Journal of Inflammation Research

Dovepress
Taylor & Francis Group

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REVIEW

Immune Landscape in Kidney Transplantation

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Abstract: Kidney transplantation is the optimal treatment for end-stage renal failure patients. However, its long-term survival rate remains relatively low, with immune rejection being a crucial risk factor. In recent years, notable progress has been made in the study of the immune regulation network in kidney transplantation. The key roles and molecular mechanisms of diverse immune cells in rejection have been gradually clarified. Innate immune components (such as neutrophils, macrophages, natural killer cells, etc.) activate inflammatory signals via pattern recognition receptors and collaborate with the complement system and platelets to mediate early graft damage. In adaptive immunity, T/B cell subsets drive donor-specific immune responses through direct/indirect recognition pathways, forming the core effector mechanism of immune rejection. We retrieved relevant articles from databases such as PubMed and Web of Science using keywords including "kidney transplantation" and "immunity", focusing on the most recent research published in the past decade. Articles were screened and evaluated based on high scientific standards regarding research quality and relevance. This review centers on the dynamic interaction network between innate and adaptive immunity after kidney transplantation. It systematically elaborates the roles of various immune cell subsets throughout the rejection process and further explores the application prospects of xenogeneic kidney transplantation, immune monitoring techniques, and precision individualized immunotherapy, all with the aim of exploring new directions for future kidney transplantation immunology research.

Keywords: kidney transplantation, immune cells, alloimmune response, immune rejection

Introduction

Kidney transplantation is currently the best treatment option for end-stage renal disease patients.[1] With the continuous progress of modern science and technology, although the early survival rate and functional recovery of recipients after kidney transplantation have been significantly improved, the long-term survival rate remains unsatisfactory.[2] Rejection is a crucial factor severely influencing the survival rate and survival time of transplanted kidneys.[3] Regarding rejection, immune responses, encompassing innate immunity and adaptive immunity, play a central role.[4] Among these, T cell-mediated rejection (TCMR) and antibody-mediated rejection (ABMR) within adaptive immunity are the primary types of rejection following kidney transplantation.[3]

In recent years, with the breakthroughs in technologies like single-cell sequencing and mass cytometry, our understanding of the immunity after kidney transplantation has not been confined to broad immune cell categories anymore. Instead, it has gradually delved into individual immune cell subsets and the level of dynamic immune landscape evolution.[5–7] This transformation has unveiled the spatiotemporal heterogeneity of the immune rejection after transplantation and the complex interaction network among different immune cell subsets. It also underscores the necessity of delving deeply into the evolution of the immune landscape in kidney transplantation.

The convening of the Banff Conference and the establishment of the Banff definitions are momentous milestones in the development of international transplant pathology. After the first conference in 1991, the Banff definitions for transplant kidney complications were published in 1993.[8] Rejection reactions were classified into four categories: hyperacute rejection, borderline rejection, acute rejection, and chronic allograft nephropathy. This classification could

Received: 11 July 2025
Accepted: 9 October 2025
Published: 30 October 2025

not clearly distinguish the cellular and humoral immune pathogenic mechanisms of rejection reactions. Initially, the pathological categorizations of rejection reactions were mainly limited to TCMR. It was not until 2005 that, based on the establishment of the C4d staining method in transplant kidney biopsy tissues, the Banff definitions first proposed classifying rejection reactions into TCMR and ABMR according to the pathogenic mechanism, thus opening up a new era for the diagnosis and treatment of ABMR in transplant kidneys.[9] As transplant research has progressed, the Banff definitions have been continuously refined. In the Banff 2019 definitions,[10] according to the manifestations of acute and chronic lesions, TCMR was further divided into acute TCMR (aTCMR) and chronic active TCMR (caTCMR); ABMR was divided into active ABMR (aABMR), chronic active ABMR (caABMR), and chronic ABMR (cABMR). This classification emphasizes that ABMR is a continuous immune injury process that can occur at any stage after transplantation. Its diagnosis requires the combination of biopsy pathological observations (such as microvascular inflammation, C4d positivity, etc.) and donor-specific antibodies (DSA) tests. However, it has been found that certain cases of ABMR lack C4d staining or detectable DSA,[11] reflecting the complexity of transplant medicine and prompting a reexamination of the existing standards. It's worth noting that the Banff definitions were updated in the 《American Journal of Transplantation》 in 2022.[12]

In this review, we approach the topic from the perspective of transplantation immunity following kidney transplantation. We summarize the immune evolution post - transplantation, with a particular focus on the roles and mechanisms of the cellular components within innate immunity, encompassing phagocytes (neutrophils and macrophages), dendritic cells, and natural killer cells, as well as the non - cellular components including the complement system and platelets. We also pay particular attention to T and B cells in adaptive immunity during kidney transplantation. Additionally, we delve into the applications of xenogeneic kidney transplantation, immune monitoring techniques, and precision individualized immunotherapy, but excluding the related content of stromal cells such as non - immune cell types like endothelial cells and fibroblasts. Our aim is to offer perspectives that can facilitate a deeper understanding of the immune mechanisms underlying kidney transplant rejection and aid in the development of novel treatment strategies.

Immunological Mechanisms and Classification of Allograft Rejection: The Synergistic Effect of Innate and Adaptive Immunity

Allogeneic kidney transplant rejection is a complex inflammatory process mediated by the coordinated action of the innate and adaptive immune systems. From an immunological mechanism perspective, this process involves complex cell interactions and the participation of multiple co-stimulatory molecules and cytokines. (I) Adaptive immunity: It plays an important role in transplantation immunity. Mainly including T cells and B cells, they respectively cause TCMR and ABMR after kidney transplantation.[3] (II) Innate immunity: It is an essential stage of rejection after kidney transplantation and a necessary condition for adaptive immunity. The innate immune system participates in the immune response of kidney transplantation through both cellular and acellular components. Regarding cellular components, Antigen-Presenting Cells (including dendritic cells and macrophages), neutrophils, natural killer cells play roles by recognizing transplant antigens, presenting antigen information, and mediating inflammatory responses; acellular components include the complement system, cytokine network, and damage-associated molecular patterns (DAMPs), and these molecules participate in the rejection process by regulating inflammatory responses and immune cell activation.[13,14]

According to the time of occurrence of clinical renal allograft rejection, histopathological and immunological characteristics, and Banff classification, the allograft rejection in kidney transplantation can be generally classified into four main types (Table 1).[11,14]

Innate Immunity and Kidney Transplantation

Neutrophils

In the composition of peripheral blood leukocytes, neutrophils are dominant, accounting for 50–70% of human leukocytes.[15] Renal ischemia-reperfusion injury (IRI) is a clinically common pathological phenomenon where the originally simple ischemic injury of the ischemic kidney worsens after blood supply restoration. It is an extremely important and inevitable process in kidney transplantation and a major cause leading to delayed recovery of graft

Table 1 Main Types of Allograft Rejection After Kidney Transplantation

Types of Rejection Reactions		Occurrence Time	Main Mechanisms	Morphologic/Serologic
HAR		Immediately after the restoration of blood circulation in the transplanted kidney to several hours.	Humoral immunity mediated by pre-existing antibodies (against HLA or blood group antigens).	Diffuse intravascular coagulation with thrombosis, neutrophil infiltration within glomerular capillaries, and renal cortical necrosis.
AR	aTCMR	At any point following surgery, it typically occurs in the early phase, with the high-incidence period being within three months after the operation.	T cells recognize antigens and mount an immune response that targets the graft.	Interstitial inflammation, tubulitis, and intimal arteritis in transplanted kidney tissue.
	aABMR	At any point following surgery, it is prevalent during the early phase, with a higher incidence within 30 days after the operation.	DSA bind to antigens on the vascular endothelium, activating inflammatory responses.	Microvascular inflammation, which includes glomerulitis and peritubular capillary inflammation, the presence of C4d deposition in peritubular capillaries, along with positive or negative findings in DSA testing.
CR	caTCMR	It often occurs three months after transplantation.	Sustained T cell-mediated immune injury.	Interstitial inflammatory cell infiltration and tubulitis lesions, inflammatory cell infiltration within the region of interstitial fibrosis and tubular atrophy, along with atrophic tubulitis lesions, chronic allograft vasculopathy, non-specific interstitial fibrosis, and tubular atrophy lesions.
	caABMR	From several months to several years after the surgery.	Sustained DSA-mediated microvascular injury.	It includes the pathological features of aABMR. Meanwhile, the characteristic chronic lesions of chronic allograft glomerulopathy resulting from cABMR factors, multilayering of peritubular capillary basement membranes, and/or chronic allograft vasculopathy are observable.
	cABMR	Terminal stage	Chronic irreversible damage resulting from previous ABMR.	There are distinct chronic lesions of allograft glomerulopathy and multilayering of the peritubular capillary basement membrane, and the active lesions have largely disappeared.
MR		AR is superimposed on CR.		Both AR and CR possess dual pathological characteristics.

