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Chronic alloantibody mediated rejection

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Abstract

Alloantibodies clearly cause acute antibody mediated rejection, and all available evidence supports their pathogenic etiology in the development of chronic alloantibody mediated rejection (CAMR). But the slow evolution of this disease, the on-going immunosuppression, the variations in titer of alloantibodies, and variation in antigenic targets all complicate identifying which dynamic factors are most important clinically and pathologically. This review highlights the pathological factors related to the diagnosis of CAMR, the time course and natural history of this disease. What is known about CAMR pathogenesis is discussed including alloantibodies, the role of complement, gene activation, and Fc effector cell function. Therapy, which is problematic for this disease, is also discussed, including on-going and potential therapies and their limitations.

Keywords

Chronic rejection; Human allografts; Alloantibodies; Complement; Antibody mediated rejections

1. Introduction

Alloantibodies were first associated with the chronic rejection of human renal allografts when chronic allograft arteriopathy developed in patients with de novo anti-donor antibodies (HLA) [1]. Subsequent studies showed an association of circulating HLA antibodies with an increased risk of long term graft loss [2–4]. Acute renal allograft rejection in patients with donor specific anti class I HLA antibodies showed some identifying characteristic pathological features (e.g., neutrophils in capillaries) [5,6], but these studies did not identify a direct or indirect link to alloantibodies. This linkage was provided by showing that the complement fragment C4d was present in peritubular capillaries (PTCs) in some patients with acute rejection [7]. This finding was then associated with circulating donor specific antibodies and graft pathology [8,9] and confirmed by many others, leading to the introduction of the diagnosis of acute antibody mediated rejection (acute humoral rejection) in the Banff classification [10]. These findings were then extended to show that glomerulopathy and arteriopathy in chronic rejection were linked to C4d deposition in peritubular capillaries (PTC) and donor specific alloantibody (DSA) [11]. A new term, chronic antibody mediated rejection (CAMR) or chronic humoral rejection, was created for this diagnosis [12]. These observations were confirmed and then extended also to include capillaritis and basement membrane multilaminations of the PTC [13]. About 30–50% of patients with chronic rejection and transplant glomerulopathy or arteriopathy have C4d deposition in PTC, but the frequency varied considerably by center [9,14–17]. Most if not all cases with C4d positive antibody mediated rejection, even if it is subclinical, have detectable

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circulating antibodies [18]. The presence of donor specific de novo anti-HLA antibodies (DSA) associates with a poorer kidney graft survival as compared to subjects without de novo anti-HLA antibodies [19–23].

