The Role of Long-Lived Plasma Cells in Antibody-Mediated Rejection of Kidney Transplantation: An Update

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Abstract

Background: Antibody-mediated rejection (ABMR) following kidney transplant is closely associated with poor prognosis of the recipients. Long-lived plasma cells (LLPCs) produce alloantibodies as long as life time and play a crucial role in ABMR. **Summary:** LLPCs generate from germinal centers and reside in survival niches in the bone marrow as well as the inflamed tissues. They are the main and long-term source of the antibodies. LLPCs mediate ABMR via the generation of preformed antibodies in sensitized patients and de novo antibodies after transplantation. They have been acknowledged as the leading causes of ABMR; however, LLPCs are insensitive to traditional immunosuppressive therapy that removes B cells. Strategies targeting LLPCs, such as antithymocyte globulin, proteasome inhibitors as well as monoclonal antibodies, are promising methods to persistently and

thoroughly clear the entire PC pool. **Key Message:** LLPCs play an important role in ABMR by producing alloantibodies continually, and targeting LLPCs might be a novel and effective approach against ABMR.

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Introduction

The incidence of antibody-mediated rejection (ABMR) is 1–5% in unsensitized patients, and it may rise to 25% or greater in highly sensitized kidney transplant recipients, such as ABO incompatible, history of prior transplantation and blood transfusion, as well as polytocous pregnancy [1–3]. ABMR accounts for 30–50% of early graft dysfunction and >60% of chronic rejection episodes [4–6]. Donor-specific antibodies (DSAs) play pivotal roles during ABMR, and the incidence of DSAs ranges from 20 to 30% among renal allograft recipients [7, 8]. Preventing the production and eliminating DSAs are fundamental in the management of ABMR.

To date, plasmapheresis (PP) [9] and intravenous immunoglobulins (IVIG) are the basic therapies for ABMR [10]. PP is effective to remove existing DSAs from the circulation but not aimed at novel antibody synthesis. Therefore, PP with neutralizing antibodies or blocking antibody production is commonly used.

IVIG, composed of >90% intact IgG, is a commercially prepared product from large pools of human plasma. The exact therapeutic mechanism of IVIG remains obscure. Some possible mechanisms include inhibition of B-cell immunoglobulin production, neutralization of DSAs, inhibition of cytokine and complement-mediated inflammation, and induction of B cell apoptosis through Fc receptors-mediated signals [11, 12].

Although PP and IVIG remain the cornerstone in post-transplant protocol against ABMR, the efficacy of these approaches is unsatisfactory and appears to be partial or transient [13]. The difficulty in ABMR remedy has emphasized the necessity to explore more effective strategies.

Long-lived plasma cells (LLPCs) reside in the bone marrow and inflamed tissue, and they can produce allo-antibodies as long as life time and this phenomenon plays a crucial role in ABMR. Compared to the short-lived populations, the differentiation of LLPCs is independent of B-cell precursors and they are irresponsive to common immunosuppressive agents such as cyclophosphamide and steroids. Therefore, LLPCs have presented as a promising therapeutic target in kidney transplant recipients with ABMR. In this review, we discussed the triggers and routes of B cell development, the generation of LLPCs, the roles of LLPCs in ABMR, and the strategies for its depletion.

The Generation of PCs and LLPCs

Plasma cells (PCs) are antibody-producing cells terminally differentiated from B cells and are classified into 2 categories: one is short-lived PCs (SLPCs) stemming from activated B cells and another is LLPCs generating from germinal centers (GCs). LLPCs contribute to the persistent antibody generation. The long-term survival property of PCs is mainly dominated by the micro-environmental niches and the distinctive surface markers of themselves.

Triggers and Routes of B-Cell Development

Usually, immature B cells leave the bone marrow and differentiate into the B1 and B2 subsets. B1 cells are self-renewing and non-circulating populations mainly locat-

ed in the peritoneal and pleural cavities. B2 cells are derived from lymphoid stem cells of the bone marrow. Immature B2 cells leave the bone marrow and differentiate into mature B2 cells in lymph nodes and spleen. B2 cells are the conventional circulating B cells composing nearly 95% of the whole B-cells population [14].