Abbreviations: HAR, hyperacute rejection; AR, acute rejection; CR, chronic rejection; MR, mixed rejection; TCMR, T cell-mediated rejection; ABMR, antibody-mediated rejection; aTCMR, acute T cell-mediated rejection; aABMR, active antibody-mediated rejection; caTCMR, chronic active T cell-mediated rejection; caABMR, chronic active antibody-mediated rejection; cABMR, chronic antibody-mediated rejection; HLA, DSA, donor-specific antibodies.

function.[16] Studies have demonstrated that neutrophils are closely associated with the occurrence of IRI after kidney transplantation. During the IRI process, various adhesion molecules, like P-selectin, E-selectin, intercellular adhesion molecule-1 (ICAM-1), integrin, and CD44, have been verified to participate in mediating the recruitment of neutrophils.[17] Research has shown that neutrophil infiltration can be detected in the renal interstitium 30 minutes after renal IRI occurs and peaks 24 hours later.[18,19] Although neutrophils are widely present in renal IRI, their specific mechanism of action has not been fully clarified. Rat model studies further disclosed that during the acute phase of IRI, mitochondrial formyl peptides promote neutrophil migration and reactive oxygen species (ROS) production through the ERK1/2 signaling pathway by activating formyl peptide receptor 2, thereby exacerbating renal injury.[20] Dipeptidase-1

(DPEP1) is a dimer glycoprotein specifically expressed on the brush border of proximal tubular epithelial cells, and its structural feature is being anchored to the cell membrane via glycosylphosphatidylinositol (GPI). This enzyme can regulate the interaction between immune cells (including neutrophils and monocytes) and microvascular endothelial cells in the context of renal IRI, and its expression intensity is significantly correlated with the severity of acute kidney injury.[21] Moreover, under pathological stimulation conditions such as IRI, neutrophils will release special neutrophil extracellular traps (NETs), and an increase in the concentration of this complex composed of nucleic acids and various proteins can be detected in the recipient's circulatory system in the early stage of transplantation.[22] This phenomenon may offer potential molecular markers for early IRI-mediated graft injury and also open up a new research direction for elucidating the molecular mechanism of IRI.

It should be noted that in renal transplant patients, due to the postoperative disorder of the internal environment and the use of a large number of immunosuppressive agents and hormonal drugs for treatment, the inhibitory effect of immune cells will increase. This, in turn, affects the accuracy of the detection of traditional infection indicators such as lymphocyte count, white blood cell count, and neutrophil count.[23] The neutrophil-to-lymphocyte ratio (NLR), an important reference index for systemic inflammatory response, can reflect the balance between lymphocytes (inflammatory regulatory factors) and neutrophils (inflammatory activating factors). Its clinical value has been verified in the field of organ transplantation.[24] Studies have shown that for patients receiving living donor kidney transplantation, if the preoperative test shows an abnormally elevated NLR, the risk of delayed graft function (DGF) recovery after surgery will increase significantly.[25] For transplant recipients with AR, consecutive tests within one week before pathological biopsy showed that both their NLR and neutrophil counts were significantly higher than those in other types of rejection and non-rejection patient groups.[26] Another study found that NLR is correlated with new-onset diabetes after transplantation (NODAT) in renal transplant recipients and can be a good predictor of NODAT after renal transplantation.[27] It's worthy of note that as a non-specific inflammatory marker, NLR is prone to being interfered with by infections, stress, and other clinical circumstances. Thus, when interpreting it, other clinical and pathological indicators should be taken into comprehensive consideration to avoid using it as an independent diagnostic criterion.

Macrophages

Macrophages are a group of heterogeneous cells that can express various surface receptor molecules, including damage-associated molecular patterns (DAMPs), Toll-like receptors (TLRs), and major histocompatibility complex II.[28,29] Based on their different activation methods, macrophages are classified into classically activated macrophages (M1 type) and alternatively activated macrophages (M2 type) (Figure 1).[30] Studies have demonstrated that macrophages are involved in the pathophysiological process of renal IRI in transplanted kidneys. Different phenotypes of macrophages play distinct roles. M1 macrophages can promote inflammatory responses and aggravate tissue damage, while M2 macrophages are involved in anti-inflammatory responses and tissue repair. During the 24–48 hours at the onset of IRI, M1 macrophages are predominant. When the blood supply to the ischemic kidney is restored, the inflammatory reaction is triggered. DAMPs are released in large quantities, and TLRs on the surface of M1 macrophages recognize DAMPs, activating TLR signals. This, in turn, promotes the activation of the nuclear factor (NF)-κB pathway, leading to the release of inflammatory factors such as Interleukin(IL)-1, IL-6, IL-12, IL-23, and tumor necrosis factor-α (TNF-α), exacerbating the inflammatory response. After 5–7 days, M2 macrophages become predominant. Tubular epithelial cells release granulocyte-macrophage colony-stimulating factor (GM-CSF), which induces the production of M2 macrophages. Subsequently, M2 macrophages release IL-10 to inhibit the inflammatory response and promote the proliferation of tubular epithelial cells and the repair of renal tissue damage.[31,32] Therefore, inhibiting the production and function of M1 macrophages and inducing the differentiation of M2 macrophages could be an important approach for treating renal IRI.

Macrophages also play a role in aTCMR. In the early years, an analysis of the types of inflammatory cells in the transplanted kidney tissues of aTCMR patients showed that 32–60% of the inflammatory cells in these tissues were macrophages. Moreover, the number of macrophage infiltration was inversely proportional to the prognosis of the transplanted kidney.[33] Recent studies have further confirmed that the number of M1 macrophages in the transplanted kidney tissues of aTCMR patients is significantly higher than that in those with stable transplanted kidney function.[34] This indicates that M1 macrophages might promote the occurrence of aTCMR. Interestingly, similar to the role of