2. Chronic antibody mediated rejection

CAMR is common in some indication biopsies, found in one 10-year series in 9.3% of 771 cases [24]. Typically the onset is after the first year with the prevalence rising to about 20% in the 5th year. Proteinuria is common but not invariable (~50% of patients with CAMR have >1 g/day proteinuria). Renal function is often abnormal but can remain stable for considerable time (years) [25]. The strongest risk factor is pre-transplant donor specific antibodies [26], but most cases arise in patients without a history of presensitization or even a single episode of acute antibody mediated rejection. Serologically, CAMR shows a strong correlation with Class II DSA [16,26], as compared with acute antibody mediated rejection. Chronic antibody mediated rejection (CAMR) is characterized by chronic glomerular and capillary endothelial injury [10,11,27], is usually associated with proteinuria [25,28–30] and pathological markers including transplant glomerulopathy (duplication and laminations of the glomerular basement membrane) plus excess laminations of the peritubular capillaries. CAMR correlates with alloantibodies [11,13,16,25,26,31,32] but less well with C4d [16]. The infiltrating inflammatory cells in glomerular and peritubular capillaries are primarily macrophages (CD68+) [33], which express the Fc gamma RIII receptor. Some leukocytes in glomeruli also express T-bet, a transcription factor related associated with interferon gamma [34]. Glomerular endothelial cells display increased plasmalemmal vesicle-associated protein-1, indicating altered vesicle physiology [35]. In addition to multilamination of basement membranes, loss of PTCs is seen in some patients with chronic graft injury, and this correlates inversely with serum creatinine [32]. Loss of PTCs can affect the extent of C4d positivity and contribute to the lower density of C4d positive PTC often observed in CAMR [36], although other factors including C4d assay sensitivity may contribute to variable staining. Confident diagnosis of CAMR is problematic because not all diagnostic components may be present. For example, while PTC multilamination is almost always present (91%) in patients with transplant glomerulopathy, detectable DSA in the circulation and C4d deposition in the graft are less common (70% and 32%, respectively) [16]. Overall, about 26% of patients with transplant glomerulopathy have no DSA or C4d. The frequency of transplant glomerulopathy is seen in excess of alloantibodies or C4d staining, suggesting an additional etiology of transplant glomerulopathy such as thrombotic microangiopathy (TMA), complement independent injury, or immune complex glomerulonephritis. Alternatively, the transplant glomerulopathy represents the sequela of prior antibody mediated injury with alloantibodies no longer present at the time of transplant glomerulopathy diagnosis. Subclass variation of IgG alloantibodies with variation of the efficacy of complement activation or microchimerism of endothelial cells may confound or create additional C4d staining variation. Transplant glomerulopathy with DSA but without C4d may be due to complement independent antibody mediated injury.

3. Time course and outcome

Regele observed that patients with C4d positive biopsies in the first post-transplant year have a greatly increased risk of transplant glomerulopathy after one year (6% vs 46%) [17]. This was the first clear demonstration that CAMR evolves over time. Subsequently we documented a sequence of four stages of CAMR in non-human primates: (1) production of DSA, (2) deposition of C4d in PTC, (3) development of transplant glomerulopathy and (4) loss of graft function [37,38]. In these animal studies, monkeys with kidney allografts and alloantibodies but off immunosuppression have identical pathology to humans and universally progress to kidney allograft failure [37,38]. These stages evolved over 3–4

months to more than 2 years in recipients that had no immunosuppressive drug therapy, indicating that CAMR is a slow process. Presumably, progression would be slower in patients on maintenance immunosuppressive therapy. More studies are needed in clinical transplantation to determine the natural history of CAMR and define features that predict outcome. Most studies have shown an adverse outcome for grafts with CAMR. In a study from the Mayo Clinic, transplant glomerulopathy increased the risk of graft loss by 6-fold [26]. Others have shown the combination of glomerulopathy and C4d deposition in late grafts has a markedly worse prognosis than either alone [25]. Even without glomerulopathy, C4d positive PTC is an adverse risk factor for graft loss over 3 years (40% vs 10%). In our cohort of 66 patients with CAMR, the one year graft survival was 54% and only 8% of the graft survived 5 years [24]. One contributing factor to the poor prognosis is that the diagnosis is too often made late, after considerable functional impairment. Clearly early markers are needed to diagnose CAMR before functional impairment develops. The only current method is to monitor patients for DSA and biopsy when these appear. Even with this procedure, diagnosis can only be made only when the disease is histologically obvious. Even with an ideal early detection system, better methods of treatment are needed. Therapies to mitigate the B cells response or reduce alloantibody production.

