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Polyreactive natural antibodies in transplantation

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Abstract

Purpose of review.—Antibody mediated rejection (ABMR), especially in its chronic manifestation, is increasingly recognized as a leading cause of late graft loss following solid organ transplantation. In recent years, autoantibodies have emerged as a significant component of the humoral response to allografts alongside anti-HLA antibodies. These include polyreactive antibodies also known as natural antibodies (Nabs) secreted by innate B cells. A hallmark of Nabs is their capacity to bind altered cells such as oxidized lipids on apoptotic cells. This review provides an overview of these overlooked antibodies and their implication in the pathophysiology of ABMR.

Recent findings.—New evidence reported in the past few years support a contribution of IgG Nabs to ABMR. Serum IgG Nabs levels are significantly higher in patients with ABMR compared with control kidney transplant recipients with stable graft function. Pre-transplant IgG Nabs are also associated with ABMR and late graft loss. IgG Nabs are almost exclusively of the IgG1 and IgG3 subclasses and have the capacity to activate complement.

Summary.—In conclusion, Nabs are important elements in host immune responses to solid organ grafts. The recent description of their implication in ABMR and late kidney graft loss warrants further investigation into their pathogenic potential.

Keywords

Polyreactive antibodies; Natural antibodies; Innate B cells; B1 B cells; Antibody mediated rejection

Introduction

Studies on the role of antibodies in solid organ transplant rejection have mainly focused on anti-ABO blood group and human leukocyte antigen (HLA)-specific antibodies directed at allogeneic targets on graft tissue. More recently, the clinical relevance of non-HLA antigens has been increasingly recognized [1] [2], bringing attention to autoantibodies including a category of broadly reactive antibodies also called polyreactive antibodies. These polyreactive antibodies have emerged over the past few decades as important players

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Conflict of interest

The authors have no conflict of interest

in health and disease with critical functions in maintaining homeostasis and immune protection. Their function in transplantation and allograft injury, however, remains under-defined. Here, we discuss polyreactive antibodies, focusing on current knowledge of their role in solid organ transplantation, in particular their potentially pathogenic effects in graft rejection.

Characteristics and source of polyreactive antibodies

Polyreactive antibodies are defined by their ability to bind to multiple structurally different ligands including self-antigens [3] [4]. They are also frequently referred to as natural antibodies (Nabs) as they are present from birth and produced without evidence of immunization. Polyreactive antibodies have been shown to react to a wide variety of antigens including nucleic acids, carbohydrates, proteins and lipids [4]. Their affinity is typically lower than monoreactive antibodies [5]. While polyreactive antibodies of all isotypes have been identified [6] [7] [8] IgM, IgG and IgA are the most common and comprise a significant portion of normal human immunoglobulins in sera and mucosal secretions [9] [10]. The biological properties of polyreactive Nabs enable them to carry out important functions in cell homeostasis of healthy tissue and in host defence [11]. Polyreactive antibodies, in particular IgG, have also been attributed pathogenic roles in the context of autoimmune and inflammatory diseases such a systemic lupus erythematosus (SLE) [12] and rheumatoid arthritis (RA) [13].

Several structural models have been proposed to explain the polyreactivity of monoclonal Nabs. In contrast to the rigid “lock and key” model of classic antigen-antibody binding, the antigen binding site of polyreactive antibodies are thought to have more flexibility in order to accommodate different antigenic configurations [4]. Antigen-binding sites may also exist as conformational isomers, with each isomer binding to different antigens [14]. Another model suggests that the antigen-binding pocket is endowed with multiple recognition sites enabling the binding of various antigens [15]. Additionally, polyreactivity can also be explained by protein-destabilizing conditions in vitro and in vivo [16] [17].

In mice, several lines of evidence suggest that polyreactive Nabs are produced by heterogenous innate subsets of B cells including peritoneal B-1 B cells [18], marginal zone B cells [19] and a population of $CD5^{-}$ plasmablasts and plasma cells in the bone marrow [20]. In humans, however, the identification of a distinct innate B-cell subset producing these antibodies remains elusive. What is clear is that the B cells that produce polyreactive antibodies express polyreactive receptors [21] and can be found at a relatively high frequency in human peripheral blood. Approximately half of the B cells from cord blood [22] and about 20% of circulating B cells of adults were found to exhibit polyreactivity [22] [23] [24]. Sequence analysis has determined that human polyreactive antibodies can be both germline [25] or mutated, suggesting that specificity to multiple ligands may be positively selected through affinity maturation [23] [26] [27].

Protective and pathogenic roles of polyreactive antibodies

Polyreactive Nabs have important roles in defence against invading pathogens as well as cell homoeostasis [28]. These antibodies contribute to the early antibacterial and

antiviral immune response [29] [30] [31]. The recognition of microbes is aided by their ability to react to a broad range of pathogen-associated molecular patterns including lipopolysaccharide [32], bacterial cell wall components [33] and viral antigens [34] [35]. Polyreactive Nabs also recognize pathogens indirectly by binding via pathogen-associated host serum proteins [36]. Once bound to pathogens, Nabs can neutralize, opsonize and activate complement-mediated killing of their targets [29] [37] [38]. Studies in mice and humans have demonstrated that the lack of polyreactive Nabs responses lead to ineffective antibacterial [36] [39] and antiviral responses [34] [38] [40].

