Published in final edited form as:

Curr Opin Organ Transplant. 2017 October ; 22(5): 470–476. doi:10.1097/MOT.0000000000000446.

Accommodation and Related Conditions in Vascularized Composite Allografts

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Abstract

Purpose of review—The outcome of vascularized composite allografts (VCA) often appear unrelated to the presence of donor-specific antibodies (DSA) in blood of the recipient or deposition of complement in the graft. The attenuation of injury and the absence of rejection in other types of grafts despite manifest donor-specific immunity have been explained by accommodation (acquired resistance to immune-mediated injury), adaptation (loss of graft antigen) and/or enhancement (antibody-mediated antigen blockade). Whether and how accommodation, adaptation and/or enhancement impact on the outcome of vascularized composite allografts (VCA) is unknown. Here we consider how recent observations concerning accommodation in organ transplants might advance understanding and resolve uncertainties about the clinical course of VCA.

Recent findings—Investigation of the mechanisms through which kidney allografts avert antibody-mediated injury and rejection provide insights potentially applicable to VCA. Interaction of donor-specific antibodies (DSA) can facilitate replacement of donor by recipient endothelial cells, modulate or decrease synthesis of antigen, mobilize antigen that in turn blocks further immune recognition and limit the amount of bound antibody, allowing accommodation to ensue. These processes also can explain the apparent dissociation between the presence and levels of DSA in blood, deposition of C4d in grafts and antibody-mediated rejection. Over time the processes might also explain the inception of chronic graft changes.

Summary—The disrupted tissue in VCA and potential for re-population by endothelial cells of the recipient establish conditions that potentially decrease susceptibility to acute antibody-mediated rejection. These conditions include clonal suppression of donor-specific B cells, and adaptation, enhancement and accommodation. This setting also potentially highlights heretofore-unrecognized interactions between these “protective” processes.

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Conflicts of interest

none

Keywords

vascularized composite allograft; accommodation; donor-specific antibodies; antibody-mediated rejection; chronic rejection

Introduction

Accommodation refers to a condition in which a graft apparently resists acute injury and rejection associated with the presence of donor-specific antibodies (DSA) or other noxious factors in blood (1, 2). Accommodation is one of several conditions, including enhancement, graft adaptation and operational tolerance, characterized by absence of rejection under conditions in which rejection might be expected to occur (Table 1). First described in ABO-incompatible kidney transplants and heterotopic cardiac xenografts (3, 4), accommodation is now recognized to occur in 10–30% of conventional (ABO-compatible) organ transplants (2, 5), the frequency varying with the frequency, method and sensitivity of DSA assay used and with donor and recipient characteristics that bear on risk. Whether accommodation occurs in vascularized composite allografts (VCA) and what ultimate impact accommodation might have on outcome is unknown, but the same process has been envisioned to protect tissues in various settings besides organ transplantation (6–9). We shall discuss however some aspects of accommodation and related conditions we think could prove relevant understanding the fate VCA and possibly advance management of VCA. Although work in experimental VCA provides insights of potential import on this subject, we shall focus on clinical experience and clinical literature for the present communication.

VCA, like other allografts, are highly immunogenic. In spite of immunosuppression, recent surveys and reviews estimate at least 80% of VCA including skin exhibit at least one episode of rejection, predominantly acute cell mediated rejection (CMR) (10–16). The extent of immunogenicity and high frequency of rejection has been ascribed to the presence of allogeneic skin in most VCA, as skin is often considered the most immunogenic tissue (although muscle might be more so) (17–20), although accessibility of skin for observation and biopsy contributes to this impression (14).

In contrast to the high incidence of CMR, acute antibody-mediated rejection (AMR) is rarely observed in VCA (10, 21–23). Weissenbacher et al. (24) reported one case of AMR and recently reviewed the literature (25). Chandraker et al. (26) describe AMR in a recipient pre-sensitized to the donor. Nevertheless, deliberate efforts to detect AMR by probing biopsies for deposits of C4d (21) or testing serum for presence of donor-specific antibodies (DSA) (27), have revealed few clinical correlates (14, 16). Whether the case reports of AMR should be taken as general guidance or whether the cases of AMR represent exceptions to a common lack of susceptibility to AMR (22) is unclear.

Why is AMR infrequently observed in clinical VCA? If observations of the outcome of organ transplantation are a valid source of guidance (12–14, 18, 27, 28), recipients of VCA should be at high risk for AMR. VCA often include skin, which is highly immunogenic and reliably elicits production of DSA (29). Perhaps even more important than the presence of skin or other immunogenic tissues such as muscle, is high frequency of pre-sensitization to

HLA of VCA recipients. As only one example, Duhamel et al. (29) found that ~3 years after treatment for severe burns with blood transfusions and in some cases skin allografts, 97% of subjects had anti-HLA antibodies and nearly 2/3 were highly sensitized (defined as PRA > 85%), far exceeding the mean PRA of patients awaiting kidney transplants. While a high PRA per se does not necessarily increase risk of AMR, neither does it decrease risk (30), and AMR should have afflicted many fold more VCA than reports suggest. Although the presence of bone marrow cells in some VCA might modify the intensity of alloimmune responses, neither inclusion of bone marrow nor conventional immunosuppression regimens used in recipients selectively impairs T cell-dependent B cell responses that underlie production of anti-HLA antibodies (16, 17, 19, 31, 32). We shall discuss and in Figure 1 we illustrate characteristics of VCA that might limit the incidence and intensity of antibody-mediated injury and AMR.

