Chapter 8

Immunopathology of Kidney Transplantation

Zesergio Melo, Juan A. Ruiz-Pacheco,
Claudia A. Mendoza-Cerpa and Raquel Echavarria

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.70596

Abstract

Renal transplantation is currently the best alternative for patients with end-stage renal disease. Immune responses activated against the allograft are a decisive factor in transplantation outcomes and patient survival. Although short-term graft and patient survival have improved significantly as a result of better donor matching systems, novel immunosuppressive agents and enhanced care, long-term outcomes remain unfavorable and reflect sub-clinical injury caused by chronic rejection. The immune system lies at the intersection of immunogenic tolerance and graft failure; thus, it is a major determinant of pathology in the context of renal transplantation. During the early stages of transplantation increased expression of cytokines has been observed in addition to increased expression of adhesion proteins and immune cells. This early inflammatory response does not necessarily end in graft rejection, although this will depend on the severity of the inflammation. Activation of Toll-like Receptors (TLRs), damaging molecular patterns (DAMPs), and other components of innate immunity is key to the formation of atherosclerotic plaques and the development of autoimmune diseases. Initially the donor antigens are presented to the T lymphocytes of the recipient. This activation induces their proliferation, differentiation and cytokine production. Successful kidney transplant recipients need to develop immunologic tolerance against donor antigens. In this chapter, we address some of the innate and adaptive immune mechanisms associated with kidney transplantation; emphasizing their role in allograft rejection.

Keywords: kidney, transplantation, immunopathology, graft rejection, immunology

1. Introduction

According to statistics from the United States Renal Data System (UNOS) and the U.S. Department of Health & Human Services Organ Procurement and Transplantation Network

(OPTN), there are currently close to 100,000 people in the U.S. waiting for a lifesaving kidney transplant. Only between January and May 2017, 14,075 kidney transplants took place in the United States; of which 11,702 organs came from deceased donors and 2373 came from living donors. Renal transplantation has become the treatment of choice for patients with end-stage renal disease (ESRD); though its success and widespread use are still limited by the availability of suitable organs and allograft rejection [1]. In recent decades, short-term graft survival has improved significantly as consequence of better donor matching systems, novel immunosuppressive agents and enhanced care. Unfortunately, long-term outcomes remain unfavorable and reflect subclinical injury caused by antibody-mediated allograft rejection (ABMR) [2]. The immune system lies at the intersection between immunogenic tolerance and graft failure and as such, it is a major determinant of pathology in the context of renal transplantation [3]. The immune system is a complex network of lymphoid organs, cells, and molecules responsible for body homeostasis and host defense. Although the main function of the immune system is to protect against external pathogens and molecules, the presence of foreign antigens on the donor organ also triggers innate and adaptive immune responses in the recipient that will largely determine graft performance and patient survival.

2. Activation of innate immunity in kidney transplantation

Innate immune responses are required for the activation of cellular and molecular mechanisms behind the physiopathology of kidney transplantation [4]. During the early stages of transplantation, innate immunity is essential for the activation of the adaptive immune system, whereas at later stages, innate components promote an inflammatory microenvironment that enhances allograft damage.

2.1. Cells of the innate immune system

The cellular components of innate immunity are phagocytic leukocytes (neutrophils, monocytes, eosinophils, and basophils), natural killer (NK) cells, and dendritic cells (DCs). Ischemic injury that occurs during organ transplantation promotes alloimmune responses including innate cell recruitment [5]. Infiltrating neutrophils release proteases, free radicals, and proinflammatory molecules such as interleukin 6 (IL-6), interleukin 8 (IL-8), and tumor necrosis factor alpha (TNF-α) within the graft. It has been demonstrated that a high neutrophil-lymphocyte ratio amplifies the inflammatory process during acute renal failure [6]. Furthermore, neutrophil-depleted mice and intracellular adhesion molecule 1 (ICAM-1) knockouts are more resistant to renal ischemic injury; suggesting that neutralizing neutrophil activity could increase transplant success rates by reducing early graft damage [7]. Macrophages are also an important source of interleukin 1 (IL-1), IL-6, transforming growth factor beta (TFG-β), interferon γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 2 (MIP-2) during ischemia [8]. In the context of renal damage, monocytes are recruited within the

first few days thanks to C–C chemokine receptor type 2 (CCR2) and CX3C chemokine receptor 1 (CX3CR1) ligand release. Subsequently, these monocytes are transformed into macrophages able to phagocyte damaged cells and present peptides to alloreactive T cells in peripheral lymph nodes [8, 9]. There is NK cell recruitment after ischemia and during the early stages of renal transplantation [10, 11]. NK cells keep other cells in check for major histocompatibility complex (MHC) surface expression through killer Ig-like receptors (KIR) [12]. In allotransplantation, lack of MHC Class I recognition triggers NK effector mechanisms, including perforin-dependent cell lysis and cytokine production [13]. NK cells seem to play an important role in the induction of acute renal damage and long-term graft survival as demonstrated in mice that exhibit abnormalities in recruitment of these cells and are more resistant to kidney damage [10, 11].

2.2. Role of pattern recognition receptors and damaging molecular patterns in renal transplantation

In the early 1990s, Janeway proposed that all innate immune cells had pattern recognition receptors (PRRs) that can discriminate between self-components and pathogens. Soon after, Polly Matzinger suggested that our immune system is designed to recognize signs of harm rather than to discriminate between self and nonself, which could explain how innate immune activation can occur under sterile conditions such as in allotransplantation [14]. Consequently, pathogen-associated molecular patterns (PAMPs) and DAMPs are designed to signal damage threats [15]. DAMPs and PAMPs arise in the allograft during pre- and post-transplant periods; and activation of vascular PRRs such as TLRs, C-type lectin receptors, Nod-like receptors, and retinoic acid-inducible gene-I-like receptors can trigger production of proinflammatory cytokines [4].

