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Antibody-Mediated Kidney Allograft Rejection

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1. Introduction

Successful kidney transplantation improves the quality of life and increases survival when compared with long-term dialysis. Renal transplantation is now a well established and the preferred treatment for most patients with end-stage renal disease (ESRD). In recent years, the short-term effects of kidney transplantation have been greatly achieved due to the improvement in immunosuppression medicines, better genotyping technology and monitoring methods. However, the long-term outcome of kidney transplantation has not been improved for long period. Among the various influencing factors, antibody-mediated kidney allograft rejection is now widely recognized as a major problem which decreases the long-term outcome. How many kinds of antibodies involved in the antibody-mediated rejection (AMR)? How do these antibodies produce? How do these antibodies injure the transplantated kidney function? How to eliminate these antibodies? How about the clinical effects when the new agents were applied? All these questions are being gradually and deeply studied.

2. Anti-HLA and MHC-class I related chain A antibody

At present, anti-HLA antibody (Lefaucheur et al., 2010) and anti-MHC-class I related chain Antibody (Zou et al., 2009) are the main cytotoxic antibodies, resulting in kidney allograft rejection and long-term kidney allograft survival.

2.1 Anti-HLA antibody

HLA (the human leukocyte antigen system) is the name of the major histocompatibilty complex (MHC) in humans. MHC molecules are divided into 2 main classes: HLA class I antigens (HLA-A, -B, and –C), presented on the surface of all nucleated cells and platelets; and HLA class II antigens (HLA-DR, -DQ, -DP, -DM and –DO), expressed on professional antigen-presenting cells, but also on the surface of vascular endothelial cells and renal tubular epithelial cells. There lie high polymorphism degree of the HLA system (more than 1600 alleles), so the individuals do not present identical sets of HLA antigens. After solid organ transplantation, HLA polymorphism confers immunological identity to the recipients, thus, the immune system can distinguish between self and non-self, and non-self may represent targets for the immune system. T cellular-mediated rejection (TCMR) and/or AMR will be initiated. As for AMR, donor specific anti-HLA antigens -I and -II alloantibodies would be produced.

The presence of alloantibodies against donor HLA-I and HLA-II antigens has been associated with hyperacute and accelarated graft rejection. Since HLA typing is strictly requested before renal transplantation (RTx), whatever cadaveric RTx, or living related or non-related RTx, the incidence of hyperacute and accelarated graft rejection have been greatly decreased.

However, some evidences suggest that donor specific antibody (DSA) is common in RTx recipients after 1 year of operation, which may be explained by the HLA polymorphism.

2.2 Anti-MHC-class I related chain A antibody (MICA)

MHC-class I related chain (MIC) has been reported to be an important polymorphic alloantigen system, consisting of MICA and MICB, and distributing on the peripheral blood lymphocytes, tissue endotheliocytes, and umbilical endotheliocytes, which also play a role in renal allograft rejection. Specific anti-MICA antibody can be found in sera of transplanted patients with allograft rejection (Zou et al, 2007). And the statistical analysis indicated that, anti-MICA antibodies were associated with the failure of a renal graft, regardless of good HLA typying (0 or 1 HLA mis matched) and PRA =0.

One report showed that, despite negative pretransplantation T- and B- lymphocyte flow cytometric crossmatches and blood group identity, two cases of hyperacute humoral rejection of living related kidney grafts happened (Grandtnerova et al, 2008). Retrospectively, antiendothelial IgG antibodies were detected on a panel of umbilical cord cells in the first case, and IgM antibodies against donor endothelial precursor cells were detected using a new endotheilal cell crossmatch kit in the second case. Standard crossmatch methods using donor lymphocytes failed to detect these pathogenic antibodies and did not predict the danger of hyperacute rejection.

Now, MIC typying is still not carried out in clinic. Were the antiendothelial IgG and IgM antibody all belonging to anti-MICA antibody? This question may be worth investigating.

2.3 Subtypes of alloantibodies

IgM-alloantibody and IgG-alloantibody are all common in the peripheral blood and intragraft of recipients, and they are all involved in kidney allograft rejection.

IgM antibodies against donor HLA antigens can be found before transplantation and also produced both early and late in the post-transplant course. IgM antibodies against donor HLA appear to be associated with decreased survival of kidney and heart allografts.