The origin of the vascular supply

One characteristic of grafts that determines susceptibility to rejection is the origin of the vascular supply. The blood vessels of organ grafts derive entirely from the source of the transplant and these are the main targets of DSA in clinical and experimental transplants (2, 33). Antibodies bound to the endothelium in an organ graft activate complement, modifying the physiology of the blood vessels to promote coagulation, inflammation and immunity and to compromise perfusion and vascular integrity and these changes likely underlie the pathology of AMR (7, 34).

The blood vessels of skin and other tissue transplants however derive at least in part from the in-growth of recipient blood vessels. Recipient blood vessels do not express antigens recognized by DSA and hence might be spared some of the vascular changes observed in AMR. Since ~85% of Ig resides in blood, extravascular cells are targeted to a lesser extent than blood vessels and extravascular cells may be less susceptible to complement-mediated pathophysiology (35). Recipient blood vessels clearly can and do present donor peptide in MHC, which allo-specific T cells recognize, infiltrate and trigger CMR. VCA are also found to contain numerous, possibly expanded populations of donor T cells (16, 36, 37). Whether donor-derived T cells attack blood vessels of recipient origin that grow into VCA is unknown, but a question of potential import since donor T cells presumably are less subject to control by induction regimens.

Reports describing deposits of C4d (18, 26, 38–40) might be taken as evidence that VCA contain more donor endothelium than conventional tissue transplants and hence might be subject to DSA-induced injury and rejection. However, activation of C4 and hence deposition of C4d does not necessarily depend on binding of DSA. In ischemic tissues C4d deposits might be generated by binding of autoantibodies (41, 42) or by recruitment of the lectin complement pathway (43). For these reasons, and others (44, 45) the presence of C4d cannot be taken as proof of binding of DSA to donor capillaries in VCA susceptibility to DSA-mediated injury. However, VCA could and probably do have a considerable fraction of donor endothelium because the surgical anastomosis and distance from a source of recipient blood vessels may limit neo-vascularization. Why these segments are so infrequently injured by DSA and how exactly the susceptibility to and pathogenesis of rejection of VCA departs

from those of organ grafts or “conventional” tissue grafts is clearly unknown. We will discuss accommodation and related conditions as potential explanations.

Conditions That Explain Absence of Rejection of Transplants

Allografts, particularly allografts including skin, always (or nearly always) evoke alloimmune responses. Although regimens of immunosuppression sufficiently control alloimmunity to avert acute rejection, current regimens do not prevent sensitization or fully control B cell responses to alloantigens. Thus, de novo donor-specific B cell responses can be detected in all or nearly all allograft recipients (46). Despite these responses, allografts sometimes survive in recipients with appreciable levels of DSA in blood and/or in recipients after immunosuppressive agents are withdrawn (2, 8).

Table 1 lists four “conditions” that have been taken to explain why some allografts, expected to undergo rejection, instead persist. Spontaneous operational tolerance, characterized by an allo-immune response that is qualitatively or quantitatively insufficient to mediate rejection has not been described in clinical VCA. However, we discuss below a mechanism by which antigen released from VCA might suppress responses by some allospecific B cell clones. Enhancement was first noticed by Snell and most thoroughly explored by Kaliss (47) is characterized by a paradoxical impact of DSA on the growth of tumor and survival of skin allografts (2).

Graft adaptation, i.e. the loss or modulation of antigen recognized by DSA, has been demonstrated in various in vitro systems (48, 49), but not in conventional organ transplants. Replacement or modulation of antigen by DSA should cause the levels of DSA in blood to increase (since less DSA would be absorbed by the graft) and might explain some instances in which DSA do not correlate with C4d or presage or mark rejection (14, 16, 22, 27, 39, 50, 51). However, binding of DSA to shed antigen could decrease levels of DSA detected in conventional assays. Adaptation (i.e. decreased absorption to the graft) might also explain in part the association sometimes observed between DSA in blood and chronic graft changes, the greater tendency for DSA to be associated with AMR early after transplantation and the resolution of AMR without sequelae. On the other hand, for reasons given above, one should not assume that presence of C4d in VCA excludes adaptation, as ischemia and injury could recruit autoantibodies and/or trigger the lectin pathway of complement.