Differentiation of B cells into PCs majorly involves T cell-independent as well as T cell-dependent (TD) pathways. The T cell-independent pathway, involving in either B1 or B2 to PCs growing, is mediated by B cell receptor (BCR)-independent polyclonal B cell generation. After antigen activation, serum low-affinity antibodies, like immunoglobulin M, are produced by SLPCs. In comparison, the T cell-dependent mechanism, only participates in B2 to PCs maturation and is more sensitive to protein antigens requiring co-stimulation from activated CD4⁺ T helper cells. In this state, B2 cells firmly react to antigen signals followed by an extra-follicular response leading to the generation of SLPCs secreting antibodies with moderate affinity. Next, some of the SLPCs re-enter the B-cell follicle receiving assistance from the T helper cell, which contributes to the formation of GC. Some of the PCs generated in GCs migrate to the survival niches in bone marrow where they become long-lived [15]. After class-switch recombination and somatic hypermutation, high-affinity antibodies are produced [16] (Fig. 1).

The Development of LLPCs

Before being long-lived, B2 cells experience intense proliferation and Ig gene modification in GCs and only a limited number of B cells are able to become long-lived. Studies suggest that PC longevity mainly depends on survival factors surrounding their living environments [17, 18]. But how plasmablasts migrate into the bone marrow and inflamed tissues becoming long-lived is unclear. Below we address several potential mechanisms that are involved in this process (Fig. 2). First of all, the migration of PCs to survival niches is a crucial step for the differentiation of plasmablasts to become long-lived. This step is highly regulated by chemokines and adhesion molecules. When plasmablasts lose certain C-X-C motif chemokine receptors or CC-chemokine receptors on the surface, they become insensitive to the corresponding chemokines and cannot migrate to the survival niches [19, 20].

Second, survival factors provided by the niches of bone marrow and inflamed tissues may determine the lifespan of LLPCs. Experiments have proved that LLPCs separated from the bone marrow die in culture after a few days due to lack of survival niches [17, 21]. Consistently, in inflamed tissues, LLPCs longevity disappears after the in-

Fig. 1. Triggers and routes of B-cell development. Immature B cells derived from LSCs leave the bone marrow and differentiate into mature B1 and B2 cells, then plasma cells are developed via TI and (or) TD mechanisms. The former one is non-BCR or T-cell dependent. However, the TD pathway requires the assistance from activated CD4⁺ Th cells. First, following an extra-follicular response the SLPCs are generated. Next, some of the SLPCs reenter the B-cell follicle receiving the help of Th cell, forming a GC, and then migrate to the bone marrow becoming LLPCs. LSC, lymphoid stem cells; LLPC, long-lived plasma cell; TI, T cell-independent; TD, T cell-dependent; GC, germinal center; Th, T helper; SLPC; short-lived plasma cell.

flammation is resolved [18], and several inflammatory mediators are closely related to the differentiation of LLPCs. Besides, adhesive molecules, such as vascular cell adhesion molecule-1, also provide an environment required for LLPCs life span [22–25].

Third, autophagy, a conserved lysosomal recycling process that regulates intracellular metabolism and capacitates adaptation to stress, is required for PCs homeostasis and may contribute to the longevity of LLPCs. Autophagy sustains antibodies generation by regulating the expression of the transcriptional repressor B lymphocyte-induced maturation protein 1 [26]. An elevated expression of B lymphocyte-induced maturation protein 1 has been proposed to have a cardinal role in regulating B cell from plasmablasts to LLPCs [27, 28]. In addition, autophagy is a crucial intrinsic determinant for LLPCs generation in the bone marrow, which is proved by the fact that autophagic molecule-deficient B cells have less ability to generate LLPCs [29].

Fourth, the downregulation of certain surface molecules also accounts for the development of LLPCs [30]. For example, recent evidence suggests that the long-lived subsets lack CD19 in humans [31, 32] and the loss of CD19 expression marks the progressive differentiation and longevity of PCs [27].

Fig. 2. The mechanisms involved in SLPCs to LLPCs. There are primarily 4 mechanisms contributing to LLPCs generation; they are (1) survival niches, that highly regulated by chemokines and adhesion molecules, including CXCRs and CC-chemokine receptors; (2) survival factors, such as IFN- γ and IL-17A; (3) autophagy processes, and the deficiency of autophagy will impair B cell's ability to generate LLPCs; (4) surface molecules modulation, for instance, the suppression of CD19 expression. SLPC; short-lived plasma cell; LLPC, long-lived plasma cell.