IgG1/IgG3 and IgM can specially bind to alloantigens, activate complement system, and play their immunological action. While IgG2 only weakly activate complement system, and IgG4 does not activate complement system. IgG1/IgG3 and IgM probably participate in AMR by this pathway.

This viewpoint is concordant to the observed evidence. For example, three cases of successful living donor kidney transplantation, showed strongly positive B lymphocyte flow cytometry owing to highly reactive DSA directed to HLA Ⅱ antigens. IgG solid-phase subtypes analysis suggested that, more than 50% of these antibodies were represented by non-complement binding IgG2/IgG4 subtypes (Lobashevsky et al., 2010).

Now, new technologies are quickly developed. Some new methods based on solid phase multiplex platforms, such as ELISA, flow cytometry and luminex, have been applied in clinic. These methods can detect binding of serum antibodies to specific antigens independently of complement activation. And, using additional anti-IgM/IgG antibodies,

these new technologies can distinguish between IgM and IgG anti-HLA antibodies. Additionally, it can discriminate between HLA class I and class II antibodies, and more, single antigen methods allow identification of a unique HLA specificity.

With the help of development in detection technology, clinician can obtain more precise information and make rational decision.

2.4 Potential mechanism

After these antibodies are produced, they will attack their targets represented by the graft endothelial cells, complement system would be activated, coagulation cascade happened and other inflammation factors would be produced. This procedure may be the most classical procedure of AMR.

The microcirculation characteristic of microcirculation changes of AMR include of:

(1) Microcirculation inflammation (glomerulitis (g), peritubular capillaritis (ptc))(Einecke et al., 2009); (2) Microcirculation deterioration (transplant glomerulopathy (cg), medangial matrix increase (mm)); (3) Peritubular capillary basement membrane multilayering (ptcm-score) ; (4) Diffuse C4d positivity.

A key element in the pathology of AMR is capillaritis, which is associated with glomerulitis and anti-HLA antibodies. Over time it seems likely that capillaritis will induce peritubular capillary basement membrane multilayering as a time dependent feature of late AMR.

3. Antibody-producing cells

3.1 Characterization of intra-graft B cells

During renal allograft rejection, cluster-forming CD20$^+$ B cells in the rejected graft are likely derived from the recipient and composed of mature B cells. These cells are activated (CD79a$^+$), some of them contain memory B cells (CD27$^+$) and do not correlate with intra-graft C4d deposition or with donor-specific antibody detection.

Furthermore, several non-cluster forming CD20$^-$ B-lineage CD38$^+$ plasmablasts and plasma cells infiltrate in the rejected grafts and these cells strongly correlated with circulating donor-specific antibody, and to a lesser extent with intra-graft C4d.

Both CD20$^+$ B cells and CD38$^+$ cells correlated with poor response of the rejection to steroids. Reduced graft survival is associated with the presence of CD20 cells in the graft.

And, a specific subset of early lineage B cells appears to be antigen-presenting cells and which may support a steroid-resistant T-cell-mediated cellular rejection when these cells present in the rejected graft. Late lineage interstitial plasmablasts and plasma cells may also support AMR. These studies suggest that detailed analysis of interstitial cellular infiltrates may allow better use of B-cell lineage specific treatments to improve graft outcomes.

3.2 Plasma cells and memory B cells

Now the exact cellular mechanisms responsible for AMR are still not known. It seems likely that both pre-existing plasma cells and the conversion of memory B cells to new plasma cells play a role in the increased DSA production (Stegall et al., 2010).

There indeed normally exists very little amount of long-lived plasma cells, but they may not be able to produce enough pathological alloantibodies to injury the kidney allograft. Plasma cells, DSA and C4d are associated with each other in renal transplants developing chronic rejection by sequential graft biopsies detection. Bone-marrow-derived long-lived plasma

cells appear to be a major source of donor-specific alloantibody in sensitized renal transplant recipients. Memory B cells appear to be important in early acute AMR, but few basic have been performed.

3.3 Potential survival factor: BAFF

Some factors may survive the plasma cells or enhance the production of pathological alloantibodies. B cell activating factor belonging to TNF superfamily (BAFF) may be one of the most potential survival factors. BAFF is also termed Blys, TALL-1, zTNF4, THANK and TNFSF13b, is a nomotrimer, member of the TNF superfamilies, expressed on the cell surface or cleaved and secreted. BAFF specifically binds to BAFF receptor (BAFF-R, also known as BR3 (Thompson, et al., 2001)), and BAFF can also bind to other two receptors, transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) and B-cell maturation antigen (BCMA), shared with another TNF ligand, a proliferation-inducing ligand (APRIL) (Day, et al., 2005).