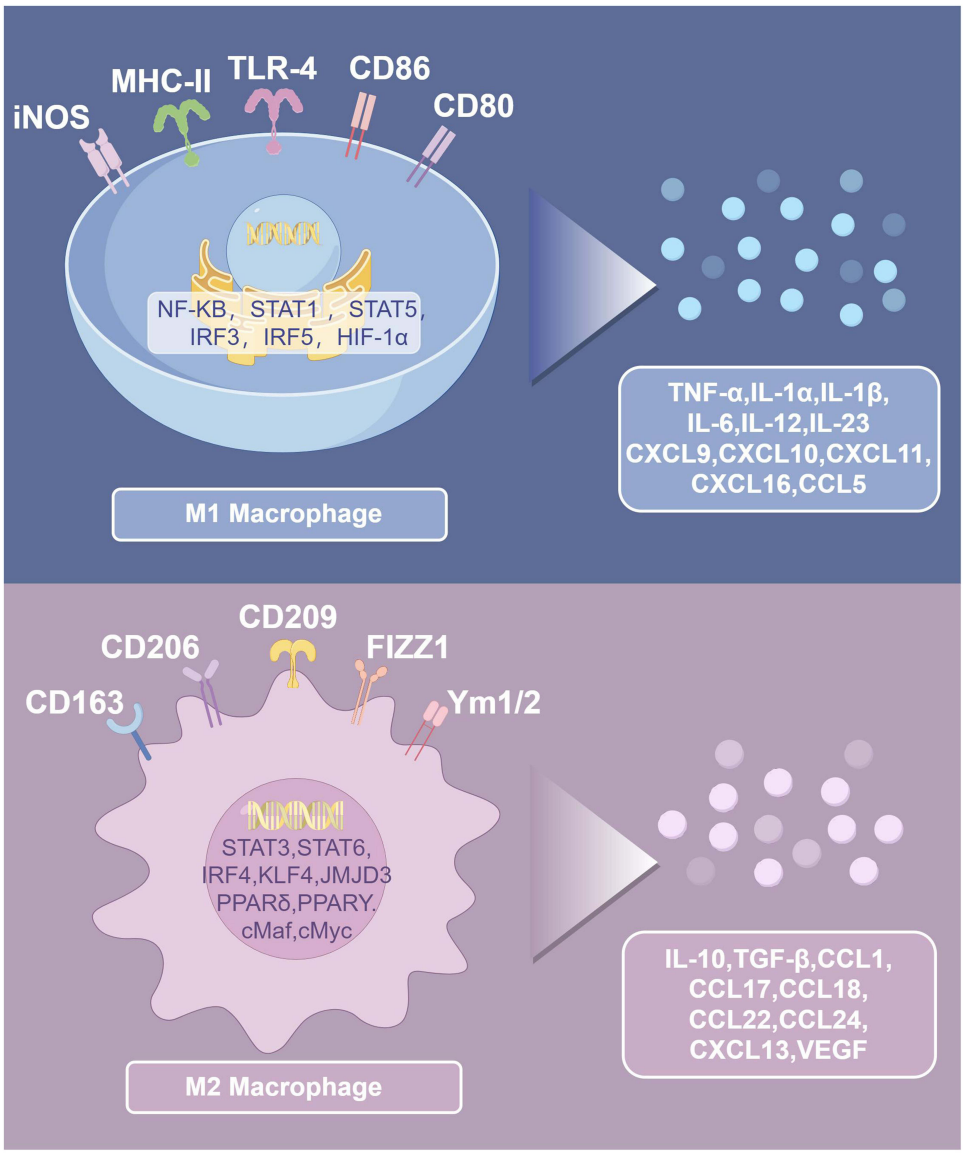

Figure 1 M1 macrophage vs M2 macrophage. Created with Figdraw.

different phenotypes of macrophages in renal IRI, studies have found that besides releasing various pro-inflammatory factors, M1 macrophages can also express inducible nitric oxide synthase (iNOS), which then promotes the production of ROS, jointly aggravating the damage of transplanted kidney tissues.[35] On the other hand, M2 macrophages can produce anti-inflammatory factor IL-10 and others to induce the production and proliferation of forkhead box P3 $(Foxp3)^+$ regulatory T cells (Treg), playing a protective role in transplanted kidney tissues.[36]

In addition, ABMR is regarded as the main cause of long-term graft loss after kidney transplantation,[37] yet its mechanism remains unclear. Macrophages in the renal tissue of ABMR patients are predominantly of the M2 type. M2 macrophages are associated with the severity of ABMR, the deterioration of graft function, and the progression of fibrosis in the transplanted kidney.[38] Examination of renal biopsy samples from children with ABMR in the transplanted kidney revealed a significant correlation between the increase in M2 macrophages in the renal tissue and the aggravation of renal fibrosis and the decline in renal function. The study also discovered that M2 macrophages were frequently located in the area of interstitial fibrosis, demonstrating type collagen I deposition, positive for α-smooth muscle actin (α-SMA), and the accumulation of myofibroblasts.[39] However, in recent years, the single-cell RNA sequencing (scRNA-seq) has witnessed rapid development and has gradually emerged as the primary approach for the identification of novel

https://doi.org/10.2147/JIR.S553007

cell subsets. Research on scRNA-seq has underscored the high plasticity and heterogeneity of macrophages. During the fibrosis process, specific macrophage subsets assume distinct roles, indicating that M2 macrophages should not be considered a functionally homogeneous pro-fibrotic population. This implies that M2 macrophages play a crucial role in ABMR, and inhibiting or eliminating M2 macrophages might exert a therapeutic effect on ABMR of the transplanted kidney. Evidently, macrophages play diverse roles in renal IRI and transplanted kidney rejection due to their functional plasticity. By regulating macrophage subtype transformation or selectively clearing specific subsets, it is anticipated to develop novel cell therapy approaches.

Natural Killer Cells

Natural killer (NK) cells, being important immune effector cells, play a key role in transplant rejection. They mainly act in the following ways: releasing perforin and granzyme to directly lyse target cells; inducing local tissue inflammatory responses; and secreting pro-inflammatory cytokines such as interferon-γ (IFN-γ) and TNF-α. During rejection reactions, the infiltration of NK cells can be significantly observed in allogeneic grafts.[40] Studies have indicated that $CD56^{dim}$ NK cells in renal transplant recipients show an activated phenotype. Specifically, the expression of CD16, CD226, and CD161 is downregulated, while the expression of human leukocyte antigen (HLA)-DR and CD25 is upregulated. In vitro experiments have demonstrated that the downregulation of CD16 is associated with the production of IFN-γ. Calcineurin inhibitors can inhibit CD16 regulation and NFAT-dependent cytokine secretion, but do not affect cytotoxic function.[41] Patients with aTCMR exhibit characteristic changes in NK cell subsets. There is an increase in the total number of NK cells, mainly manifested as the expansion of the $CD56^{bright}$ subset and the reduction of the $CD56^{dim}$ subset, along with a significant increase in the $CD56^{bright}/CD56^{dim}$ ratio. At the same time, the proportion of NKT-like cells decreases, and the $CD56^{bright}$/NKT-like cell ratio increases. These changes are related to the increased level of C-C motif chemokine 19 and the decreased level of IL-15 in the serum.[42]

The study also found that the mechanism of antibody-dependent NK cell activation is closely associated with late graft dysfunction. Its mechanism mainly involves allogeneic immune responses mediated by DSA through a complement-independent pathway. Antibody-dependent cell-mediated cytotoxicity (ADCC), which is mainly mediated by NK cells, is an effective cytotoxic mechanism. The results of the NK-cell humoral activation test (NK-CHAT) indicated that enhanced ADCC responses were significantly correlated with the deterioration of graft function and were an independent risk factor for the decline in estimated glomerular filtration rate.[43] It is worth noting that in long-term stable kidney transplant recipients, the immune function of NK cells can exhibit characteristic changes. Specifically, in $CD56^{dim}CD16^{+}$ NK cells, there is a significant decrease in the content of perforin and granzyme B. Moreover, a higher level of $perforin^{+}granzyme\ B^{+}CD56^{dim}CD16^{+}$ NK cells in kidney transplant recipients is associated with impaired graft function. On the contrary, recipients with a reduced perforin release ability of NK cells usually demonstrate better graft function.[44] This suggests that NK cell-mediated graft immune tolerance is related to the impaired expression of surface activating receptors. Another study also confirmed that, compared with healthy individuals, the expression of perforin, granzyme, and the activating receptor NKp46 is defective in patients with spontaneous tolerance after renal transplantation and stable graft function under immunosuppressants.[45]

Dendritic Cells

Dendritic cells (DCs), which are the core antigen-presenting cells, play a crucial role in the induction and regulation of immune responses within kidney transplantation immunity. In the renal microenvironment, DCs can exhibit a range of phenotypes, from anti-inflammatory tolerogenic phenotypes to pro-inflammatory phenotypes that can promote acute or chronic injury. Their functional transformation is precisely regulated by microenvironmental signals.[46] In renal IRI, DCs trigger rejection through a dual mechanism. On the one hand, donor DCs directly present allogeneic antigens to recipient T cells, thereby inducing AR,[47,48] on the other hand, DAMPs activate the toll-like receptor 4 (TLR4) pathway, which drives DCs maturation and initiates an adaptive immune response against alloantigens.[49]