The surgical process as well as ischemic injury, precondition for a systemic inflammatory reaction by releasing high mobility group box 1 (HMGB1) and heat shock proteins; as well as by increasing Toll-like receptor 4 (TLR4) expression in endothelial and peripheral blood cells [16]. The immunosuppressant cyclosporin A also induces HMGB1 release and promotes immune cell infiltration into the renal graft [17]. Furthermore, blocking HMGB1 reduced cellular infiltrate, IL-6 and TNF-α production in kidneys subjected to ischemia, and decreased of MCP-1 which is reflected in reduced nephrotoxicity [18]. On the other hand, HMGB1 appears to play a protective role; the administration of recombinant HMGB1 prevents dysfunction, tissue damage, and inflammation in animals subjected to ischemia [19].

2.3. The complement system

The complement system is a set of membrane-anchored and serum proteins that work in a coordinated way to eliminate microorganisms or damaged cells. The functions of complement include opsonization, inflammation through secondary products that result from the degradation of anaphylatoxins and formation of the membrane attack complex (MAC). There are three known complement pathways: the classical pathway that depends on the previous binding of antibodies, the alternate pathway that depends on the spontaneous hydrolysis and

binding of C3 and the pathway of lectins that depends on the binding of proteins to carbohydrates. Currently, there is evidence to suggest the participation of the three complement pathways during renal transplantation [20–22].

2.4. Innate-adaptive immunity interactions

Communication between innate and adaptive immunity largely depends on antigen presentation. T and B cells express antigen-specific receptors (TCR and BCR). The signals elicited by the TCR and BCR are insufficient to achieve the proper activation state, and costimulatory molecules and cytokines provided by innate immune cells are necessary [4]. Although DCs are the most efficient APCs, neutrophils, basophils, and eosinophils also influence the outcome of adaptive immunity. Neutrophils can recruit IL-17-producing Th17 lymphocytes by releasing CCL2 and CCL20. Interestingly, patients with a history of chronic renal dysfunction showed a significant increase in IL-17 producing cells [23]. Basophils are normally activated by IL-3 or immunoglobulin binding in different renal structures; and are an important source of cytokines, thymic stromal lymphopoietin, leukotrienes and histamines which may influence the outcome of adaptive immune responses [24, 25]. Basophils express MCH Class II and are considered important regulators of T and B cell activation. Moreover, an increase in eosinophils in renal transplant, recipients has been proposed as a predictor of allograft success [26].

3. Adaptive immune responses

3.1. Allorecognition, T-cell activation, T cell–mediated cytotoxicity, and B lymphocytes

The term allorecognition refers to recognition of diverse forms of genes between a member of the same species by T cells and involve Human major histocompatibility complex (MHC) glycoproteins. MHC is a family composed by the most studied antigens in transplantation field. These antigens are widely known as human leukocyte antigens (HLA). The genes encoding HLA antigens are highly polymorphic, this feature represents a big obstacle in the study of mechanisms of graft rejection. Class I HLA are present in membranes of the nucleated cell of humans and its function is to present small endogenous antigens to CD8 T lymphocytes. Class II are expressed on dendritic cells, macrophages, B cells, endothelial, and some types of epithelial cells. This T cell recognition event is the first step of graft rejection. There are two different ways in which T cells recognize alloantigens, i.e., direct and indirect. Direct recognition is when CD8+ and CD4+ T cells from the recipient recognize MHC class I and class II presented by APCs and donor peptides. Indirect recognition is mediated by specialized APCs form the recipient presenting to T cells [27]. Donor endothelial cells express molecules that stimulate T cells, these activated cells provide help to B cells resulting in the production of alloantibodies [28]. Although the most studied role of B cells is associated with alloantibodies and donor specific antibodies, there are controversial opinions about the deleterious role of these antibodies and its association with poor graft outcomes [29].

4. Immunotolerance in transplantation

The term immunotolerance implies the absence of recognition and renal graft attack by the immune cells of the recipient. One of the most important developments in the field of organ transplantation has been the use of immunosuppressive therapies that interfere with immune recognition and consequently delay graft rejection. Nonetheless, although immunosuppression is used, some immune adaptation may develop in the graft. To choose a clinically successful immunosuppressive therapy, several factors must be considered: they must be easily applicable in clinical practice, there should be enough evidence of their effectiveness, they must be stable over time even in conditions where the immune system is altered, and their mechanism of action should not have cross-reactions with other therapies. As a final point, it should be possible to measure and control its levels in the transplanted patient [30]. Induction of tolerance can occur through various mechanisms that include thymic deletional, central and peripheral deletional, and nondeletional mechanisms.

4.1. Mechanisms of -cell tolerance

T cell tolerance in transplantation is a regulated process that ensures the tolerance and permanence of antigens, similarly to tolerance required for the maintenance of self-antigens [31]. It consists of several stages: deletion, anergy, suppression, and ignorance. Tolerance is maintained by several mechanisms initiating in the thymus, where T cells are chosen by negative selection. The main mechanism of transplanted antigens tolerance is through intrathymic deletion of donor-reactive T cells [32]. Although there are additional mechanisms of peripheral tolerance, most T cells are eliminated by this mechanism. Peripheral deletion of T cells is an important mechanism of tolerance, in which CD4 T cells reactive to donor antigens show activation, as well as apoptotic cell death. Once the tolerance is given T cells cannot respond to antigens, a state known as anergy. A costimulatory block induces anergy and has been successfully applied for tolerance induction. The activation of the T cell requires at least two signals: an antigen-dependent T cell receptor-mediated signal 1 and an antigen-independent costimulatory signal 2 [33]. CD4 and CD25 T cell regulators are actively involved in the development of immunological tolerance toward the graft. Ignorance is another mechanism that occurs when donor antigens are not recognized by the lymphoid system of the recipient or when lymphocytes fail to invade the graft. However, this mechanism applies to nonvascularized grafts.

The aim of tolerance induction in renal transplantation is to block direct and indirect alloresponse pathways. In the first, it is necessary to establish the depletion of the recipient T cells and the activation of suppressor cells capable of regulating T cells. Some drugs can induce the death of alloreactive T cells. On the other hand, oral administration of allopeptides may also produce specific tolerance to corresponding alloantigens and generate specific production and activation of regulatory T cells.