Enhancement was originally recognized as an improvement in the survival and growth of tumor allografts caused by DSA. Enhancement of skin grafts and organs grafts has been reported but the preponderance of work has been conducted in tumor systems (2, 47). Enhancement is thought to occur when DSA blocks immune recognition of tumor cells, decreasing alloimmune responses. Nearly all work on enhancement has focused on putative DSA-induced suppression of cell-mediated immunity and hence CMR and a relationship to DSA production and protection against AMR has not been explored. Recent investigation of ABO-incompatible kidney transplants however suggests that interaction of anti-blood group antibodies with the grafts can liberate antigen and antigen so released from grafts might suppress further production of antibody against donor blood groups (52). At first glance, the observation might be thought exemplify spontaneous tolerance observed in young heart

transplant recipients (53). However, expression of blood group antigens was decreased, suggesting as one possibility that small amounts of DSA caused the antigen to be shed and the mobilized the antigen in turn could have suppressed the function of some donor-specific B cells. Antigen-induced suppression of B cells via anergy or deletion has been known for decades (54), but the pertinence of such clonal suppression for transplantation has not been explored (perhaps because mobilization of blood group saccharides spares the epitopes while mobilization of MHC might not). The greater extent of tissue disruption in VCA however might bring cause shedding of sufficient amounts of native antigen to enable this mechanism to be manifest. Whether such impact of shed antigen as it occurs is best termed clonal suppression or adaptation or enhancement is not clear. Regardless, the process could also allow accommodation to ensue, as discussed below.

Manipulation of cell surfaces can also impact on DSA interaction with HLA. Treatment of endothelial cells with anti-blood group antibodies was recently shown also to decrease expression of HLA-DR leading to decreased susceptibility to complement-mediated cytotoxicity induced by anti-HLA-DR antibodies (55), a finding consistent with adaptation. Because blood group antigens are expressed as modifications of various cell membrane proteins and neutral lipids, it is impossible to know whether the impact of the antibodies is specific for one or another core structure or a general phenomenon. However, we imagine that lectins might be used to target blood group O, A or B in endothelial cells of a VCA to a similar effect, as Dalmaso et al. (56) first showed in a non-human system.

Accommodation is defined as acquired resistance to immune and especially antibody- and complement-mediated injury (2, 57, 58). In organ transplants, accommodation is typically recognized when the presence of DSA in blood was not paralleled by rejection. Although accommodation is readily detected in ABO-incompatible organ transplants (59) it is more difficult to appreciate in ABO-compatible transplants (44, 46). Accommodation can be difficult to detect because normal organs have the capacity to absorb large amounts of antibody, depleting much or all DSA from blood. Conversely, organs injured by immune or non-immune processes can absorb fewer antibodies. Hence, the levels of DSA in blood are often found to increase after rejection rather than before (60). For this reason, we have proposed that technologies directed at detecting donor-specific B cell responses might offer keen insights into allo-immunity and accommodation (46).

Mechanisms, inception and outcome of accommodation

Accommodation is generally believed to reflect changes in graft endothelial cells and possibly other cells that impart resistance to cytotoxicity (61–64). The postulated mechanisms have been reviewed (1) and we shall not consider that subject since the pertinence for VCA remains to be established. Instead, we consider characteristics of VCA that could favor development of accommodation and related conditions over rejection (Figure 1).

One pertinent consideration for VCA is the interpretation given to the presence of C4d in tissues. More important than the question of whether presence of C4d reflects binding of DSA or autoantibodies or activation of the lectin pathway, as discussed above, might be the

question of whether C4d necessarily reflects past or present tissue injury. We observe C4 activation and C4d deposition in accommodation when significant injury is absent (7) and that is consistent with reports on the apparent absence of rejection in in some VCA with C4d deposits (14–16, 18, 25, 27, 40). More to this point is that C4d is catalytically inert and if anything protective - the amino or hydroxyl groups covalently bound to C4d being unavailable as targets for activated C4 or C3 limits ongoing complement-mediated injury.

Our original concept that low levels of DSA induce accommodation while high levels of DSA induce rejection has been repeatedly affirmed both in ABO-incompatible and in conventional transplants. However, the relationship between DSA level and accommodation in organ transplants does always hold over time, suggesting induction and maintenance of accommodation have distinct requirements or that factors that induce accommodation differ from factors that maintain accommodation. The greater extent of tissue disruption in VCA compared to organ transplants might generate more soluble (or suspended) donor HLA, which by hindering the binding of DSA and/or consuming complement, or in some instances by suppressing the further production of DSA (55) might allow the physiology of low DSA concentrations to prevail. Consistent with that possibility is the rarity of hyperacute rejection in VCA.

Another, factor of potential importance is the nature of antibodies that bind to the graft. We have discussed the possibility that some antibodies, including some DSA, might be “protective,” especially at lower concentrations (65). These antibodies, which are auto-reactive and bind especially to ischemic or injured cells, might induce accommodation as originally defined or promote repair. In either case, a VCA recipient might be disadvantaged by non-specific removal of Ig.