4. Accommodation

Initial observations in recipients of ABO-incompatible (ABOi) grafts identified that the ABO antibodies can return in patients without precipitating rejection. The grafts commonly (50–80%) have C4d positive PTC without an inflammatory response or evidence of graft injury pathologically [14]. Stable HLA-incompatible grafts have C4d positive PTC at a much lower frequency (2–4%) [39], although presensitized patients have been reported to show C4d positive in 17–26% of protocol biopsies [14,40]. This condition is called accommodation and is defined as stable allograft function without evidence of pathological injury with the simultaneous presence of alloantibodies and graft deposition of C4d. The molecular basis remains unknown but is of great interest, especially if it could be mimicked therapeutically. The mechanisms of accommodation are unknown but are associated with the expression of endothelial protective genes. In accommodated xenografts, expressions of A20 and bcl-2, as well as heme oxygenase (HO-1) are up-regulated and are important to both the development and maintenance of accommodation [41,42]. In another xenograft model of accommodation, the expression of complement regulatory proteins is thought important [43]. Some features detected in accommodated grafts are an increase in endothelial bcl-xL (anti-apoptotic) in renal allografts [44], an increase in CD55 (DAF) in stable heart grafts with C4d [45], and an increase in muc-1 expression in glomerular endothelium in ABOi grafts [46]. Graft accommodation can occur with antibodies that recognize carbohydrates on the graft endothelium, including anti-ABO as well as anti-Gal antibodies [43,47] in xenotransplantation [41]. Although anti-MHC antibodies can be associated with temporary accommodation [48], clinical data suggests that this state of accommodation is not enduringly stable and ultimately results in late graft deterioration. The long term stability of accommodation is unknown. In ABOi allografts, graft stability is present for a year or more. In the HLA allografts, some develop rejection but others seem stable for years [25].

5. Pathogenesis – antibodies

Although the primary targets of antibody mediated rejections are the conventional HLA class I and II antigens [22,49], other MHC related alloantigens (MICA) [50,51], autoantigens [52], parenchymal cell antigens, or unknown endothelial antigens [53] are considered potentially relevant. It is unclear when and if antibodies against the graft are pathogenic. Alloantibodies against the angiotensin type II receptor [54] are clearly

pathogenic by inducing malignant hypertension. In many circumstances anti-class I and/or class II clearly are pathogenic. For other autoantibodies, there is little or contradictory evidence for pathogenicity. IgG subclasses and their efficacy to fix complement may be very relevant. C1q and C4d (complement fixing) alloantibodies are associated with the transplant glomerulopathy of CAMR [55], but low levels of C4d complement fixing are not, at least acutely [56]. Patients with kidney allografts have a pre-transplant mix of subclasses in their DSAs; IgG1 > IgG2 > IgG3 > IgG4, forming three groups: strong complement fixing with IgG1 and IgG3 (28%), weak complement fixing with IgG2 and IgG4 (5%), and the majority with a mix of all subclasses (62%) [57]. The patient group with the weakest complement fixation showed a lower incidence of acute antibody mediated rejections [57]. Anti-donor antibodies of the strongest complement fixing subclass, IgG3, were present in patients with acute rejection, but not in stable patients, whereas the latter had an increase in the non-complement fixing, IgG4 subclass [58]. Non-complement fixing anti donor antibodies of the IgG2 and IgG4 subclasses can be eluted from a minority of rejected renal allografts, and they may therefore have a role (either protective or injurious) [59]. Complement and non-complement fixing antibodies synergize to fix complement more efficiently [60]. The relative titer is presumably important because high titers show more graft loss [61] as compared to low titers [62]. In ABO incompatible grafts the de novo alloantibodies may be more pathogenic [63]. Although there is some data on complement fixation of variation in IgG subclass variation on the pathophysiology of acute antibody mediated rejection, there is none on CAMR.

