BANTAO Journal 2015; 13(2): 53-58

BJ

BANTAO Journal

Review article

Immune Renal Injury: Similarities and Differences Between Glomerular Diseases and Transplantation

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Abstract

Glomerular diseases and renal transplantation are the main fields in nephrology in which the immune system plays a prevalent role. They have for long been considered as independent conditions due to the prominent role of autoimmunity in glomerular diseases and of alloimmunity in renal transplantation.
Moreover, histologic features differ between glomerular diseases and transplantation: in glomerular diseases, histologic damage involves primarily the glomeruli and secondarily the tubulointerstitium and small vessels, whereas in transplantation, allograft injury comprises primarily the tubulointerstitium and vessels and to a lesser degree the glomeruli.
However, recent research has shown that the pathogenetic mechanisms in both conditions share common pathways and that there is cross-reaction between innate and adaptive immunity as well as between auto- and alloimmunity [1].

Key words: glomerular diseases, renal transplantation, adaptive immunity, autoimmunity, alloimmunity

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Innate and adaptive immunity and complement activation

Glomerular diseases have been considered traditionally as autoimmune diseases, since the main pathogenetic mechanism involves (auto-)antibody production and immune complex formation.
In renal transplantation, which is considered as an alloimmune condition, allograft damage is the result of direct reaction of immune cells towards the graft. In this setting, attention has mainly focused on adaptive immunity, since T-cells alone are sufficient to trigger and sustain rejection. T-cells can be sensitized against alloantigens via the direct or the indirect allorecognition pathway. In direct allorecognition, T-cells recognize peptides on the intact donor MHC molecules on the surface of donor cells. In indirect allorecognition, donor MHC molecules are processed and presented as peptides on antigen presenting cells (APCs) of the host.
It has been demonstrated that indirect and direct type of alloresponse play different roles in the physiology of the rejection process. T-cell response via direct allorecognition plays a critical role during the early phase of acute rejection. Once sensitization has taken place, indirect alloresponse may become prominent and further spread and sustain the immune process playing a central role especially in late and chronic rejection episodes [2].
In glomerular diseases, the role of innate immunity was identified decades ago. The innate immunity system provides the first line of defense against infections via cellular and humoral mechanisms. Innate immunity is rapid but specific; it acts through the recognition of pathogens presented by APCs (macrophages, dendritic cells and leucocytes) and their subsequent destruction through opsonization and phagocytosis. Besides APCs, main components of innate immunity are toll-like receptors (TLRs) and the complement system.
The clinical relationship between infection and glomerular diseases is well-known: various types of infections may exacerbate or trigger glomerular diseases as streptococcal infection acute membranoproliferative GN, mucosal infections macroscopic hematuria in IgAN and staphylococcal infections ANCA-associated vasculitis (AASV).
The role of complement activation in glomerular diseases has been thoroughly investigated. Complement can be activated via the classical pathway in immune complex-mediated diseases such as lupus nephritis and cryoglobulinemic nephritis. Former membranoproliferative GN type II, now according to the new classification named "dense deposit disease" and recurrent atypical hemolyticuremic syndrome are both triggered by uncontrolled activation of the alternative complement pathway. Complement activation via the lectin pathway has been implicated in the pathogenesis of IgAN.
In renal transplantation, complement activation plays an important role in ischemia-reperfusion injury with activation of both the classical and the lectin pathway [3]. Complement activation is essential in humoral, antibody-mediated rejection (AMR) where there is depo-

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sition of the C4d component of the classical pathway in peritubular capillaries and glomeruli.
Besides the central role of complement activation both in glomerular diseases and transplantation, there is growing evidence of interaction between innate and adaptive immunity. Innate immunity interferes with dendritic cell maturation, antigen presentation and T-cell activation and can be considered as a major component of the alloimmune response [4].