4.2. Induction of immunologic tolerance

Tolerance induction requires alloreactive T-cell deletion in the thymus before these cells can be released to the periphery. Hematopoietic chimerism is a widespread method to

induce tolerance. Animal models have improved our understanding of this mechanism that ranges from tolerance induction through the injection of allogeneic cells into newborn mice to the use of adult irradiated animals injected with allogeneic donor bone marrow [34]. Tolerance induction at the peripheral systemic level needs to target mature T cells by blocking T cell molecules located on its surface, which have important roles in the activation of signaling pathways that impact cell function directly. To this end, antibodies directed against CD4 or CD8 or costimulatory molecules have been used. CD28 receptor blockade prevents proinflammatory cytokine production, as well as T cell survival and proliferation. It is also possible to interfere with the signaling pathways involved in T cell survival and proliferation, which is the case of the mTOR pathway inhibitor rapamycin. Clinical studies in humans have focused on graft tolerance induction by pretransplanting donor hematopoietic cells in human leukocyte antigen (HLA)-matched and mismatched kidney transplant recipients [35, 36].

4.3. Immunosuppressive therapy in renal transplantation

The discovery of effective immunosuppressive drugs has had great impact in the field of transplantation. Currently available immunosuppressive therapies focus on three main objectives: induction, maintenance, and treatment of rejection. For induction therapy three types of antibodies are used, the lymphocytes depleting agents, antithymocyte globulin and alemtuzumab, and basiliximab (nondepleting) [37]. Basiliximab, an IL-2 receptor antagonist and it is used in combination with other immunosuppressants, significantly reduces acute rejection in large clinical studies [38]. The use of antithymocyte antibodies in diseased donor recipients also reduces early acute rejection incidence. Nevertheless, its use has been associated with reversible leukopenia, thrombocytopenia, and cytomegalovirus infection [39].

The use of calcineurin inhibitors cyclosporine and tacrolimus has been key in reducing the risk of rejection and has greatly improved short-term graft survival outcomes. Unfortunately, in the long run they also help develop histological changes typical of nephropathy that diminish kidney graft function and increase risk of graft loss [40, 41]. A T cell costimulatory inhibitor called belatacept was introduced to avoid the deleterious effects of calcineurin inhibitors. In several studies, belatacept prevents acute rejection in renal transplantation comparable to cyclosporine [42]. Since the 1980s, several options have been developed to reduce kidney transplant rejection. Monoclonal muromonab-CD3/OKT3, monoclonal interleukin-2 receptor (IL-2R) antibodies (daclizumab and zenapax), and antiproliferative agents (mycophenolate mofetil) are part of a large list of options currently available in renal transplantation [43]. Nevertheless, some transplant experts propose a reduction in the use of immunosuppressive drugs in order to reduce the nephrotoxicity that can also end in fibrosis and graft rejection. Additionally, some transplant recipients develop diabetes, cardiovascular disease, dyslipidemia associated to immunosuppressant therapies. For this reason, it is estimated that kidney grafts can function on average 10 years after the transplantation [44, 45].

5. Graft rejection

Current immunosuppressant therapies have drastically reduced acute rejection events in kidney transplant recipients [46, 47]. Unfortunately, there is still a high percentage of short- and long-term kidney graft loses secondary to ABMR [2]. Here, we will discuss the contribution of adaptive and innate immune cells; as well as antibodies, molecules from the complement system and chemokines to disease states that lead to kidney graft rejection (**Figure 1**).

5.1. T cell–mediated rejection

T cell mediated rejection (TCMR) is characterized by infiltration of the donor graft interstitium by host CD4 and CD8 T effector and memory cells, macrophages, and dendritic cells; followed by epithelial dedifferentiation and tubulitis [48, 49] (see histopathological findings in **Figure 2**). TCMR is the predominant phenotype found in kidney transplant recipients with early rejection and it is still an important cause of graft dysfunction that when left untreated causes fibrosis, tubular atrophy, and irreversible nephron loss [50]. Genes expressed by effector T cells, APCs, and macrophages stimulated with IFN-γ are abundant in the transcriptomic signature of TCMR. These transcripts are mostly related to T cell receptor signaling, T helper differentiation and communication between adaptive and innate immune cells; highlighting the importance of these pathways in TCMR [51]. Cytotoxic molecules like perforin, granulysin,

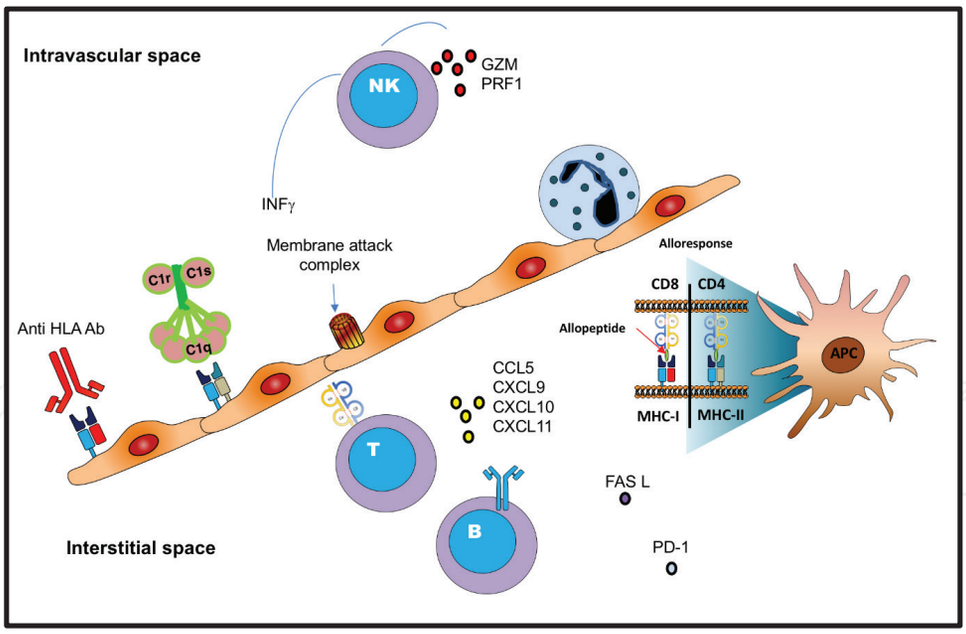

Figure 1. Mechanisms of ABMR and TCMR in kidney transplantation. Preformed and *de novo* DSAs, complement proteins, and antibody-dependent NK cell-mediated IFN-γ release and cytotoxicity have emerged as key immune players in the development of the microvascular damage characteristic of ABMR. Meanwhile, in TCMR the interaction of infiltrating T cells with intragraft APCs and macrophages triggers an inflammatory response dependent on TCR synapse and subsequent activation, and characterized by chemokine (CCL5) and cytokine (CXCL9, CXCL10, and CXCL11) release.