Cell death is an integrative part of normal cell turnover. The removal of millions of dead or dying cells everyday by a process called efferocytosis is vital to the maintenance of healthy physiological conditions. Clearance of apoptotic cells [41] as well as senescent red blood cells by [42] phagocytes is facilitated by polyreactive antibodies. Determinants recognized by Nabs include phosphorylcholine [33], phosphatidylserine [43] and the lipid peroxidation product malondialdehyde on apoptotic cells [44] and band 3 protein on red blood cells [45].

Aside from their protective function, polyreactive antibodies have also been involved in autoimmune and inflammatory conditions. In lupus, polyreactive antibodies have pathogenic potential. In particular, polyreactive IgG secreted by B cell clones derived from SLE patients appear to bind glomerular antigens resulting in neuronal damage [12]. In RA, where anti-citrullinated peptide antibodies are important hallmarks of the disease, polyreactive IgG, derived from patient synovial fluid B cells, were shown to bind citrullinated antigens [46]. In experimental RA, anti-citrullinated antibodies can enhance inflammation when transferred into mice [47]. It is interesting to note that this pathogenic potential is usually attributed to IgG Nabs while the role of IgM Nabs appears to be less clear [48]. However, a recent study using a mouse model of glomerular disease showed that natural polyreactive antibodies, particularly natural IgM, bound to glomeruli and facilitated proteinuria and glomerular damage [49].

Polyreactive antibodies in transplantation

Xenotransplantation.—Humoral immunity is a fundamental barrier to xenograft survival. The major antigenic target of xenoreactive antibodies is Galα1-3Gal (α-Gal) [50] although non-α-Gal antigens can also be immunogenic. Xenoreactive antibodies have been described as polyreactive [51] with one study showing that anti-α-Gal antibodies recognized DNA, actin, myosin and tubulin [52]. As demonstrated in previous reports, polyreactive Nabs from human serum display xenoreactivity, binding to pig lung antigens [53] [54]. In another study, human polyreactive antibodies, but not monoreactive antibodies, were shown to react to murine tissue antigens [55]. Polyreactive antibodies are also deposited on rejected xenografts [56]. These Nabs usually damage graft tissue through complement-mediated mechanisms [57].

Antibodies to ABO blood group antigens.—Without prior desensitization treatment, transplantation of an ABO incompatible graft in adults results in hyperacute rejection due to antibodies in the recipient serum recognizing donor blood group antigens on the graft endothelium. Some of these anti-ABO antibodies were shown to be polyreactive in an early

study [58]. In this report, 84% of IgM and ~50% of IgG reactive to blood group antigens also reacted to unrelated antigens such as DNA, tetanus toxoid, thyroglobulin, lysozyme and dinitrophenol.

Ischemia reperfusion injury (IRI).—Polyreactive antibodies have also been implicated in IRI, a complex, multifactorial process occurring immediately after transplantation when organs or tissues are reoxygenated after a period of hypoxia. During IRI, ischemic endothelial cells expose altered self-antigens [59] recognized by Nabs, which in turn exacerbate the inflammatory reaction and graft damage [60]. The contribution of Nabs to IRI was demonstrated in Rag2−/− mice reconstituted with wild-type mouse serum [61]. Nabs binding to these newly exposed determinants, including myosin [62], annexin IV [63] [64] and membrane phospholipids [65], and mediate cell damage by complement activation [66] [67]. Conversely, blockage of self-reactive IgM reduced the ischemic injury [67] [68].

Allotransplantation.—Antibodies to donor HLA play an important part in rejection [69] [70] [71] [72]. However, antibody-mediated rejection can occur in the absence of donor-specific HLA antibodies [73]. Several lines of evidence have now emerged suggesting that non-HLA antibodies are also implicated in transplant injury [1]. Polyreactive Nabs represent one such type of non-HLA antibodies. Their presence was revealed at the clonal level by immortalizing B cells from clinical specimens from a kidney transplant recipient experiencing rejection [74]. A number of clones were generated that secreted monoclonal polyreactive antibodies recognizing multiple self-antigens [74]. One such clone was even reported as highly expanded in the patient's blood. All polyreactive antibodies appear to react to determinants on apoptotic cells but not to viable cells [75], reminiscent of the apoptotic cell-binding capacity of natural antibodies. Using reactivity to apoptotic cells as a means to detect polyreactive Nabs IgG in the serum, it was found that kidney graft patients with ABMR had higher levels of Nabs than transplant recipients without the complication [75]. These antibodies could activate complement, leading to C4d deposition as the surface of target cells. A subsequent report associated higher levels of IgG Nabs reactive to apoptotic cells in pre-transplant serum with late kidney graft loss [76]. Taken together, these findings suggest a significant role for IgG Nabs in kidney transplant rejection. The role of these antibodies in other types of solid organ transplants is still unclear.