We have thought for some time that our original concept of accommodation as simply resistance to immune-mediated injury was overly simplistic. We reasoned that the changes that protect tissues and organs must have dys-physiologic consequences or they would be constitutive rather than induced (8, 66, 67). These consequences could include the pathologic changes of chronic rejection. If our concerns prove justified, then efforts directed at understanding accommodation and related conditions might offer new avenues for averting some of the chronic problems that plague VCA.

Conclusions

The procedures associated with transplantation of composite tissues and the manner by which VCA are vascularized establish conditions that potentially accentuate enhancement, adaptation and accommodation. These conditions include the shedding and modulation of alloantigen, exchange of recipient for host endothelial cells, blocking of antigen recognition and acquired resistance of the graft to injury induced by DSA. The combination of enhancement, adaptation and accommodation might explain why presence of DSA in blood and especially the deposition of complement might induce less acute injury than expected. However, protection of the graft might also engender a biological cost manifest as chronic pathologic.

Acknowledgments

Financial support and sponsorship

The authors' work pertinent to this paper is supported by the National Institutes of Health (AI123262, EB022033), the Department of Defense (W81XWH-13-2-0057, W81XHW-13-2-0053) and the Jewish Hospital and St Mary's Healthcare Foundation.

References Cited

1. Koch CA, Khalpey ZI, Platt JL. Accommodation: preventing injury in transplantation and disease. *J Immunol.* 2004; 172:5143–8. [PubMed: 15100249]
- 2•. Cascalho MI, Chen BJ, Kain M, Platt JL. The paradoxical functions of B cells and antibodies in transplantation. *J Immunol.* 2013; 190:875–9. This paper provides a recent summary of accommodation and related conditions that limit the impact of DSA on grafts and avert rejection. [PubMed: 23335803]
3. Chopek MW, Simmons RL, Platt JL. ABO-incompatible renal transplantation: initial immunopathologic evaluation. *Transplantation Proceedings.* 1987; 19:4553–7. [PubMed: 3321617]
4. Platt JL, Vercellotti GM, Dalmasso AP, Matas AJ, Bolman RM, Najarian JS, et al. Transplantation of discordant xenografts: a review of progress. *Immunology Today.* 1990; 11:450–6. [PubMed: 2073317]
5. Dijke EI, Platt JL, Blair P, Clatworthy MR, Patel JK, Kfoury AG, et al. B cells in transplantation. *J Heart Lung Transplant.* 2016; 35:704–710. [PubMed: 26996930]
6. Platt JL, Wrenshall LE, Johnson GB, Cascalho M. Heparan Sulfate Proteoglycan Metabolism and the Fate of Grafted Tissues. *Adv Exp Med Biol.* 2015; 865:123–40. [PubMed: 26306447]
7. Williams JM, Holzkecht ZE, Plummer TB, Lin SS, Brunn GJ, Platt JL. Acute vascular rejection and accommodation: divergent outcomes of the humoral response to organ transplantation. *Transplantation.* 2004; 78:1471–8. [PubMed: 15599311]
8. Lynch RJ, Platt JL. Escaping from Rejection. *Transplantation.* 2009; 88:1233–66. [PubMed: 19996920]
- 9••. Wu SR, Reddy P. Tissue tolerance: a distinct concept to control acute GVHD severity. *Blood.* 2017; 129:1747–52. This manuscript describes a condition like accommodation that protects tissues from injury in graft-versus-host disease. Although accommodation was previously postulated to confer protection in other settings (see ref. # 1), this paper offers a mechanism especially pertinent for T cells and applicable in normal, non-transplanted tissues. [PubMed: 28153825]
- 10•. Petruzzo P, Lanzetta M, Dubernard JM, Landin L, Cavadas P, Margreiter R, et al. The International Registry on Hand and Composite Tissue Transplantation. *Transplantation.* 2010; 90:1590–4. Although not “recent,” this registry provides a broad glimpse at the frequency of various outcomes of VCA and notably does not include AMR. [PubMed: 21052038]
11. Pomahac B, Gobble RM, Schneeberger S. Facial and hand allotransplantation. *Cold Spring Harbor Perspectives in Medicine.* 2014; 4:a015651. [PubMed: 24478387]
12. Fischer S, Lian CG, Kueckelhaus M, Strom TB, Edelman ER, Clark RA, et al. Acute rejection in vascularized composite allotransplantation. *Curr Op Organ Transplant.* 2014; 19:531–44.
- 13••. Kueckelhaus M, Fischer S, Seyda M, Bueno EM, Aycart MA, Alhefzi M, et al. Vascularized composite allotransplantation: current standards and novel approaches to prevent acute rejection and chronic allograft deterioration. *Transplant Int.* 2016; 29:655–62. The thrust of this paper concerns therapeutics, but, as a prelude, the authors authoritatively comment on the extent of prior sensitization and the relative infrequency of AMR and describe one of the few documented cases of AMR, i.e. failure of accommodation and related conditions to protect.
- 14••. Issa F. Vascularized composite allograft-specific characteristics of immune responses. *Transplant Int.* 2016; 29:672–81. This paper provides an outstanding review of aspects of the allogeneic response but also includes discussion of key processes such as ischemia-reperfusion injury that could impact on the fate of VCA. The authors discuss the surprising infrequency of detection of DSA after transplantation.