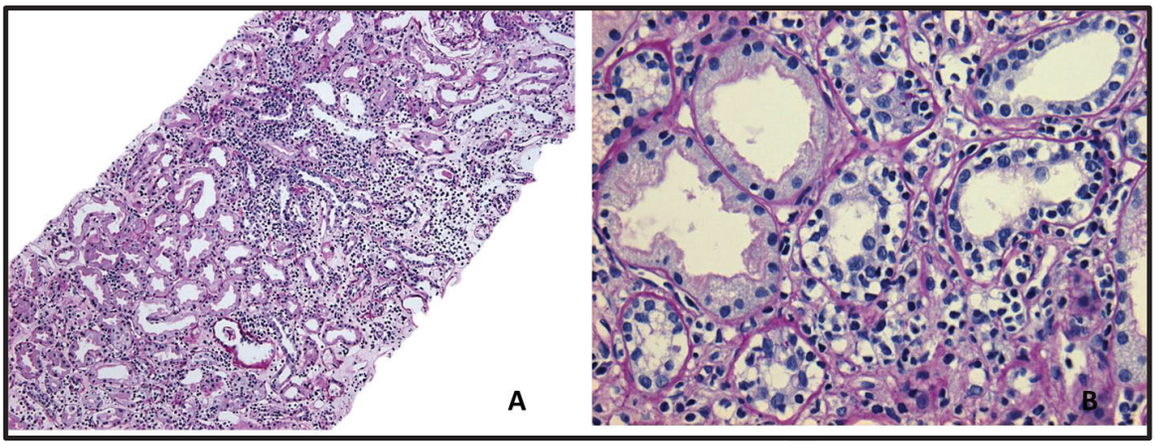

Figure 2. T cell-mediated rejection. The hallmark of TCMR is the infiltration of mononuclear cells to the interstitium and tubules. (A) Prominent intersticial inflamatory cell infiltrate. PAS 5×. (B) Higher magnification reveals infiltration of the tubular epithelium by mononuclear cells (tubulitis). PAS 40×. Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

Fas ligand, and granzyme A and B are also expressed in TCMR; though it has been demonstrated that they are not directly linked to the mechanism of injury [48, 52]. Instead, TCMR is considered an inflammatory reaction initiated by the engagement of TCR on cognate T cells with its antigen on APCs [53, 54]. It has been suggested that a very small proportion of infiltrating T cells are able to establish a TCR-mediated interaction with the allograft [55]. However, this interaction is important in the establishment of TCMR inflammatory phenotype since it activates the effector T cell and APC, induces INF-γ secretion and further promotes myeloid and T cell recruitment by inducing chemokines and adhesion molecules [56]. Interestingly, increased expression of immune checkpoints responsible for modulating T cell activation such as cytotoxic T-lymphocyte antigen 4, programmed death-ligand 1 and 2 have also been associated with TCMR; suggesting these molecules might be regulating some of the interactions between T cells and APCs within the graft microenvironment [51]. Moreover, evidence that the programmed cell death protein 1 (PD1) pathway may be critical in maintaining tolerance and preventing TCMR comes from a report case in which administration of an anti-PD1 antibody to a kidney transplant recipient with metastatic cutaneous squamous-cell carcinoma resulted in allograft rejection [57].

B cells are robust APCs that can readily capture, process and present antigen for T cell recognition. Still, the role of B cells in TCMR development was initially overlooked since studies in B cell-deficient mice reported similar rejection rates in skin and heart transplants, as well as efficient CD4 T cell priming [58, 59]. The first evidence of a possible role of B cells in TCMR came from a systematic study of gene expression patterns using DNA microarrays in biopsy samples from renal allografts that found a surprising association between dense CD20+ B cell infiltrates and both, steroid resistance and graft loss [60]. Although the prognostic significance of CD20+ B cell infiltrates in acute cellular rejection is a matter of debate, the presence of these B cell clusters in cases of pure TCMR and their close proximity to CD4+ T cells suggests they might have antibody-independent functions in allograft rejection by acting as APCs [61–64]. Interestingly, reversible rejection episodes with monocytic infiltrates and scant T cells have been described in severely T cell-depleted patients, emphasizing the central role of macrophages in allograft rejection [65].

Macrophages in TCMR exert dual functions by promoting initiation and progression of kidney injury through secretion of proinflammatory mediators and interaction with other cells in the graft; whilst also in charge of tissue remodeling and repair during the recovery phase [66, 67]. Interestingly, reversible rejection episodes with monocytic infiltrates and scant T cells have been described in severely T cell-depleted patients, emphasizing the central role of macrophages in allograft rejection [65].

An increase in IFN-γ induces CCL5, CXCL9, CXCL10, CXCL11, and MHC class I and II expression; and is an important feature of TCMR [68, 69]. In the context of TCMR, IFN-γ has protective and proinflammatory functions as evidenced by IFN-γ-deficient recipient animals or donors lacking IFN-γ receptors or IFN-γ-regulated factor 1 [68, 70].