Recipient DCs and donor DCs are specific subsets of DCs. Recipient DCs play a dominant role in CR. Mouse models have demonstrated that recipient DCs start to replace donor DCs within 24 hours after transplantation, and by day 7, 90% of the DCs in the graft have become recipient-derived.[50] Infiltrating DCs promote the CR process by presenting antigens

to helper T cells and activating B cells, yet the specific molecular mechanisms still need further investigation. Moreover, a recent study noticed a unique phenomenon where donor DCs transfer donor major histocompatibility complex (MHC) molecules to the surface of recipient conventional DCs. This might directly activate recipient DCs and trigger the activation of alloreactive T cells, thus inducing cytotoxic alloimmunity.[51,52] Single-cell sequencing studies have further shown that in biopsy tissues from patients with cABMR, classical DCs and plasmacytoid DCs are significantly enriched in low extracellular matrix regions,[6] and the proportion of DCs increases as the rejection reaction progresses from acute to chronic.[53] A clinical study has also verified an increase in DC infiltration in the grafts of CR patients.[54] Other research results indicate that compared with the non-rejection group, the proportion of DCs in the peripheral blood of patients in the biopsy-confirmed rejection group is significantly decreased, suggesting that DCs may migrate to the rejection site.[55,56] Additionally, the study discovered that the preoperative level of myeloid DCs in kidney transplant recipients has important prognostic value, and its deficiency is significantly associated with cytomegalovirus (CMV) infection and mortality after kidney transplantation.[57] These findings clarify the key role of DCs in transplantation immunity and offer relevant scientific basis for the future development of targeted immunoregulatory strategies.

Complement System

The complement system is a crucial component of innate immunity and serves as a bridge between innate and adaptive immunity. It comprises a large number of proteins present in the circulation, tissues, and cell membranes. Complement activation mainly involves three pathways: (I) Classical pathway (CP): The Fc fragment of the immune complex binds to C1q. Subsequently, C1r, C1s, C4, C2, C3, and C3 are activated to form C3 convertase, thereby initiating the activation pathway. (II) Alternative pathway (AP): Factor B binds to C3b on the surface of microorganisms. With the assistance of Factor D and properdin, the alternative pathway C3 convertase is formed to start the activation. (III) Lectin pathway (LP): Activation is triggered by the recognition of the sugar structure on the pathogen surface by MBL or ficolin (FCN). This activates MASP1, MASP2, and MASP3, which have enzymatic activities similar to C1r and C1s. MASP1 can directly cleave C3, MASP2 can hydrolyze C4 and C2 molecules, and MASP3 can feedback-regulate the activity of MASP2.[58] The three pathways converge to form C3 convertase, which further activates to form C5 convertase and cleaves C5 into C5a and C5b. C5b and C6-C9 ultimately form the membrane attack complex (MAC) to exert the cell lysis effect.[59,60]

Complement can be activated at multiple time points during kidney transplantation. These time points include before kidney organ procurement, during ex vivo organ preservation, and after transplantation in allograft recipients. As a result, complement participates in multiple processes of the occurrence and development of transplanted kidney injury.[61] Some studies have shown that complement activation can occur in donor kidneys before harvesting, particularly in donors with donation after brain death (DBD).[62] C3 fragment deposition can be detected in DBD donor kidneys, and LP and terminal pathway activation products can be detected in the blood of deceased donors.[63,64] Prolonged cold ischemia time during organ transportation and organ repair methods may also influence complement activation. Additionally, IRI creates an environment that is conducive to complement activation. In a mouse model, AP and LP activation play important roles in IRI. Monoclonal anti-complement factor B deficiency or mannose-binding lectin deficiency can protect mice from kidney IRI.[61] Other complement components in LP may also be involved, such as collectin-11, which binds to carbohydrate residues exposed on the surface of ischemic cells, promoting kidney epithelial cell injury.[65] Clinical studies have indicated that complement is activated after reperfusion, and the circulating soluble C5b-9 in recipients increases after reperfusion. In recipients with DGF, the C5b-9 level is higher, and the increase in C5b-9 concentration can predict the duration and long-term prognosis of DGF.[66,67] Generally, inhibiting complement activation and reducing the adverse effects of complement activation during kidney transplantation contribute to improving the organ survival and long-term prognosis of kidney transplant recipients.

Platelets

Platelets are not only involved in hemostasis and blood coagulation processes but also play a crucial role in inflammatory and immune responses. Activated platelets can generate a variety of mediators and cytokines to participate in the inflammatory process, which is one of the initiating factors of AR after kidney transplantation. The lipoxygenase product of platelets, 12-hydroperoxyeicosatetraenoic acid, can stimulate leukocytes to produce leukotrienes. The latter exhibits strong chemotactic and chemoexcitatory effects, acting on neutrophils and eosinophils chemotactically and also

promoting the adhesion of leukocytes to the vascular endothelium, leading to neutrophil degranulation and the release of inflammatory factors like lysosomal enzymes. Moreover, after platelet activation, pro-inflammatory molecules such as P-selectin, CD40L, and platelet factor 4 (PF4) are released. These molecules have a potent chemotactic effect on polymorphonuclear neutrophils, monocytes, causing leukocyte aggregation and adhesion to the vascular wall. They can also enhance the phagocytic oxidative ability while releasing oxygen free radicals and proteases. These substances inflict damage on the vascular endothelium of the graft and intensify the inflammatory response.[68,69]

The Adaptive Immune Landscape in Kidney Transplantation

T Cells

In the immune response of kidney transplantation, T cells play a key role through TCMR. Its mechanism is derived from the differences in HLA between the donor and the recipient. When the heterologous antigens of the transplanted kidney are recognized by the host immune system, effector T cells are activated through antigen presentation. During this process, pro-inflammatory factors such as IL-2 further amplify the immune cascade reaction, leading to severe local immune rejection of the transplanted kidney.[70] According to pathological characteristics, TCMR can be divided into interstitial infiltration type and vascular injury type, and from the perspective of disease course evolution, it can be divided into aTCMR and chronic TCMR (cTCMR).[71] It is worth noting that the occurrence of aTCMR in the early postoperative period is significantly correlated with the reduction of graft survival rate, which is an important warning index for clinical prognosis evaluation.[72]

Curiously, effector memory T cells play a pivotal role in cTCMR. Transcriptomic analyses have revealed that, in contrast to aTCMR, the OX40 (a member of the tumor necrosis factor receptor family, also known as CD134) signaling pathway is specifically upregulated in cTCMR. This pathway can markedly enhance T-cell survival and promote the generation of effector memory $CD8^+$ T cells. These cells highly express marker molecules such as killer cell lectin-like receptor G1 (KLRG-1) and B lymphocyte-induced maturation protein 1 (BLIMP-1) and display the characteristics of rapid effector function yet limited proliferative capacity. In the transplanted kidney tissues of cTCMR, a significant increase in $KLRG\text{-}1^+/CD8^+$ and $BLIMP\text{-}1^+/CD8^+$ T cells can be detected, and OX40 co-localizes with infiltrating $CD8^+$ T cells. This suggests that OX40 signaling pathway-driven effector memory $CD8^+$ T cells specifically participate in the immune injury process of chronic rejection, thereby providing novel potential targets for intervening in cTCMR.[73]