BAFF is expressed by monocyte-derived cells, such as monocytes, macrophages, dendritic cells, and activated T lymphocytes, which plays an important role in immune response (Mackay, F. and Schneider, P. 2009). The discovery of BAFF has shed new light on the importance of finely tuned B cell survival for B cell tolerance during B cell maturation and activation. Excessive production of BAFF is associated with the development of autoimmune diseases, because transgenic (Tg) mice that overproduce BAFF develop severe autoimmune disorders resemble systemic lupus erythematosus (SLE) and Sjogren's syndrome (SS) in humans, possibly as a result of improper B cell survival, predominantly affecting the maturing splenic transitional type 2 (T2) and the marginal zone (MZ) B cell populations. BAFF-induced autoimmunity in BAFF Tg mice appears to be highly dependent on B cells and possibly the production of autoantibodies. High levels of BAFF have been found in the blood of patients with autoimmune diseases, particularly SLE and SS. And BAFF is also found on T lymphocytes infiltrating labial salivary glands from patients with SS.

3.3.1 BAFF and rituximab

Rituximab can specially delete CD20$^+$ B lymphocytes, gradually applied to induce immunosuppression state at present. The impact of rituximab therapy on tertiary lymphoid organs associate with chronic active antibody-mediated rejection, a prototypic humoral chronic inflammatory condition. In certain patients, inflammatory microenvironment provides BAFF-dependent paracrine survival signal to B-cells in tertiary lymphoid organs, allowing them to escape rituximab-induced apoptosis, thereby thwarting therapeutic efficiency (Thaunat et al. 2008).

3.3.2 BAFF and alemtuzumab

BAFF is increased in renal transplant patients following treatment with alemtuzumab (Bloom et al. 2009). Alemtuzumab is an anti-CD52 monoclonal antibody that can deplete T and B cells and is used as induction therapy for renal transplant recipients. However without long-term calcineurin inhibitor (CNI) therapy, alemtuzumab-treated patients have a prospensity to develop alloantibody and may undergo AMR.

These data suggest associations between BAFF signal and AMR in alemtuzumab-treated patients.

3.3.3 BAFF and renal transplantation

In view of special bioactivity of BAFF, experiments have been carried through to explore the expression characteristic of BAFF and its potential bioactivity in renal allograft rejection, and some significant results were obtained.

3.3.3.1 BAFF expression and serum PRA

The FACS (Fluorescence Activated Cell Sorter) results indicated that, cell surface BAFF was abnormally highly expressed on peripheral T lymphocytes of some kidney transplant recipients, especially in those recipients for more than 5 years (Fig.1).
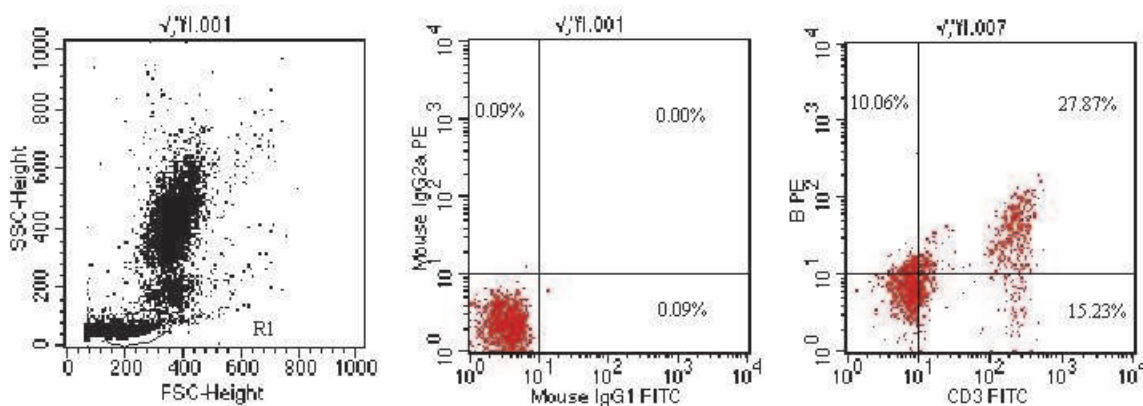
Fig. 1. BAFF expression on CD3+ T lymphocytes in RTx recipients after 5 yrs' operation