B-cell activation and antibodies

Circulating antibodies are involved in the pathophysiology of renal damage, both in glomerular diseases and in transplantation. The most typical model of autoantibody-mediated glomerulopathy is idiopathic membranous nephropathy. In membranous nephropathy, recent and former studies have identified several podocytic antigens as targets of autoantibodies. Experimental studies in the late 1950s using rats (model of passive Heyman nephritis) have first identified a large membrane glycoprotein also known as megalin. Another important finding was that activation of complement was also required for the development of proteinuria. The first evidence of in situ immune complex formation was established by Debiec *et al*. [5]. They described a case of neonatal nephrotic syndrome and biopsy proven membranous nephropathy in a newborn whose mother was genetically deficient in an enzyme expressed on podocytes, neutral endopeptidase (NEP). Circulating anti-NEP antibodies from presensitization of the mother during a previous pregnancy crossed the placenta, bound to NEP in fetal podocytes and caused MN in the newborn, which resolved after the clearance of maternal antibodies from the circulation. Autoantibodies directed against other podocytic enzymes as M-Type phospholipase A2 receptor (PLA2R) have been described more recently. Anti-PLA2R antibodies have been further associated with the idiopathic form of membranous nephropathy as well as with disease activity [6].
In renal transplantation, a substantial proportion of acute and chronic rejection episodes are mediated by circulating anti-HLA antibodies, which are either de novo or preformed. Antibodies directed against donor specific antigens (DSA) can cause different types of rejection: hyperacute, acute and chronic antibody-mediated rejection (AMR). Nowadays the occurrence of catastrophic, hyperacute AMR is extremely rare, because of the universal adoption of pretransplantation cross-matching. Acute and chronic AMR due to preformed or de novo DSA still remain one of the leading causes of graft failure. The major mechanism of antibody-mediated injury is activation of the classical complement pathway by the antigen-antibody complex, leading to formation of the membrane attack complex, which results in cellular injury. Antibodies are most commonly directed against human leucocyte antigen (HLA)/major histocompatibility-complex (MHC) class I and II antigens [7]. HLA class I antigens are expressed on all nucleated cells, whereas HLA class II antigens are restricted to antigen-presenting cells (APC) and endothelial cells. However, antibodies can also be directed against other donor specific antigens such as endothelial, MHC-class I related chain A (MICA) or MICB, platelet-specific antigens or molecules of the renin-angiotensin pathway [8].

Evolution of therapeutic approaches

The most commonly used immunosuppressive agents are corticosteroids, alkylating agents (cyclophosphamide), calcineurin inhibitors (CNIs, cyclosporine and tacrolimus), antimetabolites (MPAs, mycophenolate mofetil or mycophenolate sodium and azathioprine) and mTOR inhibitors. They have been used in both glomerular diseases and transplantation. While in transplantation evidence is based on large, multicenter, randomized, controlled trials [9,10], in glomerular diseases most of the evidence comes from small, single center studies [11,12].

Multitarget therapy

A promising trend in the treatment of glomerular diseases, by adopting the model of renal transplantation is multitarget therapy. In transplantation, we use immunosuppressive combinations and not single agents, in order to maximize efficacy and minimize side effects. T-cell activation requires three distinct signals: Signal 1: an antigen at the surface of an antigen presenting cell (APC) triggers T cell activation through binding at the CD3 receptor complex of the T cell. Signal 2: This second signal also known as co-stimulation occurs when CD80 and CD86 on the surface of APC interfere with CD28 on T-cells. Signals 1 and 2 activate several intracellular signal transduction pathways. These pathways enhance the production of cytokines such as interleukin (IL)-2, IL-15 and IL-4. IL-2 binds to CD25 (the IL-2 receptor) and activates the mammalian target of rapamycin (mTOR), providing signal 3, the stimulus for T-cell proliferation.
Immunosuppressive drugs act synergically, blocking different sites of this activation cascade. Corticosteroids are the oldest immunosuppressants and have been used in glomerular diseases and transplantation for decades. Their immunosuppressive action is mediated through a number of pathways, mainly directed towards redistribution of lymphocytes and macrophages to the lymphoid tissue and inhibition of the production of cytokines (IL-1, IL-2, IL-6), tumor necrosis factor-alpha (TNFα) and interferon-gamma (IFN-γ).
Calcineurin inhibitors, cyclosporine and tacrolimus bind to a cytoplasmic receptor, cyclosporine to cyclophilin and tacrolimus to FKBP12 and form a complex that binds to and inhibits the action of cyclophilin. Cyclophilin inhibition results in inhibition of NFATc dephosphorylation (cytosolic Nuclear Factor of Activated T cells) which