Tregs are central regulators of immune homeostasis.[74] As a small subset of $CD4^+$ T cells, their lineage differentiation and function rely on Foxp3. They limit tissue damage by preventing unnecessary immune activation and suppressing ongoing immune responses.[75] In immune tolerance, Tregs mainly achieve self-tolerance, tolerance to allogeneic antigens, and transplant tolerance by inhibiting the activation and function of reactive effector T cells.[76] Although polyclonal Tregs are relatively easy to generate, antigen-specific Tregs are more appealing. The role of antigen-specific Tregs in preventing rejection and inducing tolerance is 10 times that of polyclonal Tregs.[77] Tregs with direct allogeneic antigen specificity are crucial for inducing tolerance, while those with indirect allogeneic antigen specificity are important for maintaining tolerance. Controlling rejection and suppressing inflammation during the induction period not only prevents graft damage but also indirectly expands Tregs and establishes long-term immune tolerance.[78] Additionally, in a study of 133 kidney transplant recipients, the absolute number of Tregs in their peripheral blood samples was monitored. It was found that the absolute number of peripheral blood Tregs 1 year after kidney transplantation could predict better long-term graft prognosis and serve as a prognostic biomarker.[79] Another study showed that inducible Tregs reduced DSA levels and IgG deposition in allografts in a mouse model, indicating potential for treating humoral rejection.[80]

Tissue-resident memory T cells (TRMs) are mainly colonized in barrier tissues and some solid organs, playing a key role in local immune surveillance and rapid anti-infection. Abou-Daya et al[81] established a murine model of allogeneic kidney transplantation and found that T lymphocytes derived from the recipient's circulation infiltrate the graft and acquire the TRM phenotype, mediating CR. Tieu R et al[82] found that the maintenance of TRMs in the kidney requires the persistent presence of antigen and the presentation of IL-15, and DCs in the graft play the role of transmitting both antigen and IL-15 signals. Depletion of DCs can interrupt the maintenance of TRMs, and TRMs in the graft can prevent T lymphocyte dysfunction through survival or proliferation signals in a chronic inflammatory environment. However,

some studies have found that TRMs may be potentially harmful cells during the process of allogeneic kidney transplantation rejection. In the renal allograft microenvironment, donor- and recipient-derived TRM coexist. In early graft failure cases of kidney transplantation, donor-derived TRMs are mainly present, which are later replaced by recipient-derived TRMs. Recipient-derived TRMs have stronger effector capabilities and can play a role by producing IFN-γ and TNF-α driving the process of immune injury of the transplanted kidney.[83]

In transplantation immune response, allogeneic antigens from the donor are presented via the MHC molecules of recipient DCs. This activates the responses of $CD4^+$ and $CD8^+$ T cells, triggering the immune response against the graft and inducing rejection. When $CD4^+$ and $CD8^+$ T cells are co-activated, the immune effect is significantly amplified. This promotes the infiltration of effector T cells into the graft and induces the activation of immunosuppressive pathways such as Tregs.[84] In addition, $CD8^+$ T cells can specifically recognize the antigens of transplanted kidney tissues. They can cross the tubular basement membrane, proliferate and induce apoptosis of tubular cells.[85] γδ T cells are a type of T cells expressing γδ TCR on the surface. They are special subsets in the T cell family and play multiple roles in kidney transplantation immunity, such as anti-infection, immune surveillance and regulation of graft injury. Among them, some studies have shown that monitoring the dynamic changes of γδ T cells in the peripheral blood of kidney transplant recipients can predict the outcome of CMV infection. When the expansion rate of γδ T cells exceeds 0.06% per day, it indicates effective clearance of the infection. The starting time of its expansion is positively correlated with clinical recovery, while the emergence of antiviral drug-resistant mutant CMV strains is related to the delayed expansion of γδ T cells.[86]

B Cells

B cells are crucial in the transplantation immunity of kidney transplantation. The rejection mediated by B cells is termed ABMR or humoral rejection. ABMR is a significant clinical issue in immune rejection following kidney transplantation.[87] Its pathogenesis mainly lies in that after the body's Antigen-Presenting Cells present the antigens of the transplanted kidney, they stimulate B cells to generate antibodies against the MHC complex of the transplanted kidney. After binding with the antigens, the complement reaction is further activated, leading to damage to the transplanted kidney.[88] Different from the pathological characteristics of TCMR, when ABMR occurs in the transplanted kidney, the damaged parts are mainly the renal tubules and endothelial cells. Obvious infiltration of neutrophils and macrophages can be observed in the peritubular capillaries. Meanwhile, obvious inflammation can be seen in the glomeruli and capillaries.[89]

Regulatory B cells (Bregs), a subtype of B cells, can directly or indirectly act on other immune cells by secreting cytokines, inhibiting inflammatory responses, and maintaining immune homeostasis in the body.[90] In kidney transplantation, they regulate the differentiation and proliferation of immune cells. They participate in immune regulation in the body through various means. For example, they secrete soluble molecules such as IL-10, IL-35, IL-12, and transforming growth factor-β, as well as various enzymes like granzyme B. Additionally, they act through the Fas-FasL and programmed death-1 (PD-1) / programmed death ligand-1 (PD-L1) pathways.[91] Among these, IL-10 is the main functional cytokine secreted by Bregs. It can inhibit the responses of Th1 cells, Th17 cells, and $CD8^+$ T cells, promote the conversion of naive $CD4^+$ T cells into $Foxp3^+$ Tregs, and participate in regulating the pro-inflammatory cells of the innate immune system.[92] Moreover, Bregs can also interact with other immune cells such as DCs and Tregs to exert inhibitory immune effects.[93,94] However, the immune regulatory role of Bregs in the human body is not entirely positive. Bregs play a protective role in autoimmune diseases, transplant rejection, graft-versus-host disease, and allergies, which are diseases related to excessive immune responses. But in infectious or tumor-related diseases, the induction and overactivation of Bregs may have a negative impact on the disease process.[95]

Memory B cells and long-lived plasma cells (LLPCs) differentiate from activated naive B cells upon interaction with $CD4^+$ T cells. After antigen stimulation in the human body, they produce antibodies via germinal center (GC)-dependent or -independent pathways. In transplantation, LLPCs can generate alloantibodies, which are crucial in ABMR. They can mediate ABMR by producing preformed antibodies and regenerating antibodies post-transplantation.[96] Moreover, the antibodies secreted by LLPCs can induce inflammatory damage to graft vascular endothelial cells through complement-dependent or complement-independent pathways, and this damage is regarded as the main cause of ABMR pathogenesis.[97] The immune system's secondary response to homologous antigens exhibits a significantly enhanced effect. When memory B cells are re-exposed to allogeneic antigens, they can optimize their antigen-binding ability through somatic hypermutation during the GC

process, rapidly differentiate into plasma cells, and generate a large number of new DSAs, ultimately resulting in graft damage.[98–100] Studies have verified that a burst of DSA generation can be detected in patients with secondary transplantation sensitization.[97,101] This implies that dynamic monitoring of the activation status of memory B cells in kidney transplantation is helpful for achieving early warning of ABMR.

Immune Responses After Kidney Transplantation: Differences Among Different Populations

After kidney transplantation, the immune responses of recipients exhibit population heterogeneity, which stems from the interaction of multi-dimensional factors such as age, underlying diseases, and genetic background. Regarding the age dimension, the immune responses of elderly kidney transplant recipients differ from those of young recipients. With the aging of the global population, more elderly end-stage renal disease patients undergo kidney transplantation. Meanwhile, organs from elderly donors are used more frequently, presenting a trend of dual aging of donors and recipients. Studies have revealed that in elderly transplant recipients, the incidence of rejection is relatively low. The characteristics of their alloimmune responses are manifested as a decrease in the efficacy of specific immune responses and an increase in non-specific immune responses.[102] Another study indicated that although elderly recipients showed a decrease in the clonal diversity of alloreactive T cells (one of the signs of immunosenescence), their innate immune system demonstrated a state of chronic low-grade activation. This was manifested as hypersensitization of the monocyte TLR4 signaling pathway and an increased susceptibility to cytokine storms.[103]

Differences in the disease spectrum pose additional challenges to immune regulation strategies. For instance, among hepatitis C virus (HCV)-positive recipients, virus-specific $CD8^+$ T cells can cross-react with donor kidney HLA class I molecules via molecular mimicry mechanisms. Single-cell T cell receptor (TCR) sequencing studies have verified that such cross-reactive T cell clones can constitute 15–30% of the graft-infiltrating lymphocytes. Following HCV clearance with direct-acting antiviral agents (DAAs), the TCR sequence diversity in the transplanted kidney undergoes significant changes, indicating the dynamic influence of the virus-host-graft tripartite interaction on immune homeostasis.[104,105] Moreover, immune responses can also differ among various ethnic groups, potentially linked to factors like genetic background. In the future, further investigations into immune response disparities among different populations can be carried out to establish a population-specific precision immune intervention network, which will facilitate more precise immunotherapy.