The real-time PCR (Polymerase Chain Reaction) results showed that BAFF mRNA levels gradually increased along with the prolonged transplantation time, and BAFF mRNA levels were consistent with BAFF protein levels in different groups (Fig.2).
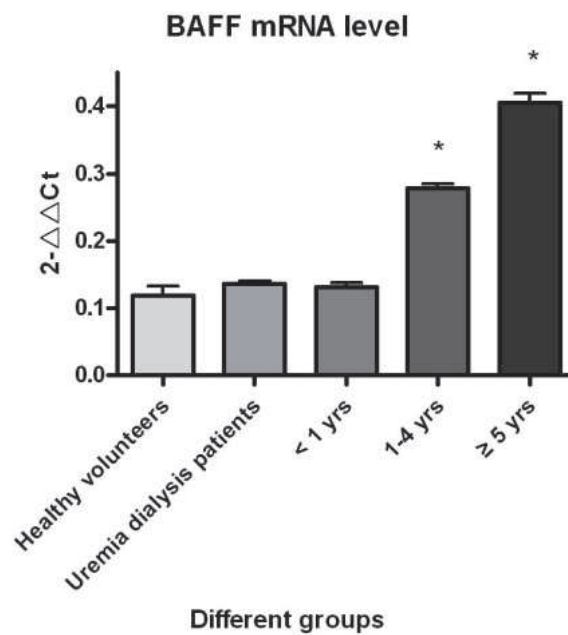

Fig. 2. BAFF mRNA levels in peripheral blood monocytes of RTx recipients after operation with different periods (<1 yr, 1-4 yr and ≥5 yr)

Healthy volunteers and uremia dialysis patients as controls

To investigate the correlation of transplanted renal function and BAFF expression, transplanted renal function was stratified and these data were statistically analyzed. In abnormal renal function group, BAFF was abnormally highly expressed on peripheral T lymphocytes, and the expression level was about as high as that in ≥ 5 years group. And there was statistically significant association between anti-HLA I & II antibodies level and BAFF expression level (Tab.1).

		anti-HLA Ⅰ & Ⅱ antibodies
CD257	Person Correlation	.587**
	Sig (2-tailed)	.008

Table 1. The correlation analysis of BAFF expression and serum PRA (panel reactive antibody)

The results indicated that BAFF expression was correlated with gradually decreasing transplant renal function, and BAFF may be involved in immune regulating network of kidney transplantation, which was the first report about BAFF and kidney transplantation.

3.3.3.2 BAFF and its receptors in the allograft rejection tissues

To further investigate the role of BAFF in AMR in renal transplantation, the correlation of BAFF and C4d deposition in excised transplanted kidney and protocol biopsies were investigated. The results showed that, BAFF could not only be found in renal allograft tissues, including AR and IF/TA (Interstitial Fibrosis/Tubular Atrophy) tissues, but also was highly expressed in these allograft sections, compared to protocol biopsy sections. BAFF can regulate the development of transitional B lymphocytes and survival of plasmacytoid lymphocytes, which implies that the BAFF signal may participate in AMR. To test this presumption, C4d and IgG were also detected in these allograft sections by immunohistochemistry. The results showed that BAFF expression significantly correlated with C4d deposition. The intensity and percentage score of BAFF were similar to those of C4d. BAFF mainly distributed in the perinephric tubular epithelial cell cytoplasm and cytomembrane, similar to the distribution of C4d. There was IgG deposition in BAFF high-expression sections, but its intensity and percentage score were much weaker than BAFF. IgG deposition was also mainly distributed in the perinephric tubular epithelial cell cytoplasm and cytomembrane.

The patients' clinical materials were shown in Tab.2. And the representative examples of immunohistochemical (IHC) staining of BAFF and C4d in renal allograft rejection tissues were listed in Fig. 3.