5.2. Antibody-mediated rejection

Evidence form multiple studies supports the humoral theory of transplantation strongly advocated by Dr. Paul Terasaki, in which antibodies are not only responsible for immediate hyperacute allograft rejection but can produce chronic vascular damage, fibrosis, and graft rejection months or even years posttransplantation [71]. Hyperacute allograft rejection occurs soon after the graft is perfused with blood of the recipient due to preformed

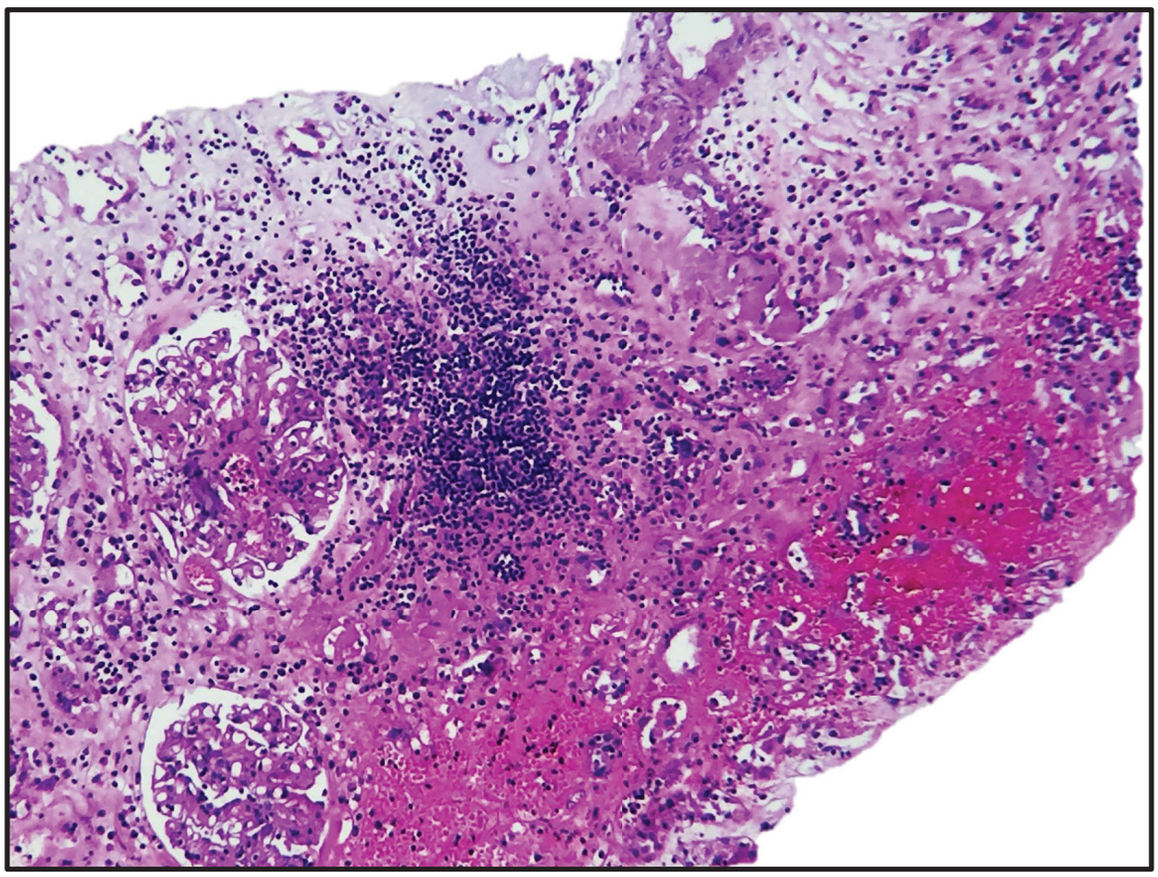

Figure 3. Interstitial hemorrhage in hyperacute allograft rejection. Microphotography shows severe capillary injury with subsequent peritubular capillary disruption. Hematoxylin & eosin 10×. Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

antibodies directed primarily at the vasculature of the donor organ [72]. These antibodies activate the complement cascade and induce neutrophil infiltration, endothelial damage, interstitial hemorrhage (**Figure 3**), edema, fibrin deposition, platelet aggregation, and thrombosis; causing the organ to fail within a few hours after transplantation. Hyperacute rejection used to be a frequent occurrence in transplantation before cross-match tests were designed to screen potential recipients for circulating anti-HLA antibodies to the prospective donor [73].

Antibody-mediated rejection (ABMR) pathogenesis involves mechanisms of graft injury caused by donor-specific anti-HLA antibodies (DSAs) and non-HLA antibodies; and has been associated with progressive decline in graft function and poor transplantation outcomes [74]. Molecular changes in the microvasculature characteristic of tissue remodeling and repair are common manifestations of ABMR, as well as neutrophilic infiltration and fibrosis (**Figure 4**) [50]. ABMR can be acute or chronic, and can also manifest in cases of mixed TCMR/AMBR rejection [2]. It is estimated that close to 20% of renal allograft recipients will develop *de novo* DSAs within 10 years posttransplant [75]. DSAs bind to allogenic HLA and non-HLA targets