Our knowledge about the pathogenesis and etiology of CAMR comes from experimental studies in animals, in which the components (antibody, complement, or potential effector cells) can be directly manipulated. Early studies indicated that the arteriopathic lesions that occurred in heart transplants were more severe in the mouse strain combinations known to produce detectable antibodies to donor antigens compared to the strain combinations that did not produce antibodies [64]. But with an intact T cell function, it is not possible to determine how terminal complement activation affects the T cell immunity, macrophage function or complement fixation in the graft endothelium because in both animals and humans with intact immunity, alloantibodies means sensitization and, presumably primed T cells. So it is, therefore, impossible to determine if the chronic rejection is attributable to the primed T cells, alloantibodies, or both. Nevertheless, in mouse studies infusion of class I MHC donor-specific antiserum significantly increased coronary lesions in a dose-dependent fashion, confirming that alloantibodies can instigate vascular changes that occur in transplanted hearts. Subsequent studies using B cell-deficient recipients demonstrate that fully developed, fibrous, chronic allograft vasculopathy was observed only in the presence of alloantibodies [65] confirming a contribution of alloantibodies in chronic allograft rejection. In mice chronic allograft arteriopathy can be produced by adoptive transfer of class I MHC DSA, which elicits severe arteriopathy in MHC incompatible heart transplants in immunodeficient RAG1−/− recipients in just 4 weeks even with transient DSA and C4d [66]. In rat heart allografts the severity and onset of graft arteriosclerosis was reduced in cyclosporine treated recipients deficient in C6 (affecting the terminal components of complement, C5b–C9) [67]. Graft vasculopathy still arises in recipients after adoptive transfer of non-complement fixing IgG1 DSA (which causes no C4d deposition) into RAG-C3 double knockout mice, suggesting that a pathological component includes a complement independent pathway [68]. Thus one possible explanation for the imperfect association of C4d positive and chronic allograft arteriopathy or glomerulopathy is that in certain circumstances or models, lesions may be complement independent. One potential etiology is that antibodies or complement activation may activate the endothelium directly through gene activation. Alloantibody without complement is able to trigger a variety of endothelial responses in culture (e.g., proliferation and expression of FGF receptors) [69]. Further studies in our laboratory linking antibodies and Fc receptors have shown the pathogenesis of antibody mediated chronic

allograft arteriopathy depends on NK cells, which also express Fc gamma RIII [70]. Endothelial responses to antibody in vivo in mice and humans have been demonstrated by an increase in certain phosphorylated signaling proteins in the vasculature, such as S6 ribosomal protein and others [71].

Alloantibodies may augment acute T cell-mediated rejection and bind to graft cells, cell debris, or shed alloantigens to form opsonic multivalent antibody–antigen complexes enhancing their internalization by the Fc receptors on macrophage/dendritic cells, thereby facilitating their presentation to alloreactive T cells [72]. These findings support the hypothesis that alloantibodies in addition to their pathogenic contribution to AHR and CAMR may provide complement mediated co-stimulatory help for alloreactive T cells to mediate mixed complex antibody and cellular rejection.

6. Pathogenesis – complement

Complement (C4d) is widely and characteristically deposited in the capillary endothelium in acute antibody mediated rejection, arguing that complement fixation is important in the pathogenesis [73]. Supportive evidence comes from the demonstration that alloantibodies that fix complement (C4d or C1q on Luminex beads) are associated with a worse outcome that alloantibodies that do not fix complement [55,56]. Furthermore, preliminary studies suggest that acute antibody mediated rejection is inhibited by anti-C5 antibodies with less follow-up transplant glomerulopathy [74]. Decay accelerating factor is important in inhibiting acute antibody mediated rejection with low titers of antibodies [75]. In chronic rejection the evidence is not so clear that complement fixation is necessary. First, the C4d pattern may be focal and not widespread in the capillaries [76]. Second, a substantial number of cases studied by Sis et al. [77] showed that evidence of endothelial injury could be detected by gene expression analysis (microarrays [59]) in patients with donor reactive HLA antibodies, even if C4d was not detectable in the graft. These authors concluded that C4d was not sufficiently sensitive to detect chronic antibody mediated injury possibly due to C4d assay sensitivity. Alternatively, some of these lesions may be related to non-complement fixing antibodies. We know that in specific mouse models, chronic vascular rejection is complement-independent, and it is possible that this also applies to humans. Further studies will be needed to test this hypothesis.

