation may be far more frequent than commonly thought [17]. Healthy organs can absorb anti-donor antibodies in large amounts, removing those antibodies from the circulation [27]. Thus, we envision that organs may well be accommodated in recipients having no detectable anti-donor antibody, because the functioning graft serves as a 'sink' for that antibody. Consistent with that possibility, Adeyi et al. [61] found that the prevalence and level of anti-donor antibodies in the blood increase profoundly after an organ allograft is removed; we observe the same for organ xenografts [62]. 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. The organ damaged by antibodies and complement is less able to absorb antibodies from the blood, and hence the level of those antibodies increases. We should add one further point – C4d and C3d are typically seen in accommodated allografts and xenografts [18,22,37]. Hence, deposition of C4d in an organ graft cannot be taken by itself as evidence of acute vascular, or humoral or antibody mediated rejection (whichever term may be preferred).

Concluding Remarks

We conclude that a fuller understanding of accommodation would profoundly benefit the field of transplantation. Not only might accommodation be crucial to successful xenotransplantation, but it might promote advances in allotransplantation, and perhaps to recovery from other disease states. Because severe vascular injury is all but inevitable in the xenograft, and injury occurs early and dramatically in the course, accommodation may be easiest to initially investigate in that setting.

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Figure 1. Occurrence of accommodation and sites of potential mechanisms

(A) The outcome of organ transplantation. The outcomes of organ transplantation include hyperacute rejection (HAR), acute vascular (AVR) or antibody-mediated rejection, acute cellular rejection (ACR) and chronic rejection. These outcomes are often observed in the temporal sequence shown in the figure. HAR, AVR and chronic rejection can be mediated by antibodies. Accommodation (ACC) is defined as the survival and function of an organ transplant in the face of an antibody response that would otherwise cause injury and rejection. Accommodation can prevent HAR and AVR. As discussed in the text, accommodation might prevent chronic rejection or allow it to occur by avoiding more acute types of injury, or it might actually cause chronic rejection. **(B) Mechanisms of accommodation.** Transplantation of nearly every type engenders a B cell response. Anti-graft antibodies can ultimately injure organ grafts [10] through a series of events that include binding of antibody (Ab), activation of complement (C) and endothelial changes and injury induced by complement. Accommodation modifies the outcome of organ grafts at one or more of the steps in this sequence. These steps and the corresponding mechanisms are as follows: (i) change in antigen so that antibody does not bind; (ii) increased control of complement; and (iii) resistance to injury-mediated by complement. The original description of accommodation [4] postulated that accommodation might also be caused by a change in antibody, such that complement activation or other effector properties are mitigated. We now consider such changes to represent immunological “regulation” rather than accommodation, since they reflect changes in the immune response and not in the graft (discussed in the text). Manifestation of accommodation by change in antigen or by complement regulation may preclude detecting or evaluating resistance to injury caused by antibody and complement.