Fig. 3. Current and potential therapeutic drugs targeting plasma cells. Current therapeutic approaches mainly target B cells to inhibit the generation of SLPCs, such as CD20 monoclonal antibody. Frequently, the LLPCs are refractory to conventional immunosup-

pressive drugs, but second generation of PIs, Mas, and microRNAs targeting the survival of LLPCs are promising remedies to deplete LLPCs. ATG, antithymocyte globulin; LLPC, long-lived plasma cell; MA, monoclonal antibodies; PI, proteasome inhibitor.

LLPCs in Immunopathology of Kidney Transplant

Recently, LLPCs have taken the spotlight in kidney transplant, as they have been acknowledged as the leading causes of ABMR, accounting for over 50% of kidney graft loss [33]. Generally, LLPCs mediate the graft injury via the generation of DSAs, including preformed antibodies in sensitized patients and de novo antibodies after transplantation. Human leukocyte antigen (HLA) is the major origin of DSAs and it can be divided into 2 categories, that is, Class I and II. Besides, some non-HLA antibodies also participate in ABMR, which frequently leads to false negative of DSA by routine clinic analysis. Antibodies against angiotensin II type 1 receptor, ABO blood type antigen, complement component 1q-binding sites, and collagen IV antigens are non-HLA DSAs involving in ABMR [34].

These allo-antibodies bind to HLA Class I and II as well as non-HLA antigens expressed on endothelial cells, and initiate complement fixation, activation, and complement component 4d deposition. Finally, these events elicit endothelial cytotoxicity with the reduction of blood flow, hypoxia, and damaged graft function.

The Roles of LLPCs in the Production of Preformed DSAs

The incidence for preexisted alloantibodies is awfully high that over 50% of highly sensitized recipients have it [35, 36] and LLPCs are the major sources of panel-reactive antibodies (PRAs), including preformed DSAs, which consequently leads to a positive serum cross-match before kidney transplant [37].

In recipients with repeated blood transfusion, the antigens of foreign hemocytes activate the allogenic B cells and promote the development of LLPCs, which accounts for the existence of preformed DSAs. Similarly, foreign HLA antigens from prior allograft are another reason leading to LLPCs activation and PRAs/preformed DSAs production [36, 37]. Recently, spousal kidney transplant has attracted the attention of clinicians with the promising outcomes [38–40]. However, in husband-to-wife transplantation, recipients who were previously pregnant are associated with an inferior graft survival with biopsy-proven antibody-mediated graft injury [40]. The above phenomenon can be explained as follows: preformed IgG antibodies to HLA Class I antigens from husband are generated in wife during coition, and they are presumably reactivated by kidney allograft implantation, consequently leading to the sustained alloantibodies production.

The Roles of LLPCs in the Production of de novo DSAs

De novo DSAs in recipients are the principal reason for the dysfunction and failure of allograft. The unmatched HLA or non-HLA allo-antigens from donors trigger the differentiation of LLPCs in which several steps are involved.

First, immature B cells recognize the HLA antigens of unmatched donors via the surface BCRs, and then stimulate the BCR signaling pathway followed by the transcriptional activation of a series of genes, which are tightly associated with B-cell activation [41, 42].

Second, the BCR mediates the antigen uptake and processing, and then presents antigen to T cells, which ulti-

mately triggers entirely the activation and differentiation of the B cells [2, 5, 6]. LLPCs are afterwards generated stepwise and produce DSAs persistently through a long-term, stimulating the occurrence and development of ABMR.

Third, the transplanted kidney environment may attract PCs homing to the graft and trigger the recapitulation of lymphoid organogenesis [43] within the graft niches where the LLPCs are developed. LLPCs do not proliferate and escape from the apoptosis pathway, acting as long-term antibody-producing factories.

Drugs Targeting LLPCs

LLPCs are responsible for allograft rejection and resemble a challenge for the therapy of kidney transplant. There are an increasing number of studies about the therapeutic strategies targeting B-cell or PC responses, among which several regimes also have effects on LLPCs (Fig. 3). Below we address their therapeutic effects and mechanisms.