7. Pathogenesis – NK cells

Several studies suggest the potential importance of Fc receptors on either NK cells or macrophages in antibody mediated rejection. NK cells may participate in rejection and acceptance of transplanted organs. NK cells may affect target cells through natural cytotoxicity or antibody dependent cellular cytotoxicity (ADCC). ADCC, triggered by interaction of Fc gamma RIII on NK cells with immunoglobulin bound to antigen on target cells, leads to IFNgamma and TNF gamma production and expression of T-bet among other effects. NK cells, via their Fc receptors, are necessary for hyperacute xenograft rejection mediated by non-complement fixing anti-Gal antibodies [78]. Recent studies have shown that antibody mediated chronic allograft vasculopathy in the mouse manifests NK cell infiltration in the intima. Depletion of NK cells or genetic deficiency of mature NK cells prevented antibody mediated chronic vasculopathy [79]. This process was complement independent, but required the Fc portion of IgG. In human renal allografts increased levels of NK transcripts have been detected in CAMR [80] and increased numbers of T-bet positive cells were present in glomeruli. Further studies are warranted to elucidate the importance of NK cells in human CAMR.

8. Alloantibody responses

Alloantibody responses that develop in follicular B cells from antigen in the afferent lymph are processed and presented by follicular dendritic cells. A secondary response is dependent and augmented by immune-complexes displayed on follicular dendritic cells and also plays a major role in activating B cells and selecting high-affinity B cells. The secondary response depends on the initial antibody to fix complement creating an antigen–antibody complex with C3b/C3d receptors that bind dendritic cells [81]. In some cases allogeneic MHC antigens would most likely be recognized directly on the transplant. Ischemia-dependent inflammation after transplantation activates chemokine secretion that recruits antigen-presenting cells including B cells to the graft. Migrating donor mononuclear cells within the transplanted graft reach the draining secondary lymphoid organs. Alternatively cell debris shed from the graft can reach the draining lymph node. The role and relevance of soluble transplant antigen is unknown but would most likely target the splenic perifollicular mantle zone B cells.

B cell deficient mice show delayed acute allograft rejection [82,83], suggesting that B cells contribute to acute rejection. In a primate model of prolonged islet transplantation, Rituximab, in conjunction with rapamycin, appeared more efficacious than conventional T cell-directed therapy [84]. However, in these experiments the mechanism may be complex and include deficient B cell antigen presentation, direct effects of alloantibody, or complement co-stimulation of T cells [85].

8.1. Post-antigen phase of development

Naïve B cells are stimulated by processed antigen and become activated [86]. B cells then exit G0 and enter G1 in which multiple signaling pathways from the BCR, CD19 co-receptor, CD22, and other receptors initiate post-translational signals stabilizing the D-type cyclins, and modulate the cyclin-dependent kinases, and phosphorylate the retinoblastoma protein. Other pathways control cell survival, translational efficiency, or increase metabolic fitness including mTOR (a Rapamycin target), PI3K, and LXR. In the germinal center where antigen selection leads to high affinity antibodies, geographic location is everything, and specific cells migrate to specific anatomical locations of the secondary lymphoid structures to enable communication with other cell types [87]. Upregulation of CCR7 permits B cells migration to the T–B border initiating cognate interactions with antigen specific T cells. In this interaction, the B cells present processed antigen on MHC class II molecules to activate peptide/MHC specific T cells. Both B and T cells profit from this interaction: B cells present antigen and co-stimulate T cells through CD28-B7, which also provide T cell help to the B cells with CD40. The critical T cells that promote high affinity antibodies are the T follicular cells (Tfh), whose migration to the germinal center are dependent on CXCR5 chemokine receptor CXCL13 ligand interactions [88]. The master regulator of Tfh is BCL6, defining Tfh as a distinct CD4 subset [88]. Although B cells are important as APCs, naive B cells are relatively rare so that dendritic cells, not restricted by antigen specific receptors, are thought to be the initial priming cells to naive CD4 cells in the T cell areas. After initial antigen recognition and migration to the T cell/B cell border, T–B cognate interactions induce BCL6, and some CD4 cells become Tfh cells. High levels of CXCR5 will retain Tfh in the follicle and drive germinal cell B cell differentiation. B cells are more likely required for Tfh maintenance that for Tfh differentiation.