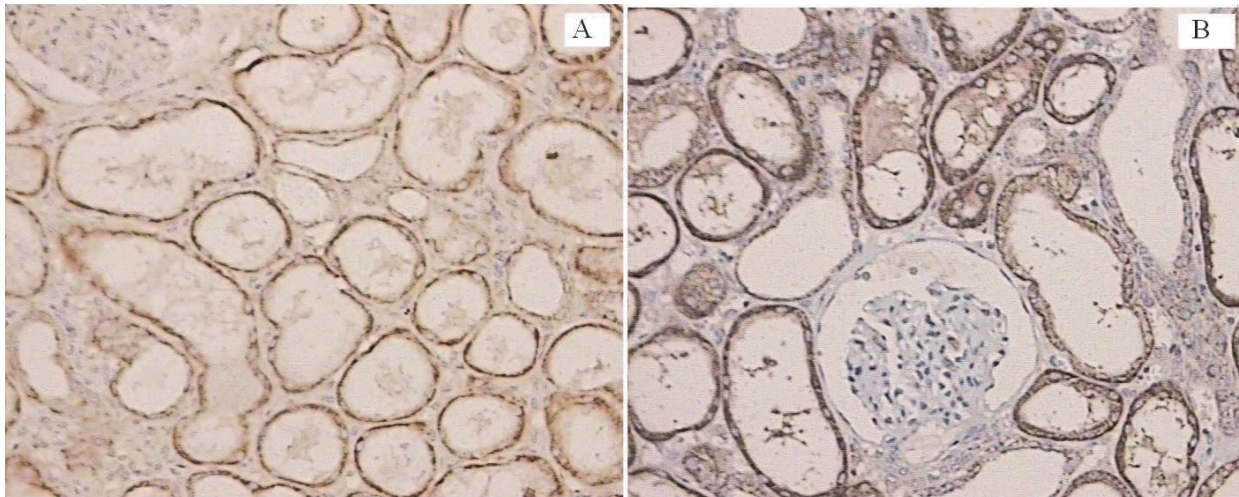| groups		gender Male/ female	Age (year) (means±SD)	PRA(%)	HLA-DR non-matched level	POD(day, means±SD)
Graft failure	AR(n=10)	6/4	39±10 (19~58)	17±4.1	0.8±0.6 (0~2)	9±8
	UAC(n=9)	4/5	42±8 (32~56)	5±4.2	0.7±0.7 (0~2)	1875±784
Graft normal	Protocol renal biopies (n=10)	7/3	37±5 (26~48)	7.4±3.5	0.7±0.7 (0~2)	17±4

Table 2. All the accepted patients' clinical materials

Fig. 3. Representative examples of immunohistochemical staining of BAFF and C4d in renal allograft rejection (original mannification 200X).Positive staining was observed as a dark brown color. Renal allograft rejection tissues showed strong expression of C4d (A) and BAFF (B).

We performed further study by IHC to investigate the receptors of BAFF involved in the renal allograft rejection. The TACI, BCMA and BAFF-R (BAFF receptor, BR3) were all detected. And the APRIL, much high homogenicity with BAFF, was also done. Meanwhile, the plasma cell marker CD138 was also investigated.

The obtained data showed that, high immunogenicity of BAFF, APRIL and their receptors, TACI, BCMA and BAFF-R, and CD138 can be found in renal allograft rejection tissues (including of acute and chronic rejection) (Fig.4), while these molecules all have low immunogenicity in other etiological tissue (excluding of acute and chronic rejection).

All data were analyzed according to C4d expression. In C4d negative group, BAFF, BAFF-R, BCMA and CD138 were all low immunogenicity, while APRIL and TACI have high immunogenicity. In C4d positive group, BAFF, BAFF-R, BCMA, APRIL, TACI and CD138 were all high immunogenicity. The statistical analysis suggested that, the expression of BAFF, BAFF-R, BCMA and CD138 significantly correlated with C4d deposition (Fig.5). These results suggest that BAFF signal may participate in AMR, and APRIL signal may simultaneously participate in cell-mediated and antibody-mediated rejection.

4. Diagnosis of AMR

4.1 Diagnosis of acute AMR

AMR may occur early or late, may be acute or chronic and is associated with poor renal allograft function and survival. According to the speed of rejection, three AMR conditions are now recognized: hyperacute, subacute and chronic AMR.

The following items are required in diagnosis of acute AMR:

1. Histopathological evidence of either acute tubular injury (with no other identifiable cause for it), glomerulitis, endothelitis or capillaritis with neutrophil or mononuclear cell infiltratem capillary thrombosis;
2. Serologica evidence of circulating antibodies;
3. Diffuse C4d positivity in peritubular capillaries (PTC).

These diagnosis criteria are based on Banff 2005 guidelines, in which, C4d deposition in the peritubular capilary (PTC) is considered as the mark of AMR.