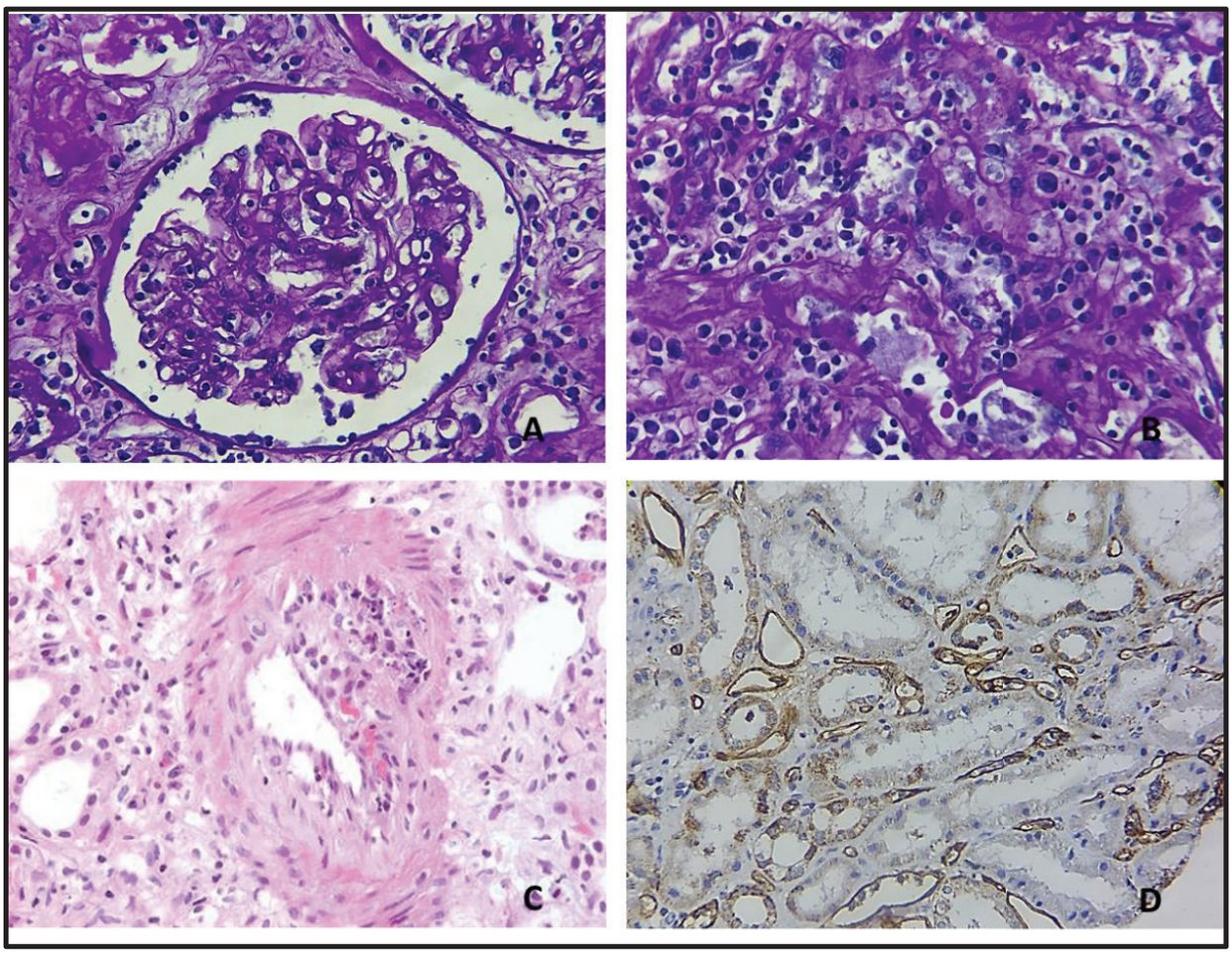

Figure 4. Antibody-mediated rejection. Two of the three criteria required for AMR. (A to C) Microvascular inflammation: glomerulitis, peritubular capilaritis, and intimal arteritis. PAS and H&E 40×. (D) Linear staining of C4d in peritubular capillaries IP 40×. Courtesy of Dr. Claudia Mendoza-Cerpa, Laboratory of Pathology, IMSS-CMNO, Guadalajara; México.

expressed by graft microvasculature and induce antibody-dependent cell cytotoxicity, complement activation and modulation of signaling pathways within vascular cells. These events promote the development of irreversible lesions that compromise graft function that eventually lead to rejection [76].

Complement activation is a well-established mechanism of ABMR [22, 77–79]. Although in some models, a causal relationship between antibody-mediated complement activation and graft damage has not been demonstrated [80]. DSAs bind to their targets on donor endothelial cells where they cause complement activation, and membrane attack complex formation. Interestingly, DSAs also activate an endothelial proinflammatory gene program to support allograft injury through noncanonical NF-κB signaling [81]. The graft microvasculature limits antibody injury by inducing the expression of the complement inhibitors CD55 and CD59 [82]. IgG subclasses exhibit variability in their hinge region that controls Fc region affinity for FcγRs and complement components [83]. Transcriptomic studies of ABMR biopsies have revealed an enrichment of endothelial, NK cells and IFN-γ-inducible transcripts. NK cells secrete IFN-γ upon FcγR crosslinking, a positive feedback mechanism that enhances HLA expression on endothelial cells and results in more DSA deposition and activation of local immunity [82].

6. Future directions

Improving kidney transplantation outcomes and patient survival is a challenging task. It is now clear that the cooperation between the innate and humoral arms of the immune system plays complex roles in graft tolerance and rejection. For this reason, understanding the immune mechanisms responsible for graft rejection in allotransplantation has becomes essential in our quest to develop better diagnostic tools and immunosuppressant therapies that can successfully be translated into the clinic.

Acknowledgements

This work was supported by the National Council of Science and Technology of Mexico (CONACYT project number 653).

Author details

Zesergio Melo[1,2]*, Juan A. Ruiz-Pacheco[1], Claudia A. Mendoza-Cerpa[2] and Raquel Echavarria[1]

*Address all correspondence to: zesergiomelo@gmail.com

1 CONACyT-Centro de Investigacion Biomedica de Occidente, IMSS-Guadalajara, Mexico

2 Laboratory of Pathology, IMSS-CMNO, Guadalajara, Mexico

References

[1] Levey AS, Coresh J. Chronic kidney disease. Lancet. 2012;**379**(9811):165-180

[2] Djamali A, Kaufman DB, Ellis TM, Zhong W, Matas A, Samaniego M. Diagnosis and management of antibody-mediated rejection: Current status and novel approaches. American Journal of Transplantation. 2014;**14**(2):255-271

[3] Gaber LW, Knight RJ, Patel SJ. A surgeons' guide to renal transplant immunopathology, immunology, and immunosuppression. Surgical Clinics of North America. 2013; **93**(6):1293-1307

[4] Cucchiari D, Podestà MA, Ponticelli C. The critical role of innate immunity in kidney transplantation. Nephron. 2016;**132**(3):227-237