- 15••. Sicard A, Kanitakis J, Dubois V, Petruzzo P, Badet L, Thaumat O, et al. An integrated view of immune monitoring in vascularized composite allotransplantation. *Curr Op Organ Transplant*. 2016; 21:516–22. Although aimed at reviewing recent literature, this paper broadly and critically discusses some technologies that could be applied to detecting and weighing the significance of donor-specific immune responses to VCA. The paper is notable for mention of donor-specific B cell responses, discussed more completely in ref. #46.
- 16•. Kaufman CL, Marvin MR, Chilton PM, Hoying JB, Williams SK, Tien H, et al. Immunobiology in VCA. *Transplant Int*. 2016; 29:644–54. This paper provides broad and authoritative review of recent advances that could contribute to understanding the genesis and regulation of alloimmune responses to VCA.
17. Lee WP, Yaremchuk MJ, Pan YC, Randolph MA, Tan CM, Weiland AJ. Relative antigenicity of components of a vascularized limb allograft. *Plast Reconstr Surg*. 1991; 87:401–11. [PubMed: 1998012]
18. Leto Barone AA, Sun Z, Montgomery RA, Lee WP, Brandacher G. Impact of donor-specific antibodies in reconstructive transplantation. *Exp Rev Clin Immunol*. 2013; 9:835–44.
19. Madariaga ML, Shanmugarajah K, Michel SG, Villani V, La Muraglia GM 2nd, Torabi R, et al. Immunomodulatory Strategies Directed Toward Tolerance of Vascularized Composite Allografts. *Transplantation*. 2015; 99:1590–7. [PubMed: 25757218]
20. Klimov M, Matar AJ, Farkash EA, Medeiros E, Qiao J, Harrington E, et al. Survival of Allogeneic Self-Assembled Cultured Skin. *Transplantation*. 2016; 100:2071–8. [PubMed: 27479166]
21. Kanitakis J, McGregor B, Badet L, Petruzzo P, Morelon E, Devauchelle B, et al. Absence of C4d deposition in human composite tissue (hands and face) allograft biopsies: an immunoperoxidase study. *Transplantation*. 2007; 84:265–7. [PubMed: 17667820]
- 22••. Thaumat O, Badet L, Dubois V, Kanitakis J, Petruzzo P, Morelon E. Immunopathology of rejection: do the rules of solid organ apply to vascularized composite allotransplantation? *Curr Op Organ Transplant*. 2015; 20:596–601. Although the title of this paper emphasizes “immunopathology” the authors give much broader consideration to biological and immunological differences between VCA and organ transplants. Anyone looking for an introduction to the immunobiology of VCA would find no better place to start than this review.
- 23•. Schneider M, Cardones AR, Selim MA, Cendales LC. Vascularized composite allotransplantation: a closer look at the Banff working classification. *Transplant Int*. 2016; 29:663–71. This paper summarizes the Banff “working” classification and grading criteria for rejection of VCA, established at the 9th Banff Conference in 2007 (*Am J Transplant* 2008; 8, 1396–1400). Among the limitations of the classification scheme discussed are the absence of criteria for antibody-mediated rejection and for chronic rejection.
24. Weissenbacher A, Hautz T, Zelger B, Zelger BG, Mayr V, Brandacher G, et al. Antibody-mediated rejection in hand transplantation. *Transplant Int*. 2014; 27:e13–7.
- 25••. Weissenbacher A, Loupy A, Chandraker A, Schneeberger S. Donor-specific antibodies and antibody-mediated rejection in vascularized composite allotransplantation. *Curr Op Organ Transplant*. 2016; 21:510–5. This paper presents the limited information available about DSA and AMR in VCA, including the valuable experience of the authors. Based on experience with solid organ transplants, the authors presume DSA are pathogenic and discuss assays for DSA and therapeutic strategies to control production.
- 26••. Chandraker A, Arscott R, Murphy GF, Lian CG, Bueno EM, Marty FM, et al. The management of antibody-mediated rejection in the first presensitized recipient of a full-face allotransplant. *Am J Transplant*. 2014; 14:1446–52. This paper reports an exceptionally well documented course and resolution of AMR in a pre-sensitized face transplant recipient. The authors trace the course in relation to serial analysis of DSA levels and specificity, histology and immunopathology. This case might have been ideal for investigation of clonal suppression and other conditions, as AMR resolved. [PubMed: 24797454]
27. Sarhane KA, Tuffaha SH, Broyles JM, Ibrahim AE, Khalifian S, Baltodano P, et al. A critical analysis of rejection in vascularized composite allotransplantation: clinical, cellular and molecular aspects, current challenges, and novel concepts. *Front Immunol*. 2013; 4 article 406.
28. Edtinger K, Yang X, Uehara H, Tullius SG. Current status of vascularized composite tissue allotransplantation. *Burns Trauma*. 2014; 2:53–60. [PubMed: 27602363]