Renal Xenotransplantation

The shortage of donor organs is one of the most significant challenges in kidney transplantation and organ transplantation in general. In response to this shortage, numerous scientists have focused their research on xenotransplantation. Since Professor Princeteau of France first attempted to transplant a rabbit kidney into a uremic patient in 1905, the field of xenotransplantation has seen extensive exploration. Primates have emerged as potential candidates for xenotransplantation due to their close genetic relationship with humans. Scientists have experimented with transplanting the kidneys of orangutans and baboons. However, these animals often carry human-susceptible viruses, have limited availability, and long breeding cycles, making practical implementation challenging. With the advancement of research, the advent of the gene-editing technology CRISPR-Cas9 has provided a boost to this field.

Currently, gene-modified pigs are regarded as an ideal organ source for xenotransplantation, and scientists have conducted relevant research. The immune systems of humans and other primates react strongly to the α-1,3-galactose (α-Gal) antigen on the surface of pig endothelial cells, which is the core mechanism triggering HAR in xenogeneic organ transplantation. When a pig organ, such as a kidney, carrying α-Gal is transplanted into a primate recipient, the pre-existing antibodies in the recipient's body immediately recognize and attack this glycoprotein molecule, leading to extensive thrombosis in the blood vessels and ultimately causing the transplanted organ to rapidly lose its function. By using CRISPR-Cas9 gene-editing technology to genetically modify pigs and precisely knockout the key genes involved in α-Gal synthesis, the expression of this molecule in tissues like vascular endothelium can be effectively blocked. This technology also aids in modifying many other genes that may enhance human tolerance to pig organs.[106–108] In two cases

of pig kidney xenotransplantation carried out by New York University, pigs with a single-gene knockout of α-1,3-galactosyltransferase (GGTA1) were used. The donor pig thymus was implanted under the renal capsule to create a "thymic kidney", which was then transplanted into brain-dead patients. This design aims to promote the recipient's T cells to recognize the pig kidney as an autologous organ through the "re-education" of the recipient's T cells in the donor thymus, thereby reducing T cell-mediated rejection. During the 54-hour observation period in these two cases of thymic kidney transplantation, no signs of hyperacute or antibody-mediated rejection were observed.[109] In addition, knocking out the genes of β-1,4-N-acetylgalactosaminyltransferase (β4GalNT2) that encodes SDa polysaccharide and cytidine monophosphate-N-acetylneuraminic acid hydroxylase (CMAH) that encodes N-glycolylneuraminic acid (Neu5Gc) in pigs can effectively reduce the acute vascular rejection mediated by non-αGal antigens.[110] Meanwhile, human complement regulatory proteins such as hCD46 and hCD55 can be introduced to inhibit the damage inflicted by the human complement system on the graft.[111] Transfection of human thrombomodulin and human endothelial protein C receptor (hEPCR) helps inhibit the formation of microvascular thrombosis.[112,113] Moreover, the expression of human heme oxygenase-1 (hHO-1) can play an immunomodulatory and anti-inflammatory role.[114] On the other hand, the risk of cross-species transmission of porcine endogenous retrovirus (PERV) cannot be overlooked. Recent research, through 69 gene edits on Yucatan minipigs, successfully achieved the knockout of three glycosyl antigens, the inactivation of PERV, and the overexpression of seven human transgenes,[115,116] which has advanced the progress of xenotransplantation towards clinical application.

The emergence of gene-edited pigs marks that the development of xenotransplantation has stepped into a new phase. Nevertheless, there is still a long path ahead before its clinical application. Delayed rejection, the long-term function of the graft post-surgery, and ethical approval are the challenges that xenotransplantation still confronts. Moreover, survey data from Chinese kidney transplant recipients and those on the waiting list indicate that the overall acceptance of this group towards xenotransplantation is positive. However, their understanding of specific xenotransplantation knowledge is not comprehensive. Compared with the knowledge gap about rejection and other unknown risks, they are more worried about the risk of infection and have expressed the hope that the expected survival period of porcine kidney xenografts can be similar to that of allografts.[117] This mirrors the dual expectations of this group for the safety and efficacy certainty of xenotransplantation. In the future, it is essential to conduct further research to address the technical and difficult issues in xenotransplantation, carry out public education, emphasize enhancing the theoretical understanding level of xenotransplantation, and promote the improvement of relevant laws and regulations. This is to accelerate the translation of xenotransplantation from bench to bedside.

Other Complications Following Kidney Transplantation

The prevention and treatment of complications after kidney transplantation remain a formidable challenge. Complications mainly include infections, vascular complications, chronic renal allograft dysfunction (CRAD), and immunosuppressant-related side effects. These complications have a negative impact on the quality of life of patients and the long-term survival of grafts.

Infection is one of the important complications. In a retrospective cohort analysis of 1224 kidney transplant recipients, the incidence of sepsis was 5.1%, and 60% of sepsis cases originated from the urinary system.[118] This indicates that infection, particularly urinary tract infection, is a crucial source of sepsis after kidney transplantation, highlighting the need for strengthened clinical prevention and control. Opportunistic viral infections such as CMV and BK virus (BKV) are prevalent after kidney transplantation and are linked to significant complication rates and mortality.[119] Another study demonstrated that the incidence of CMV in middle-aged kidney transplant recipients was notably higher, reaching 93.9%. Further assessment of relevant factors revealed that the recipient's age, the type of induction therapy employed, and the preoperative serum status of the donor and recipient were significantly associated with the incidence of CMV in the recipient post-surgery.[120] BKV reactivation poses another significant challenge in the postoperative management of kidney transplant recipients. Approximately 30% of recipients can detect BKV viremia within two years after transplantation, which may lead to renal dysfunction and graft failure.[121] Another study confirmed that BKV is an important risk factor for BKV-related nephropathy in kidney transplant recipients, affecting around 10% of kidney transplant recipients and causing approximately half of these patients to ultimately progress to graft failure.[122]

Vascular complications after kidney transplantation cannot be overlooked. The common vascular complications mainly consist of vascular stenosis, arterial dissection (in the internal and external iliac arteries, renal allograft artery), pseudoaneurysm, rupture or thrombosis.[123] The occurrence of vascular complications is linked to a shortened graft survival time, resulting in 1.66% of graft loss and 0.16% of recipient death.[124] Hence, early detection, diagnosis, and treatment of vascular complications after renal transplantation are of great significance. Digital subtraction angiography is the gold standard for diagnosing various vascular complications. However, special attention must be paid to the risk of contrast-induced nephropathy (CIN) that patients with renal insufficiency may encounter.[125] Although the guidelines of the European Society of Urogenital Radiology (ESUR) suggest that the risk of CIN after transplantation is not higher than that of non-transplant patients,[126] the risks and benefits still need to be carefully evaluated in clinical decision-making.

