

Potential Role Of B-Cells In Compromizing Graft Outcome In Kidney Transplantation

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Running Title

Graft specific B cells

Introduction

Incremental increase in the frequency of memory vs naïve B cells has been associated with poor long-term allograft survival. Role of graft-specific B cells in chronic allograft rejection is still unknown. Identification of graft-specific B cells is of importance in better understanding the mechanisms of graft lesions, earlier diagnosis of acute & chronic rejection, and to guide specific B cell-targeted therapy. This review article provides overview of research surrounding the importance of graft specific B cells in kidney transplantation.

Human Leukocyte Antigen (HLA) Antibodies Post Renal Transplantation

Donor specific HLA antibodies have been associated with acute and chronic immunological graft injury [1-3]. Their correlation carry many pitfalls. When anti-donor antibodies are not detected, it is not clear whether it is because the antibodies quantity are too small, their disappearance from the serum related to their sequestration in the transplanted organ [4], or whether none are produced because of unresponsiveness of the recipient against donor antigens [5,6]. Moreover, it is not unusual to find patients who developed antibodies post transplantation demonstrating a decrease in antibody titer up to complete elimination of those antibodies. Such patient generates antibodies rapidly after re-exposure to the sensitizing antigen. Similar observations were seen in multiparous women who developed antibodies at some stage of their lives but later on fade out despite the clear

presence of quiescence memory cells. Thus, detection of antibodies against HLA in the serum after transplantation depend on a balance between immunogen, antibodies generation, sequestration of the antibodies by the transplanted graft plus block of antibodies by regulatory factors [7].

Identification of HLA specific B cells

Memory B cells may be poly-reactive than antibodies produced by Long Lived plasma cells [8]. During a secondary infection, serum could only protect when challenged with a homologous virus, whereas memory B cells could protect against both homologous and heterologous variant virus when challenged. The results from viral studies reflect an important issue in transplantation. First, during pre-transplant preparation step, it suggests that analysis of the reactivity against the donor HLA of sensitized patients using serum alone may be insufficient for optimal HLA matching. Second, after secondary transplantation in sensitized patients, de-novo donor specific antibodies (DSA) associated with unpredicted or multiple HLA specificities may be arising from memory B-cell precursors.

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The ability to detect and identify the specificity of circulating B cells with the potential to make HLA antibodies should provide tool to analyze antibody formation and shed light on the balance between production, inhibition and sequestration at any given time in the post-transplant period. Perry et al. recently reported on an assay to detect in vitro HLA specific antibody secreting cells from the bone marrow of sensitized kidney transplant recipients [9]. T and B-cell ELISPOT have also been used to measure HLA specific B cell frequency against a given antigen. ELISPOT assay does not measure the frequency of cells that actually bind the antigen and only measures biological events such as cytokine release [10] or production of immunoglobulin after differentiation in vitro [11,12].

Based on the structural similarity between B cell receptor and immunoglobulin binding sites, it is postulated that HLA-specific B cells should bind to HLA molecules with specificity comparable to that of the secreted immunoglobulin. Indeed, identification of HLA specific B cells by staining through binding of the B cell receptor using fluorescently labeled tetramers of identified HLA class I specificities has been described [13]. A different approach is to utilize commercially available single antigen coated, color-coded microspheres, multiplexed in an assay that is currently the mainstay of soluble antibody detection in the circulation [14-16]. However, this powerful assay has also highlighted the challenges of cross- and poly-reactivity of allo-antibodies [17, 18] have recently described a method utilizing single HLA coated beads to enumerate HLA committed B cells [18]. Class I HSB identified in non-transplanted individuals were described by [19] who identified HLA specific B cells using tetramers and of who isolated B cells from blood donors using HLA-A2 tetramers [20]. Up to our knowledge no studies reported identification of HSB class II in transplanted recipients. Frequency of HSB from transplanted recipients was higher than in non-transplanted individuals that has been observed with tetramers studies [21, 22] especially frequency of HSB in the poor outcome group. CD27 [26] and CD38 [23] phenotypes considered markers of memory and transitional immunoglobulin secreting cells among total B cells. An observation of memory B cells depletion following alemtuzumab induction therapy, majority of CD27 positive B cells and CD38hi/IgDhi, CD38+/IgD- were depleted in the 3 months samples compared to pre-

transplant samples and re-populated at 12 months that was reported by [24] and [25] with alemtuzumab induction therapy. Interestingly, majority of B cells remaining in the memory compartment were HLA specific B cells especially in the group of recipients with poor outcome and that may be because they could escape depletion by induction therapy. [21, 22] reported similar findings when they identified HLA class I specific B cells from end-stage renal patients and healthy volunteers using tetramers. While in study majority of HSB identified by HLA-coated beads were within the mature naïve (CD27-IgD+) compartment from five immunized transplant recipients [18]. A phenomenon of anti-HLA antibodies generation has been described after some bacterial or autoantibodies directed against the heavy chain of soluble HLA-E could explain HLA class I reactivity [26, 27] and even after vaccination [28]. Further, in the case of induction therapy at time of transplantation it has been shown that depletion of T and B cells below certain level can lead to homeostatic proliferation of memory B cells that escape the depletion producing de novo expansion of anti-HLA B cells and production of circulating HLA antibodies that may lead to humoral chronic rejection if the antibodies cross-react with shared epitopes presented by donor graft [29].

Management of Graft Infiltrative Specific B Cells

Understanding the basic biology of B cells allow for use of specific therapeutics for instance, anti-CD20 (Rituximab) successfully control memory and active naïve B cell responses, targeting the B cell survival factor with anti-BAFF/BLyS (anti-BAFF; belimumab) reduces mature B cell pool as well germinal center B cell responses, additional inhibition of plasma cells can be achieved by combined inhibition of BAFF and APRIL with TACI-Ig; (atacept) [30]. Depletion of short-lived antigen specific cells can be achieved with the small molecule inhibitor of proteasome, bortezomib (Velcade), which promotes plasma cell apoptosis and inhibits cell proliferation [31].

In conclusion comparable assays are being used to quantify plasma cells and memory B cells specific for HLA or pathogens in transplant patients. These assays will guide clinicians to quantify the efficacy of immunosuppression targeting each B cell or plasma cell subset.

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