- 29•• Duhamel P, Suberbielle C, Grimbert P, Leclerc T, Jacquelinet C, Audry B, et al. Anti-HLA sensitization in extensively burned patients: extent, associated factors, and reduction in potential access to vascularized composite allotransplantation. *Transplant Int.* 2015; 28:582–93. This paper reports an important investigation into the frequency and extent of sensitization of patients given skin allografts for treatment of burns. What makes this work especially valuable is the comparison of sensitization of these subjects with sensitization in a large cohort of subjects awaiting kidney transplantation.
30. Dunn TB, Noreen H, Gillingham K, Maurer D, Ozturk OG, Pruett TL, et al. Revisiting traditional risk factors for rejection and graft loss after kidney transplantation. *Am J Transplant.* 2011; 11:2132–43. [PubMed: 21812918]
- 31•. Brazio PS, Woodall J, Panda A, Brown EN, Ha JS, Azimzadeh AM, et al. Infused Bone Marrow Fails to Prevent Vascularized Composite Allograft Rejection in Nonhuman Primates. *Am J Transplant.* 2015; 15:2011–2. Presence of vascularized bone with VCA has been postulated to constrain alloimmune responses and hence rejection. This letter reports that bone marrow per se does not decrease the frequency and severity of rejection in VCA in a non-human primate model. The authors conclude that bone marrow per se does not modify immunity; however, the findings also invite inquiry about whether vascularized bone and isolated bone marrow cells have disparate impact on accommodation and related conditions in VCA. [PubMed: 25908397]
- 32•• Cetrulo CL Jr, Drijkoningen T, Sachs DH. Tolerance induction via mixed chimerism in vascularized composite allotransplantation: is it time for clinical application? *Curr Op Organ Transplant.* 2015; 20:602–7. This paper provides new insights into application of tolerance for VCA. Although tolerance might not be necessary for success of VCA in some individuals, surveys on the outcome indicate that compliance with immunosuppression poses the greatest immunological risk to VCA. Tolerance potentially avoids that risk. Whether and how tolerance regimens impact on accommodation and related conditions however is unknown.
33. Platt JL. New directions for organ transplantation. *Nature.* 1998; 392(Suppl 6679):11–7.
34. Saadi S, Takahashi T, Holzkecht RA, Platt JL. Pathways to acute humoral rejection. *Am J Pathol.* 2004; 164:1073–80. [PubMed: 14982860]
35. Koch CA, Kanazawa A, Nishitai R, Knudsen BE, Ogata K, Plummer TB, et al. Intrinsic resistance of hepatocytes to complement-mediated injury. *J Immunol.* 2005; 174:7302–9. [PubMed: 15905577]
36. Clark RA, Chong B, Mirchandani N, Brinster NK, Yamanaka K, Dowgiert RK, et al. The vast majority of CLA+ T cells are resident in normal skin. *J Immunol.* 2006; 176:4431–9. [PubMed: 16547281]
37. Lian CG, Bueno EM, Granter SR, Laga AC, Saavedra AP, Lin WM, et al. Biomarker evaluation of face transplant rejection: association of donor T cells with target cell injury. *Mod Pathol.* 2014; 27:788–99. [PubMed: 24434898]
38. Landin L, Cavadas PC, Ibanez J, Roger I, Vera-Sempere F. CD3+-mediated rejection and C4d deposition in two composite tissue (bilateral hand) allograft recipients after induction with alemtuzumab. *Transplantation.* 2009; 87:776–81. [PubMed: 19295326]
39. Kaufman CL, Ouseph R, Blair B, Kutz JE, Tsai TM, Scheker LR, et al. Graft vasculopathy in clinical hand transplantation. *Am J Transplant.* 2012; 12:1004–16. [PubMed: 22325051]
40. Hautz T, Zelger B, Brandacher G, Mueller H, Grahmmer J, Zelger B, et al. Histopathologic characterization of mild rejection (grade I) in skin biopsies of human hand allografts. *Transplant Int.* 2012; 25:56–63.
41. Weiser MR, Williams JP, Moore FDJ, Kobzik L, Ma M, Hechtman HB, et al. Reperfusion injury of ischemic skeletal muscle is mediated by natural antibody and complement. *J Exp Med.* 1996; 183:2343–8. [PubMed: 8642343]
42. Kulik L, Fleming SD, Moratz C, Reuter JW, Novikov A, Chen K, et al. Pathogenic natural antibodies recognizing annexin IV are required to develop intestinal ischemia-reperfusion injury. *J Immunol.* 2009; 182:5363–73. [PubMed: 19380783]
43. Daha MR, van Kooten C. Role of complement in IgA nephropathy. *J Nephrol.* 2016; 29:1–4. [PubMed: 26567162]
44. Platt JL, Cascalho M. Donor specific antibodies after transplantation. *Pediatric Transplant.* 2011; 15:686–90.