Origin of polyreactive antibodies in transplant recipients

The precise origin of polyreactive IgG Nabs observed in kidney transplant recipients is not clear. As mentioned above, polyreactive Nabs, mostly IgM, are present in healthy individuals [6] [23] [77] but aberrant levels, especially IgG Nabs, are detected in various autoimmune diseases [48]. It is likely that innate B cells constitutively producing IgM Nabs at the steady-state, undergo class-switch recombination (CSR) and produce IgG Nabs, detectable by assessing the serum reactivity to apoptotic cells. A possible mechanism could resemble sensitizing events responsible for the development of anti-HLA antibodies through blood transfusion and exposure to HLA-mismatched foetuses during pregnancies. In that scenario, cell damage encountered by transplanted tissue during the surgical procedure or by the native kidney during end-stage renal disease, results in tissue injury and release of apoptotic bodies. Exposure to these apoptotic determinants then triggers polyreactive B cell

activation and CSR. In support of this view, the accumulation of apoptotic cells has been associated with inflammation and disease [78]. Stimulation of Toll-like receptors on B cells is another potential mechanism resulting in the development of polyreactive antibodies in transplantation. Graft cell death initiated by IRI leads to the release of damage-associated molecular patterns, which, in turn, activate TLR-signalling pathways [79]. In support of this mechanism, polyreactive serum antibody levels were enhanced following TLR 3, 4, 7 and 9 stimulation in mice [80]. There are also several lines of evidence linking apoptosis with vascular injury following transplantation. The inhibition of pro-apoptotic effector caspases reduces microvascular injury in liver and heart transplant models [81] [82] while the over-expression of anti-apoptotic Bcl-2 reduced coronary artery vasculopathy [83]. Following a similar scenario, Dieude et al. [84] showed in a mouse model that vascular injury leads to the release of exosome-like apoptotic cell vesicles that induced B cell responses and the production of anti-LG3 antibodies.

Function of polyreactive antibodies in transplant rejection

The pathogenic potential of polyreactive antibodies in kidney graft rejection is still uncertain. On one hand, their presence may result from cellular injury encountered by the graft but may have no direct consequences. On the other hand, the finding that virtually all pre-transplant polyreactive IgG Nabs associated with late kidney graft loss are complement-fixing IgG1 and IgG3 [76] strongly suggests that these antibodies are more than bystanders and contribute to tissue destruction alongside classical DSA. In ABMR, a major mechanism of graft injury occurs when complement is fixed by antibodies bound to graft tissue. Activation of the complement cascade leads to formation of the membrane attack complex and chemotaxis of inflammatory cells. It is also possible that immune complexes formed by the binding of polyreactive antibodies to target antigens can activate C1q further contributing to complement-mediated inflammation.

The pathogenicity of polyreactive antibodies may also be exerted via activation of endothelial cells of the graft. Antibodies to HLA have been shown to directly activate endothelial cells in the kidney and heart setting [85] [86], and via sublytic complement injury [87]. Endothelial activation leads to a pro-inflammatory state, resulting in subsequent immune cell recruitment and tissue damage. It is, however, unclear how polyreactive Nabs, which do not usually bind to viable cells, would activate endothelial cells.

Another appealing possibility is that polyreactive antibodies can amplify the microvascular damage induced in grafts undergoing rejection by synergizing with DSA. Recent reports suggest that antibodies to non-HLA may act in synergy with classical DSA to mediate graft rejection. For instance, studies showed that the presence of both DSA and AT1R antibodies resulted in lower reduced freedom from rejection compared to presence of each antibody individually [88] [89]. Four separate monoclonal polyreactive antibodies isolated from kidney transplant recipients were found to cross-react to several HLA molecules pointing to a potential synergistic effect with DSA [74] [90]. These mechanisms, however, are still hypothetical at this point.

Conclusions

There is now little doubt that polyreactive Nabs have to be taken into consideration when assessing the humoral immunity to solid organ grafts. However, many questions related to their exact impact on rejection remain unanswered. In particular, a direct causal evidence of their implication in graft tissue destruction is still awaited. Elucidating the mechanisms whereby polyreactive Nabs can exert their pathogenicity would considerably advance the field and facilitate the design of effective management strategies. Further clarification of the nature of the antigens recognized by these antibodies would also allow the development of additional assays for their detection. Advances in proteomic approaches such as those used to identify anti-endothelial cell and anti-apoptotic cell vesicle targets [84] [86] may help in achieving this goal. At this stage, we can be confident that future studies will continue to uncover novel characteristics and functions of these overlooked antibodies as well as addressing their significance in the development of ABMR.

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Bulleted summary:

- Serum natural polyreactive antibodies correlate with antibody-mediated rejection of kidney grafts
- Pre-transplant serum natural antibodies associate with late kidney graft loss
- IgG natural antibodies are primarily complement-fixing IgG1 and IgG3
- IgG natural antibodies can cross-react to HLA on beads used to detect anti-HLA antibodies by Luminex