subsequently leads to reduced cytokine release, including IL-2. Mammalian target of Rapamycin (mTOR) inhibitors (sirolimus and everolimus) bind to the same intracellular receptor as tacrolimus, FKBP12. Instead of forming a complex with calcineurin, mTORi's, bind to mTOR, interfering with signal 3 of T-cell activation by inhibiting rapamycin, which is a key kinase for the cell cycle, thereby resulting in cell-cycle arrest in the G1-S phase. Antimetabolites include the older drug azathioprine and the newer derivates of mycophenolate acid (MPAs), mycophenolate mofetil (MMF, cellcept) and mycophenolate sodium (myfortic). Azathioprine antagonizes purine metabolism and inhibits synthesis of DNA, RNA and proteins. It may decrease proliferation of B- and T-cells, which results in lower immune activity. The newer antimetabolites, MPAs, are more selective inhibitors of purine synthesis. Mycophenolate inhibits inosine monophosphate dehydrogenase (IMPDH) and suppresses de novo purine synthesis by lymphocytes, thereby selectively inhibiting proliferation of activated T-cells.

In renal transplantation, use of combinations of immunosuppressive agents increases efficacy and reduces drug-related toxicity. The multitarget therapeutic approach has been adopted in glomerular diseases, with promising results. One such case is the use of combination therapy consisting of calcineurin inhibitor (tacrolimus) with mycophenolate mofetil and corticosteroids for the treatment of severe, mixed proliferative and membranous lupus nephritis (class III and V on renal biopsy). After the positive results in the first 40 patients, published in 2008 by Bao *et al.* [13], a large, multicenter, randomized controlled trial (RCT) with a total of 368 patients with proliferative lupus nephritis was published recently, in 2015, by Liu *et al*. [14]. This was one of the largest trials in lupus nephritis. When the same multitarget regimen (tacrolimus, mycophenolate mofetil and corticosteroids) was compared with conventional therapy (intravenous pulses of cyclophosphamide and steroids) for induction therapy of LN, there were significantly higher remission rates in the multitarget therapy group after six months.

Minimization of Immunosuppression

Nowadays, immunosuppressive protocols include more selective and more potent drugs than in the past. Despite enhanced efficacy and use of reduced doses of immunosuppressive agents compared to the past decades, cumulative toxicity of immunosuppression still remains a substantial problem in renal transplantation. Main side effects of calcineurin inhibitors are hypertension, hyperlipidemia and diabetes mellitus, which are all major risk factors for cardiovascular complications. Cardiovascular events are still the leading cause of death in transplanted patients. Moreover, CNIs are nephrotoxic; the nephrotoxicity of cyclosporine was described in the early 1990s. CNI nephrotoxicity can schematically be divided into "acute" and "chronic". Acute, potentially reversible nephrotoxicity i. e. without evidence of histologic damage, or "acute arteriolopathy" results from vasoconstriction of the afferent arteriole of the glomerulus, due to increase of vasoconstrictor factors as endothelin and thromboxane and activation of the renin-angiotensin system (RAS), as well as a reduction of vasodilators like prostacyclin, prostaglandin E2 and nitric oxide (NO). Reversible tubular dysfunction is also recognized as a feature of acute CNI nephrotoxicity. Chronic CNI nephrotoxicity still remains the Achilles' heel of current immunosuppressive regimens [15]. Myers *et al*. were the first who demonstrated in heart transplant recipients, that cyclosporine is associated with irreversible damage to renal architecture [16]. This damage affects all renal compartments: vessels (arteriolar hyalinosis), tubulointerstitium (tubular atrophy and interstitial fibrosis) and glomeruli (thickening of Bowman's capsule and glomerulosclerosis). In the hallmark study by Nankivell *et al.* with protocol biopsies, it was shown that CNI toxicity progresses with time after transplantation and by 10 years CNI nephrotoxicity was seen in virtually all cases [17].