In addition, CRAD is relatively common. CRAD is a clinical syndrome characterized by irreversible decline in transplanted kidney function, along with pathological features such as inflammation, interstitial fibrosis, and glomerular focal segmental sclerosis and atrophy. Essentially, it belongs to a type of chronic rejection reaction.[127,128] CRAD is not only an immune-related complication after kidney transplantation but is also influenced by multiple non-immune factors. Currently, the identified non-immune factors include donor brain death, increasing donor age, calcineurin inhibitor nephrotoxicity, hypertension, diabetes, hyperlipidemia, and chronic viral infection.[129]

It is worth noting that the immunosuppressive agents used to maintain graft survival are themselves significant factors contributing to acute and chronic graft injury. Calcineurin inhibitors (CNIs), such as tacrolimus and cyclosporine, which serve as the core maintenance immunosuppressive regimen, their nephrotoxicity represents one of the major non-immune factors causing acute and chronic renal impairment. The mechanism of action of CNI nephrotoxicity is intricate, encompassing the induction of renal vasoconstriction, particularly of the afferent arterioles, resulting in reduced renal blood flow and ischemic injury, direct cytotoxic effects leading to tubular injury and striped fibrosis, as well as the rare yet severe thrombotic microangiopathy.[130] Moreover, mammalian target of rapamycin (mTOR) inhibitors, like sirolimus, may impact wound healing and delay the recovery of renal function.[131] Consequently, the management of immunosuppressive agents poses substantial challenges. Over-immunosuppression and under-immunosuppression are analogous to the two extremes of a balance. Insufficient immunosuppression elevates the incidence of rejection, which can affect the survival of the transplanted kidney, while over-immunosuppression increases complications such as infections, which can affect the survival of transplant recipients. Hence, it is of great importance to minimize the adverse reactions of immunosuppressive drugs and optimize the immunosuppressive regimen for renal transplant recipients while ensuring an adequate anti-rejection effect. In conclusion, This abovementioned content reveals the complexity and diversity of kidney transplantation-related complications (Figure 2), highlighting the need for comprehensive consideration of multiple factors in clinical prevention and treatment.

Future Perspectives in Kidney Transplant Immunology

The innovation of immune monitoring technology offers crucial support for the precise diagnosis and treatment of kidney transplantation. High-throughput sequencing (HTS) technology can dynamically evaluate the diversity of immune responses and the characteristics of clonal evolution by deeply analyzing the immune repertoires of TCR and B cell receptors (BCR). It plays an important role in predicting the efficacy of cancer immunotherapy.[132] In the field of kidney transplantation, there is an expectation to utilize HTS technology to monitor the immune response of recipients to grafts and alert about the risk of transplant rejection. Multiparameter flow cytometry can simultaneously analyze the phenotypes and functions of multiple immune cells and reveal the cellular mechanisms of rejection reactions.[133] Highly sensitive immunoassay techniques (such as ELISA and fluorescence microscopy imaging) can accurately quantify the expression levels of key immune molecules to assist clinical decision-making.[134] In the future, the integrated application of these technologies will provide more precise means for optimizing the immune management strategy after transplantation.

Biomarkers play a crucial role in the immunodiagnosis of kidney transplantation. Currently, pathological biopsy serves as the "gold standard" for immune rejection diagnosis. Nevertheless, due to its invasive nature, it can lead to risks of complications like bleeding and infection. Moreover, there is a diagnostic lag, making it challenging to achieve early warning and real-time dynamic monitoring of rejection. Donor-derived cell-free DNA (dd-cf DNA), a newly emerging immune monitoring index after transplantation,[135] has drawn extensive attention in recent years. Dd-cf DNA exhibits

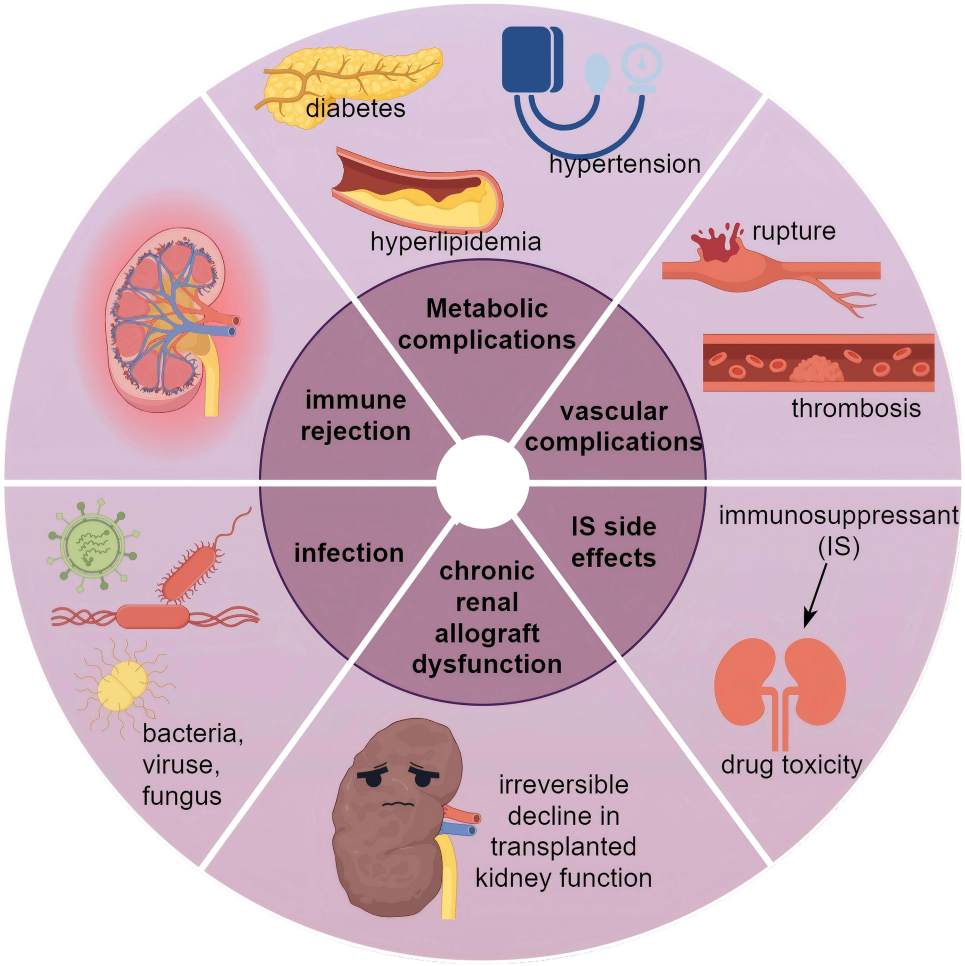

Figure 2 Main complications after kidney transplantation. Created with Figdraw.

excellent diagnostic performance in detecting rejection, featuring non-invasiveness, high sensitivity, repeatable detection, and the ability to evaluate treatment effects in real time. It can be regarded as a candidate biomarker for comprehensively monitoring transplanted kidney injury, demonstrating great potential.[136] The commonly used detection methods for dd-cf DNA currently include real-time fluorescence quantitative polymerase chain reaction (PCR), droplet digital PCR, and next-generation sequencing.[137] In the future, prospective multi-center studies are necessary to determine the optimal dd-cf DNA detection method, the value of combined diagnosis with other biomarkers, and its impact on the long-term outcomes of kidney transplant recipients. Additionally, further optimization of the detection technology is required to enhance the accuracy and specificity of its diagnosis.

Individualized immunotherapy represents the future development direction of kidney transplantation. With the rapid advancement of technologies like gene sequencing, bioinformatics, big data analysis, and artificial intelligence, the application of precision individualized medicine in kidney transplantation has become feasible. By comprehensively analyzing and evaluating multi-dimensional data including patients' genetic information, clinical phenotypes, and immune status, it can offer a foundation for individualized patient treatment, thereby achieving precise immunosuppressive therapy, donor selection, and complication prevention. For instance, through detecting the HLA gene typing of patients, donors can be selected more accurately to decrease the incidence of immune rejection.[138] Based on patients' gene typing, the response to immunosuppressive agents and rejection risk can be predicted, enabling the selection of the most appropriate drugs and doses.[139] Additionally, gene editing technology can be utilized to customize individualized transplanted organs to enhance their compatibility with the recipient's immune system.[140,141] It is anticipated that the development of precise individualized immunotherapy will significantly improve the treatment efficacy and quality of life of kidney transplant patients.

https://doi.org/10.2147/JIR.S553007

Conclusion

Transplantation immunity in kidney transplantation is a complex network immune regulation system (Figure 3). This review summarizes the evolution of the immune landscape and clinical challenges following kidney transplantation. The subsequent content synthesizes the key findings and future directions.