(A) CD256 (×400)   (B) TACI (×400)

(C) BAFF-R (×400)   (D) BCMA (×400)

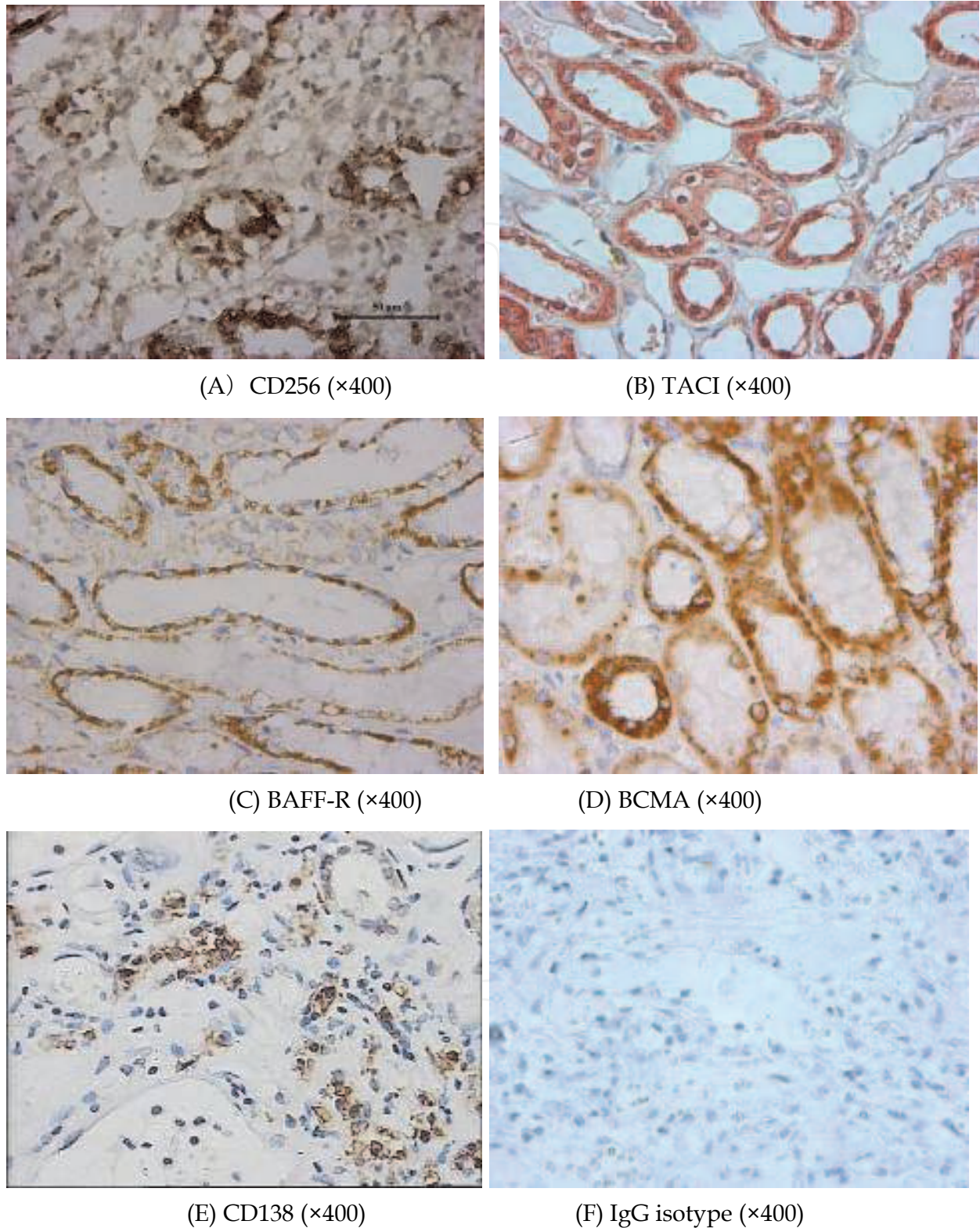(E) CD138 (×400)   (F) IgG isotype (×400)