Antithymocyte Globulins

Antithymocyte globulin (ATG) is prepared by immunizing rabbits or horses with nonfractionated pediatric thymic cells. It has been widely used in desensitization and ABMR and its possible mechanisms are delineated below.

First, Igs contained in ATG trigger complement-mediated LLPC lysis by targeting surface markers of LLPCs. In vitro, ATG is able to induce apoptosis against LLPCs, in a clinically relevant dose, through the caspase- and cathepsin-mediated pathways [44–46]. Second, Igs contained in ATG directly work against PC surface proteins that interfere with LLPC generation and induce apoptosis.

Proteasome Inhibitors

The rapid and effective elimination of DSA during ABMR is rarely achieved with traditional immunosuppressive therapies. Proteasome inhibitor (PI)-based therapy has been shown to be promising for the refractory ABMR.

Bortezomib in Kidney Transplant

Bortezomib, the first PI tested and approved in clinic, has been successfully used in multiple myeloma (MM, a PC neoplasia). Recently, it is presented as a potential first-line therapy for kidney transplant recipients with ABMR

[47] by depressing donor-specific PCs, LLPCs [48], and HLA antibody-triggered complement activation [49].

Within 1 week after kidney transplant, LLPCs are generated followed by the production of large amounts of antibodies [50, 51]. These excessive antibodies contribute to ER stress by misfolded protein accumulation. If these misfolded proteins cannot be eliminated on time, LLPCs will undergo apoptosis [52, 53].

The use of bortezomib inhibits the function of proteasomes and slows down the clearance of unfolded proteins, leading to overwhelming ER stress and cell apoptosis. This is the main pathway by which bortezomib contributes to LLPC apoptosis and DSA reduction. Besides, bortezomib also induces cell apoptosis by the intrinsic mitochondrial pathway and the extrinsic death-receptor pathway, which include the inhibition of NF- κ B by preventing the degradation of its inhibitor I κ B; dysregulation of cyclin-dependent kinase activity, an imbalance between the pro-apoptotic and anti-apoptotic Bcl-2 family proteins, and so on.

It is noteworthy that bortezomib kills highly active PCs that produce high amounts of IgG antibodies exclusively. The activated LLPCs with a higher level of ER stress are especially sensitive to bortezomib; otherwise, some SLPCs are in a low state of antibody production and they are hardly affected by bortezomib [54]. Therefore, bortezomib rarely impairs the protective immunity and it presents obvious advantage in kidney transplant.

Bortezomib in Pre-Transplant Desensitization. Several researches have demonstrated the potential safety of bortezomib-based therapy in the treatment of highly sensitized wait-listed patients and its effect to facilitate successful kidney transplant [55–58]. For example, in a prospective iterative trial of bortezomib-based desensitization, 86% patients achieved the reduction of HLA antibodies and this was correlated with the dosing of bortezomib. Moreover, bortezomib-based treatment is also effective in the inhibition of HLA Class II antibodies as well as antibodies against public epitopes, which usually refractory to IVIG-based regimes.

Bortezomib in Post-Transplant ABMR. Bortezomib-based regimen is suggested to be the major therapy for post-transplant ABMR. Bortezomib provides prompt and persistent decrease in DSA levels [59]. The efficacy of bortezomib-based therapy on de novo antibodies has been acknowledged by accumulating researchers recently. Several therapeutic strategies containing bortezomib have been proven efficient to treat the acute ABMR [60–62]. Bortezomib not only successfully decreased antibodies against HLA Classes I and II, but also reduced some non-

Fig. 4. Summary of the current and potential treatments against ABMR by targeting LLPC and its survival niches. ATGs may trigger complement-mediated LLPC lysis. PIs induce apoptosis of LLPCs owing to the accumulation of unfolded proteins. CD38 is highly expressed in B-cell ontogeny in both the early and late stages of maturation. CD38 blockade is possible to suppress LLPCs' generation; however, more studies are in demand. Interaction of B-cell maturation antigen with BAFF and APRIL is essential for LLPCs survival; therefore, depleting these proteins may result in LLPCs apoptosis. CXCL12 is vital for LLPCs migration and survival. Blockade of CXCL12 contributes to LLPCs depletion. As miRNA is also crucial for LLPCs survival, silencing some miRNAs (e.g., miRNA-155, miRNA-17-92) may be a promising approach. PI, proteasome inhibitor; BCMA, B-cell maturation antigen; BAFF, B-cell activating factor; ATG, antithymocyte globulin; LLPC, long-lived plasma cell.