9. Germinal center

Germinal center B cell differentiation depends upon the mutating enzyme activation induced cytidine deaminase (AID) [89], where its activity causes affinity maturation through somatic hypermutation and class switch recombination. Two selection mechanisms are thought to

occur [90]. The first censors against self-reactivity and is controlled by Fas–Fas Ligand interactions. The second selects for high-affinity BCRs. This process is dependent on interactions with both follicular dendritic cells and Tfh. A critical branch-point in B cell development then occurs with the development of post germinal center memory B cells within the germinal center that give rise to pre-plasma cell memory B cells, plasmablasts and long-lived plasma cells [91].

10. B cells in allografts

B cells are not too common in acute rejection, but in long term allografts are readily apparent, often concentrated in nodular aggregates. Some renal allografts with dysfunction have a poorer prognosis when B cells were prominent in the infiltrate [92,93]. However, subsequent studies have not found a consistent correlation [94]. B cells in nodules express AID, suggesting that they are undergoing hypermutation and selection within the graft itself. Lymphoid neogenesis occurs in some grafts late after transplant [95] raising the possibility of a self sustaining entirely local immune reaction can promote long term graft injury [52]. In the heart, nodules of B cells are commonly found under the endocardium, known as the Quilty lesion [96]. This is generally regarded as not pathologic (i.e., not rejection) however its significance is still unclear.

11. Plasma cells

Plasma cells are present in increased frequency in late allografts with rejection and positive C4d [97]. Allograft biopsies regardless of diagnosis have increased levels of immunoglobulin gene transcripts as function of time post-transplant [98]. It is unclear if these plasma cells and their antibodies are specific to the allograft or represent non-specific sequelae of chronic inflammation. A potential pathogenetic role is the demonstration of class II DSA by infiltrating plasma cells cultured from nephrectomy specimens [99]. Others have shown that a variety of autoantibodies arise in transplant recipients which may also play a role in promoting apoptosis or injury [52,100,101]. Plasmablasts are the majority of plasma cells and are short-lived, cycling, and secreting [102]. Plasmablasts are also dependent on BAFF/BLys signals by extra-follicular dendritic cells. The plasmablast response then contracts with a few cells become long-lived plasma cells that reside in the sinusoids of the secondary lymphoid organs, and most importantly in the bone marrow. These cells display high-affinity BCRs, evidence of somatic hypermutation and do not turnover [91]. Their survival depends on growth and survival factors in these specific niches, and they are highly dependent on interactions with stromal cells to provide adhesive and survival signals such as APRIL that maintain antibody secretion [103]. Long-lived plasma cells results in persistent high titers of antigen specific alloantibodies that cause a significant barrier to transplantation in a sensitized patient. Plasma cells in renal allografts is associated with a more adverse outcome. Plasma cell rich acute rejection in the first year had a worse prognosis compared to acute rejection without prominent plasma cells [104]. Others have shown an association of plasma cells with C4d deposition and donor specific antibody [105]. Gene expression studies [98] showed that B cell and plasma cell (Ig) transcripts increases with time after transplant in biopsies taken for graft dysfunction. It is possible that these B cells and plasma cells are directly or indirectly pathogenic or that they are incidental and passively acquired with progressive or late graft dysfunction. Studies by Thaunat et al. in 2 patients have shown that the plasma cells in rejecting renal allografts secrete donor specific alloantibody [106]. This supports a hypothesis that a local alloantibody immune response is present in situ, possibly without detectable circulating antibodies. The allo-graft, therefore, can become a niche for plasma cells.