45. Platt JL. Accommodation: how you see it, how you don't. *Am J Transplantat*. 2011; 11:2007–8.
46. Lynch RJ, Silva IA, Chen BJ, Punch JD, Cascalho M, Platt JL. Cryptic B cell response to renal transplantation. *Am J Transplant*. 2013; 13:1713–23. [PubMed: 23750851]
47. Kaliss N. Immunological enhancement. *Int Rev Exp Pathol*. 1969; 8:241–76. [PubMed: 4904707]
48. Ceppellini R, Garotta G, Malavasi F, Trucco M. Modulation of expression of HLA components at the cell surface induced by anti-beta 2m reagents. *Tissue Antigens*. 1981; 17:28–36. [PubMed: 7018011]
49. Andres G, Yamaguchi N, Brett J, Caldwell PRB, Godman G, Stern D. Cellular mechanisms of adaptation of grafts to antibody. *Transplant Immunology*. 1996; 4:1–17. [PubMed: 8762003]
50. Petruzzo P, Kanitakis J, Testelin S, Pialat JB, Buron F, Badet L, et al. Clinicopathological Findings of Chronic Rejection in a Face Grafted Patient. *Transplantation*. 2015; 99:2644–50. [PubMed: 25989498]
51. Kanitakis J, Petruzzo P, Badet L, Gazarian A, Thaunat O, Testelin S, et al. Chronic Rejection in Human Vascularized Composite Allotransplantation (Hand and Face Recipients): An Update. *Transplantation*. 2016; 100:2053–61. [PubMed: 27163543]
52. Tasaki M, Saito K, Nakagawa Y, Imai N, Ito Y, Aoki T, et al. Acquired Downregulation of Donor-Specific Antibody Production After ABO-Incompatible Kidney Transplantation. *Am J Transplant*. 2017:115–128. The authors report that levels of anti-blood group antibodies in blood and production by B cells decrease in ABO-incompatible transplant recipients (analogous to findings in ref #53) but the mechanism(s) underlying these decreases were not elucidated. In the present review and Figure we discuss how interaction of DSA with alloantigen, including HLA, present in VCA could in some cases eventuate in clonal suppression. [PubMed: 27343838]
53. Fan X, Ang A, Pollock-BarZiv SM, Dipchand AI, Ruiz P, Wilson G, et al. Donor-specific B-cell tolerance after ABO-incompatible infant heart transplantation. *Nature Medicine*. 2004; 10:1227–33.
54. Goodnow CC. Balancing immunity and tolerance: deleting and tuning lymphocyte repertoires. *PNAS*. 1996; 93:2264–71. [PubMed: 8637861]
55. Iwasaki K, Miwa Y, Uchida K, Kodera Y, Kobayashi T. Negative regulation of HLA-DR expression on endothelial cells by anti-blood group A/B antibody ligation and mTOR inhibition. *Transpl Immunol*. 2017; 40:22–30. [PubMed: 28017877]
56. Dalmaso AP, Benson BA, Johnson JS, Lancto C, Abrahamsen MS. Resistance against the membrane attack complex of complement induced in porcine endothelial cells with a Gal alpha(1-3)Gal binding lectin: up-regulation of CD59 expression. *J Immunol*. 2000; 164:3764–73. [PubMed: 10725736]
57. Lynch RJ, Platt JL. Accommodation in organ transplantation. *Curr Op Organ Transplant*. 2008; 13:165–70.
58. Cascalho M, Platt JL. Harnessing B cells in immunotherapy. *Immunotherapy*. 2016; 8:237–9. This paper discusses the possibility that B cell functions might be manipulated deliberately to modify the impact of immunity on transplants, i.e. to promote accommodation over tolerance as an outcome of humoral immunity. [PubMed: 26860221]
59. Morath C, Zeier M, Dohler B, Opelz G, Susal C. ABO-Incompatible Kidney Transplantation. *Front Immunol*. 2017; 8 article 234.
60. Cooper JE, Gralla J, Cagle L, Goldberg R, Chan L, Wiseman AC. Inferior Kidney Allograft Outcomes in Patients With De Novo Donor-Specific Antibodies Are Due To Acute Rejection Episodes. *Transplantation*. 2011; 91:1103–9. [PubMed: 21403588]
61. Dorling A, Stocker C, Tsao T, Haskard DO, Lechler RI. In vitro accommodation of immortalized porcine endothelial cells: resistance to complement mediated lysis and down-regulation of VCAM expression induced by low concentrations of polyclonal human IgG antipig antibodies. *Transplantation*. 1996; 62:1127–36. [PubMed: 8900314]
62. Grehan JF, Levay-Young BK, Fogelson JL, Francois-Bongarcon V, Benson BA, Dalmaso AP. IL-4 and IL-13 induce protection of porcine endothelial cells from killing by human complement and from apoptosis through activation of a phosphatidylinositol 3-kinase/Akt pathway. *J Immunol*. 2005; 175:1903–10. [PubMed: 16034134]