[5] Salvadori M, Rosso G, Bertoni E. Update on ischemia-reperfusion injury in kidney transplantation: Pathogenesis and treatment. World Journal of Transplantation. 2015;**5**(2):52-67

[6] Erdem E. Neutrophil lymphocyte ratio in aute renal failure. Indian Journal of Nephrology. 2015;**25**(2):126-127

[7] Kelly KJ, Williams WW, Colvin RB, Meehan SM, Springer TA, Gutierrez-Ramos JC, et al. Intercellular adhesion molecule-1-deficient mice are protected against ischemic renal injury. Journal of Clinical Investigation. 1996;**97**(4):1056-1063

[8] Takada M, Nadeau KC, Shaw GD, Marquette KA, Tilney NL. The cytokine-adhesion molecule cascade in ischemia/reperfusion injury of the rat kidney. Inhibition by a soluble P-selectin ligand. Journal of Clinical Investigation. 1997;**99**(11):2682-2690

[9] Li L, Huang L, Sung SS, Vergis AL, Rosin DL, Rose CE, et al. The chemokine receptors CCR2 and CX3CR1 mediate monocyte/macrophage trafficking in kidney ischemia-reperfusion injury. Kidney International. 2008;**74**(12):1526-1537

[10] Zhang ZX, Wang S, Huang X, Min WP, Sun H, Liu W, et al. NK cells induce apoptosis in tubular epithelial cells and contribute to renal ischemia-reperfusion injury. Journal of Immunology. 2008;**181**(11):7489-7498

[11] Zhang ZX, Huang X, Jiang J, Lau A, Yin Z, Liu W, et al. Natural killer cells mediate long-term kidney allograft injury. Transplantation. 2015;**99**(5):916-924

[12] Ljunggren HG, Kärre K. In search of the 'missing self': MHC molecules and NK cell recognition. Immunology Today. 1990;**11**(7):237-244

[13] Moretta A, Pende D, Locatelli F, Moretta L. Activating and inhibitory killer immunoglobulin-like receptors (KIR) in haploidentical haemopoietic stem cell transplantation to cure high-risk leukaemias. Clinical and Experimental Immunology. 2009;**157**(3):325-331

[14] Matzinger P. Tolerance, danger, and the extended family. Annual Review of Immunology. 1994;**12**:991-1045

[15] Medzhitov R, Janeway CA. Decoding the patterns of self and nonself by the innate immune system. Science. 2002;**296**(5566):298-300

[16] Wu H, Chen G, Wyburn KR, Yin J, Bertolino P, Eris JM, et al. TLR4 activation mediates kidney ischemia/reperfusion injury. Journal of Clinical Investigation. 2007;**117**(10):2847-2859

[17] González-Guerrero C, Cannata-Ortiz P, Guerri C, Egido J, Ortiz A, Ramos AM. TLR4-mediated inflammation is a key pathogenic event leading to kidney damage and fibrosis in cyclosporine nephrotoxicity. Archives of Toxicology. 2017;**91**(4):1925-1939

[18] Wu H, Ma J, Wang P, Corpuz TM, Panchapakesan U, Wyburn KR, et al. HMGB1 contributes to kidney ischemia reperfusion injury. Journal of the American Society of Nephrology. 2010;**21**(11):1878-1890

[19] Wang C, Liu XX, Huang KB, Yin SB, Wei JJ, Hu YF, et al. Preconditioning with recombinant high-mobility group box 1 induces ischemic tolerance in a rat model of focal cerebral ischemia-reperfusion. Journal of Neurochemistry. 2016;**137**(4):576-588

[20] Frémeaux-Bacchi V, Legendre CM. The emerging role of complement inhibitors in transplantation. Kidney International. 2015;**88**(5):967-973

[21] Sacks SH, Zhou W. The role of complement in the early immune response to transplantation. Nature Reviews. Immunology. 2012;**12**(6):431-442

[22] Stegall MD, Chedid MF, Cornell LD. The role of complement in antibody-mediated rejection in kidney transplantation. Nature Reviews. Nephrology. 2012;**8**(11):670-678

[23] Chung BH, Kim KW, Kim BM, Doh KC, Cho ML, Yang CW. Increase of Th17 cell phenotype in kidney transplant recipients with chronic allograft dysfunction. PLoS One. 2015;**10**(12):e0145258

[24] Colvin RB, Dvorak HF. Letter: Basophils and mast cells in renal allograft rejection. Lancet. 1974;**1**(7850):212-224

[25] Stone KD, Prussin C, Metcalfe DD. IgE, mast cells, basophils, and eosinophils. The Journal of Allergy and Clinical Immunology. 2010;**125**(2 Suppl 2):S73-S80

[26] Weir MR, Hall-Craggs M, Shen SY, Posner JN, Alongi SV, Dagher FJ, et al. The prognostic value of the eosinophil in acute renal allograft rejection. Transplantation. 1986; **41**(6):709-712

[27] Game DS, Lechler RI. Pathways of allorecognition: Implications for transplantation tolerance. Transplant Immunology. 2002;**10**(2-3):101-108

[28] Vella JP, Vos L, Carpenter CB, Sayegh MH. Role of indirect allorecognition in experimental late acute rejection. Transplantation. 1997;**64**(12):1823-1828

[29] Coelho V, Saitovitch D, Kalil J, Silva HM. Rethinking the multiple roles of B cells in organ transplantation. Current Opinion in Organ Transplantation. 2013;**18**(1):13-21

[30] Auchincloss H Jr. In search of the elusive Holy Grail: The mechanisms and prospects for achieving clinical transplantation tolerance. American Journal of Transplantation. 2001;**1**(1):6-12

[31] Alpdogan O, van den Brink MR. Immune tolerance and transplantation. Seminars in Oncology 2012;**39**(6):629-642

[32] Manilay JO, Pearson DA, Sergio JJ, Swenson KG, Sykes M. Intrathymic deletion of alloreactive T cells in mixed bone marrow chimeras prepared with a nonmyeloablative conditioning regimen. Transplantation. 1998;**66**(1):96-102