12. Therapies

Although mycophenolate mofetil (MMF) and calcineurin inhibitors are common in maintenance immunosuppression and may limit alloantibody production in some transplant patients, many maintain or develop alloantibodies. The reduction of circulating alloantibodies is attempted by the use of plasmapheresis or intravenous immunoglobulin (IVIG). However effectiveness is limited or transient because of the volume of distribution of IgGs is high, and the inhibiting characteristics of IVIG are short lived. Rituximab, a monoclonal anti-CD20 antibody, a possible drug to treat CAMR, depletes B cells, which later can develop into alloantibody secreting plasma cells. The potential efficacy of Rituximab is demonstrated in other antibody mediated conditions, e.g., acute antibody mediated rejection in kidney transplant recipients [107], ANCA-associated vasculitis [108], idiopathic membranous glomerulonephritis [109], resistant cases of rheumatoid arthritis [110], multiple sclerosis [111], or experimental diabetes [112]. Rituximab rapidly depletes B cells by apoptotic, complement-dependent, and antibody dependent cytoxic mechanisms [113,114]. The reductions in antibodies were at best modest and inconsistent [114,115] so that the clinical efficacy of Rituximab in some subjects cannot be attributed to a decrease in titer. In Rituximab treated ANCA-associated vasculitis efficacious clinical end points often occur before the predicted reduction in antibody titers [108]. Bortezomib, an anti-myeloma drug, shows efficacy in the treatment of acute antibody mediated rejections [116–120]. Surprisingly, although this proteosome inhibitor presumably targets plasma cells, it had little effect on DSA titers [121]. Potential therapeutic agents also include those that can modulate B cell or plasma cells activation/survival. BAFF, a co-stimulator of B cell survival and expansion is a potential target because a humanized inhibitory antibody to BAFF is efficacious in SLE [122,123]. TACI, a receptor for BAFF and APRIL, is also a potential target. TACI-Ig binds BAFF/APRIL to reduce these B cell signals and show efficacy in SLE [122]. In non-human primates TACI-Ig reduces alloantibodies transiently [124]. An inhibitory receptor is present on plasma cells, Fc gamma RIIB, and a monoclonal antibody against it has been used to direct cells with cytotoxic Fc receptors to amyloidogenic light chain plasma cells [125]. Although some of these therapies have benefit in acute antibody mediated rejection, there are no data on the efficacious treatment of CAMR.

13. Conclusions

Alloantibodies clearly cause acute antibody mediated rejection, and all available evidence supports their pathogenic etiology in the development of chronic alloantibody mediated rejection. But the slow evolution of this disease, the on-going immunosuppression, the variations in titer of alloantibodies, and variation in antigenic targets all complicate identifying which dynamic factors are most important clinically and pathologically. Many important pathogenic questions need answers. Are the basement membrane thickening and laminations of the glomerular peritubular basement membranes and the intimal hyperplasia of chronic vasculopathy a consequence of inflammation or gene activation by alloantibodies and/or complement activation? If inflammatory cells are required, are they macrophages or NK cells? Is the linkage between inflammatory cells and antibody due to Fc receptors, and if so, which cells? How does Fc/antibody engagement and activation lead to gene activation to cause these fixed anatomic abnormalities? Does complement activation provide co-stimulatory signals that recruit T cells, macrophages, dendritic cells, B cells, and NK cells to the allograft, and if so, how do these cells contribute to allograft injury and failure? A most intriguing question is that in animals and man, chronic alloantibody mediated rejections are observed in the relative absence of acute T cell rejection. Because IgG alloantibody is present, T helper cells, presumably Tfh, are present and sensitized. Are T follicular helper cells, Tfh, differentially sensitized as compared to Th1 or Th2 CD4 cells that mediate the acute T cell rejection? The therapeutic challenges are daunting. Do you target the antibody

production from the plasma cells, the B cells that develop into plasma cells, or the Tfh that provide B cell co-stimulatory signals or just the effector phase through complement inhibition or Fc inhibition. Is it possible to determine before transplantation the optimal genetic door-recipient combination to minimize the probability of inducing alloantibodies?. We hope answers to these questions will come in the near future from additional experimentation and randomized clinical trials.

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