HLA antibodies targeting ABO blood group antigen, and angiotensin II type 1 receptor, which resultantly related to better graft function after bortezomib therapy.

But it is worth noting that Bortezomib-based regimen has presented rather good results in the short term, but the long-term prognosis is sub-optimal [60]. Up to now, experience with the chronic ABMR is relatively limited.

Second Generation of PIs in Kidney Transplant

Though bortezomib is effective in allograft rejection, new medications with less adverse events and more convenient administration routes are still needed. Several second-generation PIs have been identified in preclinical and clinical development, including carfilzomib, PR-047, ixazomib, CEP-18770, MLN9708, and NPI-0052. Unlike bortezomib in enzyme binding kinetics, the pharmacology of these new PIs may lead to different efficacy levels and improved safety profiles. However, most of the second-generation PIs have not been applied into clinic and the indications are limited in hematologic and solid tumors.

Monoclonal Antibodies

Monoclonal antibodies (MAs), such as rituximab, daratumumab, and belimumab, specifically targeting PCs differentiation and survival have become available in kidney transplant recipients.

MAs Targeting PC Differentiation

CD20 Monoclonal Antibody. Rituximab, the first approved MA by FDA, is a B-cell-depleting antibody directed against CD20 and widely used for the desensitization of highly sensitized patients as well as against ABMR in kidney transplant. However, it may not reduce acute rejection rate and contribute little to sufficient long-term graft survival [63]. As CD20 is extensively expressed on immature and mature B cells, but absent on LLPCs, rituximab (anti-CD20) treatment is not LLPC targeting, which likely explains why it has little effect on PRA levels or LLPC populations.

CD38 Monoclonal Antibody. The newly approved medication of daratumumab, a CD38-targeted MA, may throw new light in the treatment of ABMR. CD38 is expressed in B-cell ontogeny in both the early and late stages of maturation (at high levels on antibody-secreting PCs) but not during intermediate stages [64, 65]. Daratumumab mainly reacts through antibody-dependent cell-mediated cytotoxicity, antibody-dependent cellular phagocytosis, and inhibition of the enzymatic activity of CD38 on PCs in MM [66]. However, no researches on daratumumab have been shown in LLPCs generation or renal transplant with ABMR. Thus, there is a long way to go before daratumumab can be used in kidney transplant recipients.

B-Cell Activating Factor Monoclonal Antibody. Belimumab, a newly biological agent approved by FDA in 2011,

specifically blocks the bioactivity of B-cell activating factor (BAFF) and shows efficacy and safety in systemic lupus erythematosus patients [67, 68]. Schuster et al. [69] found that increased serum BAFF levels reflected worse ABMR after kidney transplantation. Theoretically, belimumab therapy may be effective in kidney transplant patients with ABMR. B-cell maturation antigen, a receptor of BAFF is also important for LLPCs maturation and its antibodies are promising in ABMR.

MA Targeting PC Niches and Survival Factors

LLPCs are not long-lived per se without the anti-apoptotic stimuli from the survival niches and factors [18]. If newly generated PCs are not able to enter a survival niche properly, they may undergo apoptosis [51]. Various chemokines and cytokines, such as CXCL12, IL-6 and so on, are vital for LLPCs migration and survival [17, 19, 28, 70] and antibodies targeting several of them have been shown to be effective in curing autoimmune diseases. However, researches of these factors in ABMR are rare.

Conclusion and Perspective

A focus on the LLPCs in kidney transplant has opened a new avenue in dealing with preformed and de novo DSAs in allograft rejection. A comprehensive understanding the roles of LLPCs in ABMR is desired to improve allograft survival. Emerging regimes aiming LLPCs are available, such as ATGs, PIs, MAs and so on (Fig. 4);

however, large-scale studies on them in alloimmunologic disorders are lacking. Moreover, due to the distinctive features of these allograft population, including the complicated underlying diseases, relatively poor respiratory and circulatory function, frequent combination medications as well as the long-term treatment course, there are still quite a lot of problems that needs to be addressed.

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Author Contributions

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