One of the most recent trends in transplantation is "immunosuppression minimization". The efforts towards minimization include two categories of immunosuppressive agents: calcineurin inhibitors and corticosteroids.

CNI sparing protocols comprise:

1. Complete avoidance of CNI. This approach had poor outcomes with unacceptable high rates of early, acute rejection and infection episodes [18].
2. CNI minimization. Combinations of very low doses of CNI in combination with mTORi or MPAs have shown slight improvement of GFR, but histologic damage still occurs.
3. The last approach is CNI withdrawal and conversion to mTORi. Early conversion, from 4 weeks to 1 year post-transplantation is preferable to late conversion. Late conversion is beneficial only in patients with preserved renal function (eGFR>40ml/min) and proteinuria less than 800mg/24hrs [19]. An open label, observational study from our Center showed beneficial effects of late conversion in terms of GFR improvement in selected patients with baseline GFR at conversion > 40ml/min [20].

Corticosteroids, even at low maintenance-doses, have numerous and potentially serious side-effects. Since 2000, many steroid-sparing protocols have been implicated in renal transplantation with good results. Early steroid withdrawal is preferable to late withdrawal [21]. Both steroid- and CNI-sparing protocols must be used with caution in selected groups of stable renal transplant recipients with low immunological risk.

Long-term immunosuppression is used in glomerular diseases, too. The most characteristic glomerular disease, in which cumulative toxicity of immunosuppression is a major issue, is lupus nephritis. Lupus nephritis is an organ and life-threatening disease. Moreover, it has a long course with a high rate of relapses. Given the se-

verity of the disease, the need for long-term, often aggressive immunosuppression and the fact that it affects a patient population comprising of young women at childbearing age, efforts to minimize immunosuppression toxicity have been started early. The first step to reduce cumulative toxicity of cyclophosphamide was the Eurolupus trial, published by Houssiau *et al.* [22]. In a Caucasian population, it showed equal efficacy of a regimen comprising a total of 3g of cyclophosphamide for remission induction of proliferative LN, compared to higher "conventional" doses of iv cyclophosphamide used in the classic "NIH regimen". After the revolutionary study by Chan *et al.* in 2000 [23], which showed equal efficacy of mycophenolate mofetil when compared to cyclophosphamide for remission induction in proliferative LN, the efficacy of MPA's as induction therapy was further confirmed in larger, multicenter studies [24,25]. One successful effort to minimize corticosteroids in lupus nephritis was a randomized, controlled trial, "MyLupus Trial". When reduced-dose steroids were compared to standard-dose steroids, in conjunction with Myfortic as induction therapy in proliferative LN, reduced-dose steroids showed equal efficacy in remission induction [26].
ANCA-associated vasculitis (AASV) is another potential life-threatening systemic disease that affects the glomeruli, causing rapidly progressive glomerulonephritis often with accelerated loss of renal function. It affects predominantly elderly patients with comorbidities, in whom overimmunosuppression may have detrimental effects. Efforts to minimize toxicity have been made by the EUVAS and other groups for the last two decades [27,28].