Fig. 4. The representative IHC staining results of APRIL, TACI, BAFF-R, BCMA and CD138 were listed (×400). The APRIL, BAFF-R,BCMA and CD138 signal were developed with 3,3'-diaminobenzidine tetrahydrochloride (DAB), the dark brown particles were the positive signal. And TACI signal was developed with 3-amino-9-ethycarbozole (AEC), the red particle was the positive signal. (F): the IgG isotype of the used antibodies.
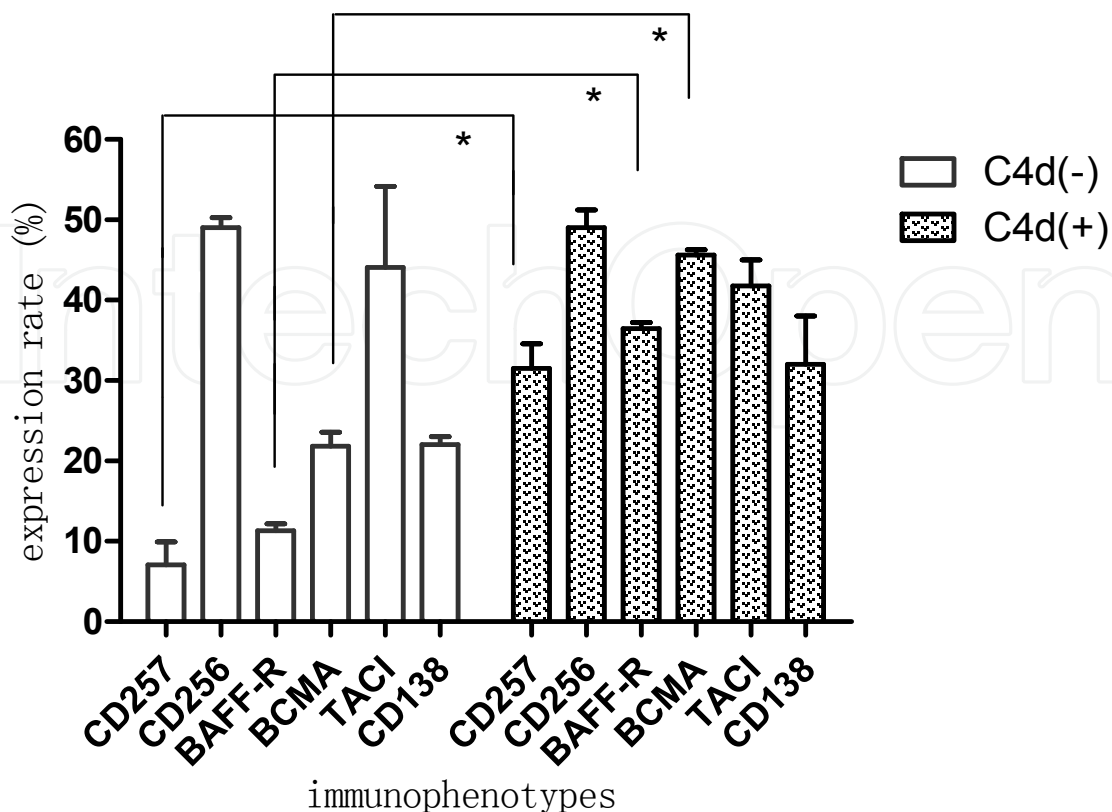
Fig. 5. All data was analyzed according to C4d immunoreactivity, C4d(-) represented C4d negative group and C4d(+) represented C4d positive group. There were significant difference of the expression rate of BAFF, BAFF-R and BCMA between C4d(-) group and C4d(+) group. P<0.05 was considered as statistical significance. * *P*<0.05.

4.2 Suspicious for AMR

However, C4d staining is found to be not completely useful in diagnosis of AMR with the advancement of knowledge about AMR. For example, C4d staining in post-reperfusion renal biopsy is not useful for the early detection of AMR when CDC crossmatching is negative (David-Neto et al., 2010). In ABO-incompatible transplant cases, AMR is difficult to be diagnosed by C4d analysis.

Banff 09 meeting discussed several aspects of solid organ transplants with a special focus on antibody mediated graft injury, and revised the diagnosis indexes.

Because C4d may not be sensitive in the diagnosis of AMR: many cases of transplant glomerulopathy with anti-HLA are C4d negative (Sis et al., 2009). Therefore, the recent update of the Banff classification introduced the diagnostic category "**suspicious for AMR**" if C4d (in the presence of antibody) or alloantibody (in the presence of C4d) cannot be demonstrated but morphologic evidence of antibody-mediated tissue injury is present. Moreover, in microarray studies, expression of endothelial transcripts was increased in biopsies with DSA and associated with graft loss even in C4d negative biopsies.