63. Zhang X, Reed EF. Effect of antibodies on endothelium. *Am J Transplant*. 2009; 9:2459–65. [PubMed: 19775314]
64. Jindra PT, Hsueh A, Hong L, Gjertson D, Shen XD, Gao F, et al. Anti-MHC class I antibody activation of proliferation and survival signaling in murine cardiac allografts. *J Immunol*. 2008; 180:2214–24. [PubMed: 18250428]
65. Platt JL, Cascalho M. IgM in the kidney: a multiple personality disorder. *Kidney Int*. 2015; 88:439–41. This paper discusses the possibility that natural antibodies might promote healing and repair and in that way potentially contribute to accommodation. Since some natural antibodies are germline encoded; potentially, these antibodies could be produced in large amounts for therapeutic applications. [PubMed: 26323070]
66. Platt JL, Nath KA. Heme oxygenase: protective gene or Trojan horse. *Nature Medicine*. 1998; 4:1364–5.
67. Tang AH, Platt JL. Accommodation of grafts: implications for health and disease. *Human immunol*. 2007; 68:645–51. [PubMed: 17678718]

Key Points

VCA undergo AMR less often than expected given the extensive pre-sensitization of many recipients to allogeneic HLA (via blood transfusion and skin transplants). In part, this low frequency could reflect re-population of the graft with recipient blood vessels but it could also reflect processes that protect donor segments in VCA from AMR.

VCA might undergo less frequent and less severe AMR if antigen shed from the graft suppresses the function of some allo-specific B cells (clonal suppression).

The binding of DSA to shed antigen could also hinder development of AMR by blocking alloimmune recognition, a process called enhancement.

The interaction of DSA with the graft could cause loss of antigen by modulation and/or shedding, decreasing the impact of further antibody binding and hence susceptibility to AMR.

The interaction of small amounts of DSA with the graft, perhaps owing to aforementioned mechanisms, could induce changes that make the graft resistance to antibody-mediated injury and hence AMR.

Figure 1. Mechanisms that could avert antibody-mediated rejection of vascularized composite allografts

Vascularized composite allografts (VCA), like skin grafts, probably evoke powerful donor-specific T cell and B cell responses and production of large amounts of donor specific antibodies (DSA) (a lymphocyte, either T cell or B cell, with antigen receptor is shown in the figure). (A) Direct surgical or spontaneous anastomosis of recipient blood vessels with donor blood vessels should allow DSA to directly contact donor cells, eventuating in antibody-mediated rejection (AMR), as seen in organ transplants. However, AMR is observed less often in VCA than in organ allografts, particularly kidney allografts, and might be less severe. Decreased incidence and/or severity of AMR in VCA might be explained by one or more of several mechanisms. (B) Where the endothelial lining of blood vessels in VCA derives from the recipient (by ingrowth of recipient vessels or migration of endothelial cell precursors), DSA will not bind and rejection will not ensue. Recipient blood vessels can be attacked however by alloreactive T cells recognizing donor peptide associated with self-MHC (not shown). (C) Tissue injury associated with the transplant procedure could liberate donor antigen, which, in sufficient amounts, might interact with B cell antigen receptor causing suppression of function (clonal suppression). The smaller amounts of DSA subsequently produced could cause donor antigen to be modulated or liberated, increasing

clonal suppression. The liberated antigen associated with self- or donor-MHC (not shown) might block cognate recognition by alloreactive T cells (enhancement). The smaller amounts of DSA could also act on donor endothelium to induce accommodation (acquired resistance to immune and inflammatory injury). The decrease in donor antigen in the graft owing to adaption and the liberated antigen also weigh toward accommodation since less DSA can bind to donor blood vessels (due to less antigen and/or blocking by free antigen). Interaction of DSA with liberated antigen might also cause formation of immune complexes leading to some apparently reactive conditions of VCA (not shown).

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Table 1

Biological Conditions Underlying Absence of Rejection of Allografts

Condition	Immunity To Donor*	Type of Transplant*	Mechanism
Operational Tolerance	Absent or Decreased	Organ	Loss or Suppression of Alloreactive Clones
Enhancement	Decreased	Tissue>Organ	Blockade of Antigen Recognition by DSA
Adaptation	Present	Tissue or Organ	DSA-Mediated Loss of Antigen
Accommodation	Present (DSA+)	Organ	Ab and/or C-Induced Resistance to Injury

* The presence of donor-specific immunity and the type of transplant list represent the preponderance of reports. In this communication, we suggest mechanisms by which clonal suppression, enhancement, adaptation and accommodation might occur in vascularized composite grafts.

Ab, antibody; C, complement; DSA, donor-specific antibodies