Targeting therapy

B-lymphocytes play a central role in the pathogenesis of glomerular diseases and are also implicated in antibody-mediated rejection (AMR) in renal transplantation [29]. Besides producing antibodies, B-cells have many other functions: they interact with T-cells, they may act as antigen presenting cells and they clonally expand. A number of monoclonal antibodies that target different receptors and lead to sustained (6-12 months) depletion of B-cells, are currently available. The most commonly used is the chimeric, ligand monoclonal, anti-CD20 antibody rituximab. Rituximab has been used in a variety of conditions in renal diseases, in glomerulonephritis as well as in transplantations. The wide range of the therapeutic implications of Rituximab, has been reviewed by our group in 2013 [30].
After the proof of non-inferiority of rituximab as induction therapy in both RCT's, RAVE and RITUXVAS [31,32]. R/rituximab has been approved as induction therapy for AASV. After the positive results of the MAINRITSAN trial [33], which showed better results of rituximab compared to azathioprine for maintenance of remission, the therapeutic setting has completely changed in this renal-disease category, too.
In lupus nephritis, in our experience, rituximab in combination with MMF is effective as maintenance treatment in patients with proliferative LN [34]. Its therapeutic effect may potentially be related to down-regulation of the T cell costimulatory molecule CD40 ligand [35,36]. In a multicenter RCT, the LUNAR trial, rituximab in combination with conventional therapy (3 g of mycophenolate mofetil and corticosteroids) showed no additional benefit compared to placebo in terms of remission induction [37]. It has shown efficacy in cases of refractory LN, in combination with conventional therapy. In membranous nephropathy, our experience with rituximab in 12 cases showed that it was efficient with sustained remission long-term and minimal toxicity [38]. Similar results have been shown by others, including a very recent French study presented in an abstract form at the last ASN [39,40,41 (abstract)].
One of the more recent fields of investigation is blockade of costimulation, i.e. the second signal of T-cell activation. Both monoclonal antibodies abatacept and belatacept inhibit the CD28/CD80-86 pathway of costimulation. Abatacept (cytotoxic T-lymphocyte associated antigen4-Ig) binds to CD80 and CD86 on antigen presenting cells, blocking the interaction with CD28 receptor on T-cells. It has been approved since 2005 for treatment of moderate to severe rheumatoid arthritis, refractory to methotrexate and anti-TNF treatment [42]. In glomerular diseases, efforts have been made towards use of abatacept in lupus. Two trials of abatacept in active lupus nephritis, given additionally to conventional therapy, failed to prove efficacy [43,44]. In primary glomerular diseases, there is a case series of 5 patients with FSGS (4 with recurrent FSGS after renal transplantation and 1 with primary FSGS) treated with abatacept. All patients had positive immunostaining for CD80 (B7-1) in podocytes of kidney biopsies. Abatacept was given additionally to intensive plasmapheresis and all 5 patients achieved either partial or complete remission [45]. We have treated one patient with massive nephrotic syndrome due to FSGS recurrence after renal transplantation with abatacept in combination with plasmapheresis, unfortunately with negative results. Though the podocyte CD80 pathway seems important in some proteinuric glomerular diseases, further investigation towards use of costimulation blockade in this condition is warranted.
Belatacept, is a derivate of abatacept, which binds with more avidity to CD86 and is preferably used in kidney transplantation. Belatacept in transplantation was evaluated in two, open-label, randomized, multicenter, controlled trials (BENEFIT, BENEFIT-EXT). Both studies showed that belatacept was not inferior to cyclosporine in terms of patient and graft survival and was associated with better renal function short term [46,47]. Though a higher infection rate was observed in the belatacept group, after these trials, belatacept was approved in 2011 from the Food and Drug Administration (FDA) as the first costimulation blocker for use in renal transplantation.

In conclusion, new insights into the pathogenesis of glomerular diseases and renal transplantation have elucidated common pathways of allo-and autoimmunity and links between innate and adaptive immunity, with potential for new therapeutic targets.

Conflict of interest statement. None declared.

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