4.3 Remained questions

The risk for graft loss is not captured well by the current Banff diagnoses because many cases with AMR features (anti-HLA and microcirculation changes) were C4d negative and thus

given other diagnosis. However, when AMR is redefined as the presence of HLA antibody and microcirculation changes, regardless of C4d status, it is the most frequent phenotype associated with subsequent graft loss. In contrast, nonspecific scarring (IFTA), calcineurin inhibitor toxicity and TCMR are rare diagnosis in grafts that subsequently failured. Thus, antibody-mediated microcirculation injury accounts for the majority of kidneys presenting with indications for biopsy and subsequently failing, but many cases are C4d negative.

Subclinical AMR seems to be complicated by a substantial proportion of positive-crossmatch transplantations even in the absence of allograft dysfunction, and may result in chronic histological abnormalities and shorten allograft function (Loupy et al., 2009).

So, although much advancement have been obtained in diagnosis, there is still absent of specific marker to aid the diagnosis and therapeutic of AMR.

5. Therapeutic strategies of AMR

Once AMR happen, it requires intensive therapy, but no standard treatment has been established now. To eliminate the alloantibodies and antibody-producing cells are the main strategy of AMR treatment.

5.1 Therapeutic strategies of acute AMR

Now, several strategies are being routinely applied, such as plasmapheresis, high-dose intravenous immunoglobulin (IVIG) and plasmapheresis (PP) with low-dose IVIG. Some new interventions have been applied in clinic, such as the use of rituximab (anti-CD20 chimeric antibody)(Rodriguez et al. 2010; Takagi et al., 2010), bortezomib (a proteasome inhibitor-mediated plasma cell depletion)(Raghavan et al. 2010; Walsh et al., 2010), and eculizumab (recombinant human C5-inhibitor)(Lonze et al., 2010; Tillou et al.,2010), for preventing acute AMR. These methods are promising therapeutic avenues currently under investigation.

IVIG has many ideal advantages as a therapy for AMR.

1. It can down regulate B-cell activation and antibody production.
2. It can induce anti-inflammatory cytokines and contain blocking antiidiotyic antibodies to anti-HLA antibodies;
3. IVIG has the unique ability to block complement-mediated injury through inhibition of C3 activation.

Rituximab (anti-CD20 chimeric antibody) can deplete B cells and interfere with antigen-presenting cell (APC) activity of B cells subsequently decreasing T-cell activation,

Bortezomib is one kind of proteasome inhibitors. The preliminary results indicate that bortezomib therapy provides effective reduction in DSA levels with long-term suppression in transplant recipients.

Bortezomib therapy's advantages:

1. It provides effective treatment of AMR and TCR with minimal toxicity.
2. It provides sustained reduction in iDSA and non-iDSA levels.

While, other center reported that, Bortezomib treatment did not significantly decrease DSA within the 150-day posttreatment period in any patient; lack of efficacy on long-lived plasma cells. So, one cycle of bortezomib alone does not decrease DSA levels in sensitized kidney transplant recipients in the time period studied. These results underscore the need to evaluate this new desensitization agent properly in prospective, randomized and well-controlled studies (Sberro-Soussan et al., 2010).

5.2 Therapeutic strategies of subacute and chronic AMR

Now, there seems to have not any good methods to treatment the subacute and chronic AMR. Although subacute and chronic AMR are not immediately result in the graft loss, they cause chronic histological injury and shorten allograft function. Many evidences have suggested that AMR is the important factor influencing the long-term of kidney allograft. Thus, great efforts are still needed to resolve this problem.

6. Conclusion

In summary, recent advances in the diagnosis and treatment of AMR has allowed for significant improvements in the outcome of a condition usually associated with rapid graft failure. However, much work needs to be done to better understand the immunologic processes leading to AMR and how current therapies can be best used to effectively prevent and treat it.

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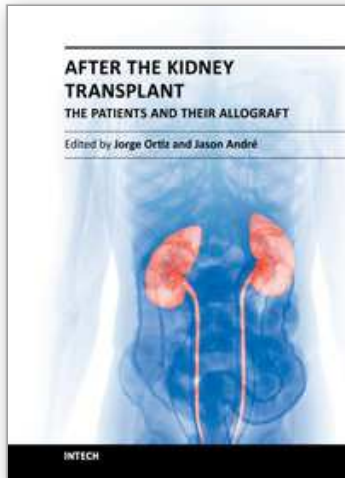
After the Kidney Transplant - The Patients and Their Allograft

Edited by Prof. Jorge Ortiz

There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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