Firstly, regarding the key immune drivers of late graft loss, ABMR and the resultant microvascular injury are the primary causes. The pathological basis of this process involves persistent endothelial cell activation and injury triggered by pre-existing or de novo DSA. CaTCMR also contributes to late graft dysfunction. Secondly, complement and platelets play pivotal roles at all stages of injury. Complement is extensively activated during IRI, AR, and CR, directly amplifying inflammation and causing tissue damage. Platelets not only contribute to thrombosis, but the inflammatory mediators released upon their activation also play a role in initiating and exacerbating the inflammatory process of rejection. Thirdly, regarding current and emerging monitoring tools and their limitations, although tissue biopsy remains the gold standard for diagnosis, non-invasive monitoring tools such as dd-cfDNA and DSA monitoring are becoming increasingly important. The integration of molecular diagnostic techniques into the Banff criteria enhances the precision of pathological diagnosis. However, limitations in sensitivity, specificity, and clinical interpretation still persist, and combination with traditional pathology is required to optimize diagnostic accuracy.

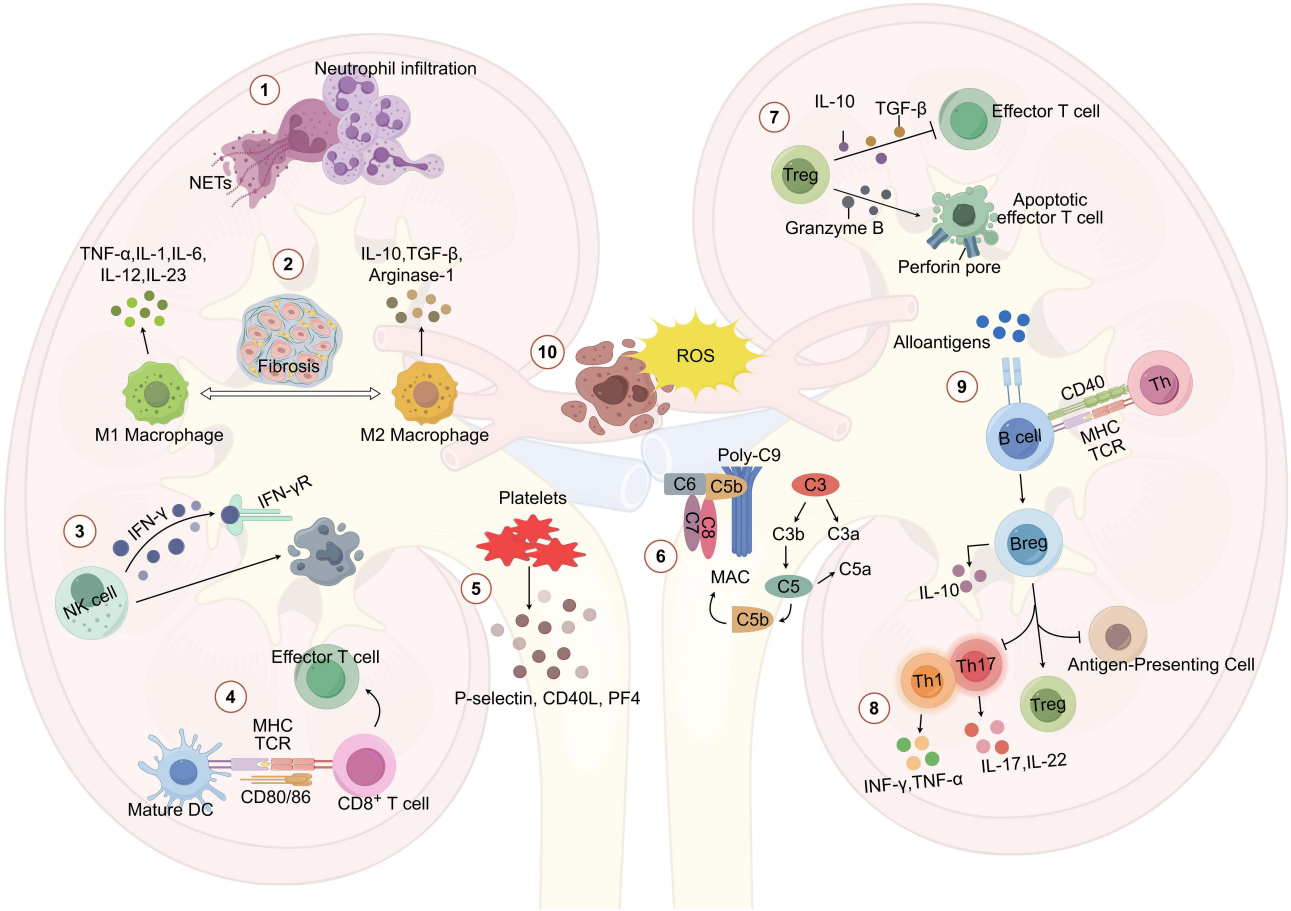

Figure 3 Immune cell-associated pathways in allograft kidney transplantation rejection.

Notes: (1) During IRI, neutrophil infiltration increases, and the release of NETs mediates renal injury; (2) Macrophage polarization into distinct phenotypes contributes to pro-inflammatory or anti-inflammatory responses and is associated with renal fibrosis; (3) Upregulation of IFN-γ in NK cells promotes cytotoxic granule release, enhancing target cell lysis; (4) DCs drive CD8+ T cell activation into cytotoxic effector T cells via antigen presentation; (5) Activated platelets release pro-inflammatory molecules (eg, P-selectin, CD40L, PF4), exacerbating inflammatory responses; (6) The three complement activation pathways converge to form C3 convertase, generating C5 convertase, which cleaves C5 into C5a and C5b. C5b subsequently binds C6-C9 to form the MAC, inducing cell lysis; (7) Tregs suppress effector T cell proliferation, cytokine secretion, and cytotoxic function by secreting IL-10 and TGF-β, and may also eliminate effector T cells via granzyme B/perforin-dependent pathways; (8) Th17 and Th1 helper T cells secrete pro-inflammatory cytokines; (9)Bregs inhibit antigen-presenting cells by producing IL-10, enhance Treg activity, and suppress Th17/Th1-mediated inflammation; (10) The pro-inflammatory microenvironment within the graft interacts with oxidative stress, aggravating tissue inflammation and rejection. Created with Figdraw.

Based on the current shift towards precision medicine, future research endeavors should concentrate on exploring the underlying mechanisms of the immune response and their effective translation into clinical treatment. At the mechanistic level, the following key directions can be targeted for breakthroughs: (i) elucidating the role of TRM-DC axis in CR; (ii) interpreting the dynamics of LLPCs to identify strategies for eliminating the source of DSA; (iii) overcoming immune barriers in xenotransplantation, such as immune responses against PERV and xenogeneic antigens. At the translational application level, the development of novel immunomodulatory therapies targeting these mechanisms is crucial. For instance, complement regulation demonstrates significant potential in alleviating IRI and DGF. Studies have shown that the complement inhibition by C1-inhibitor can downregulate the expression of the anti-aging factor Klotho in vivo by abrogating nuclear factor kappa B (NF-kB) signaling. In accordance, complement anaphylotoxin C5a led to a significant down-regulation of Klotho in renal tubular epithelial cells in vitro that was NF-kB mediated,[142] providing a new theoretical basis for targeting the complement system to improve DGF and related chronic graft dysfunction. Although there is still great room for development in the current research on kidney transplantation immunity and many challenges are faced, we are willing to believe that more breakthroughs will be achieved in the future.

Data Sharing Statement

No data was used for the research described in the article.

Consent for Publication

All authors approved the final manuscript and the submission to this journal.

Funding

This work was supported by the National Natural Science Foundation of China (grant No. 82574990), the Henan Medical Science and Technology Research Project (grant No. SBGJ202403050) and the Special Project of Traditional Chinese Medicine Scientific Research in Henan Province (grant No. 2024ZY2075).

Disclosure

The authors report no conflicts of interest in this work.

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