[33] Fehr T, Sykes M. Tolerance induction in clinical transplantation. Transplant Immunology. 2004;**13**(2):117-130

[34] Lechler RI, Garden OA, Turka LA. The complementary roles of deletion and regulation in transplantation tolerance. Nature Reviews. Immunology. 2003;**3**(2):147-158

[35] Scandling JD, Busque S, Dejbakhsh-Jones S, Benike C, Millan MT, Shizuru JA, et al. Tolerance and chimerism after renal and hematopoietic-cell transplantation. The New England Journal of Medicine. 2008;**358**(4):362-368

[36] Kawai T, Sachs DH, Sprangers B, Spitzer TR, Saidman SL, Zorn E, et al. Long-term results in recipients of combined HLA-mismatched kidney and bone marrow transplantation without maintenance immunosuppression. American Journal of Transplantation. 2014;**14**(7):1599-1611

[37] Hardinger KL, Brennan DC, Klein CL. Selection of induction therapy in kidney transplantation. Transplant International: Official Journal of the European Society for Organ Transplantation. 2013;**26**(7):662-672

[38] Nashan B, Moore R, Amlot P, Schmidt AG, Abeywickrama K, Soulillou JP. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. CHIB 201 International Study Group. Lancet. 1997;**350**(9086):1193-1198

[39] Charpentier B, Rostaing L, Berthoux F, Lang P, Civati G, Touraine JL, et al. A three-arm study comparing immediate tacrolimus therapy with antithymocyte globulin induction therapy followed by tacrolimus or cyclosporine A in adult renal transplant recipients. Transplantation. 2003;**75**(6):844-851

[40] Flechner SM. Reviewing the evidence for de novo immunosuppression with sirolimus. Transplantation Proceedings. 2008;**40**(10 Suppl):S25-S28

[41] Verghese PS, Dunn TB, Chinnakotla S, Gillingham KJ, Matas AJ, Mauer MS. Calcineurin inhibitors in HLA-identical living related donor kidney transplantation. Nephrology, Dialysis, Transplantation. 2014;**29**(1):209-218

[42] Masson P, Henderson L, Chapman JR, Craig JC, Webster AC. Belatacept for kidney transplant recipients. The Cochrane Database of Systematic Reviews. 2014;(11):CD010699

[43] Prashar R, Venkat KK. Immunosuppression minimization and avoidance protocols: When less is not more. Advances in Chronic Kidney Disease. 2016;**23**(5):295-300

[44] Miller LW. Cardiovascular toxicities of immunosuppressive agents. American Journal of Transplantation. 2002;**2**(9):807-818

[45] Scantlebury V, Shapiro R, Fung J, Tzakis A, McCauley J, Jordan M, et al. New onset of diabetes in FK 506 vs cyclosporine-treated kidney transplant recipients. Transplantation Proceedings. 1991;**23**(6):3169-3170

[46] Ponticelli C. Calcineurin-inhibitors in renal transplantation. Too precious to be abandoned. Nephrology, Dialysis, Transplantation. 2000;**15**(9):1307-1309

[47] Halloran PF, Chang J, Famulski K, Hidalgo LG, Salazar ID, Merino Lopez M, et al. Disappearance of T cell-mediated rejection despite continued antibody-mediated rejection in late kidney transplant recipients. Journal of the American Society of Nephrology. 2015;**26**(7):1711-1720

[48] Halloran PF. T cell-mediated rejection of kidney transplants: A personal viewpoint. American Journal of Transplantation. 2010;**10**(5):1126-1134

[49] Einecke G, Broderick G, Sis B, Halloran PF. Early loss of renal transcripts in kidney allografts: Relationship to the development of histologic lesions and alloimmune effector mechanisms. American Journal of Transplantation. 2007;**7**(5):1121-1130

[50] Halloran PF, Famulski KS, Reeve J. Molecular assessment of disease states in kidney transplant biopsy samples. Nature Reviews. Nephrology. 2016;**12**(9):534-548

[51] Venner JM, Famulski KS, Badr D, Hidalgo LG, Chang J, Halloran PF. Molecular landscape of T cell-mediated rejection in human kidney transplants: Prominence of CTLA4 and PD ligands. American Journal of Transplantation. 2014;**14**(11):2565-2576

[52] Sharma VK, Bologa RM, Li B, GP X, Lagman M, Hiscock W, et al. Molecular executors of cell death--differential intrarenal expression of Fas ligand, Fas, granzyme B, and perforin during acute and/or chronic rejection of human renal allografts. Transplantation. 1996;**62**(12):1860-1866

[53] Walch JM, Zeng Q, Li Q, Oberbarnscheidt MH, Hoffman RA, Williams AL, et al. Cognate antigen directs CD8+ T cell migration to vascularized transplants. Journal of Clinical Investigation. 2013;**123**(6):2663-2671

[54] Adams AB, Williams MA, Jones TR, Shirasugi N, Durham MM, Kaech SM, et al. Heterologous immunity provides a potent barrier to transplantation tolerance. Journal of Clinical Investigation. 2003;**111**(12):1887-1895

[55] Chalasani G, Dai Z, Konieczny BT, Baddoura FK, Lakkis FG. Recall and propagation of allospecific memory T cells independent of secondary lymphoid organs. Proceedings of the National Academy of Sciences of the United States of America. 2002;**99**(9):6175-6180

[56] Glimcher LH, Townsend MJ, Sullivan BM, Lord GM. Recent developments in the transcriptional regulation of cytolytic effector cells. Nature Reviews. Immunology. 2004;**4**(11):900-911

[57] Lipson EJ, Bagnasco SM, Moore J, Jang S, Patel MJ, Zachary AA, et al. Tumor regression and allograft rejection after administration of anti-PD-1. The New England Journal of Medicine. 2016;**374**(9):896-898

[58] Brändle D, Joergensen J, Zenke G, Bürki K, Hof RP. Contribution of donor-specific antibodies to acute allograft rejection: Evidence from B cell-deficient mice. Transplantation. 1998;**65**(11):1489-1493

[59] Epstein MM, Di Rosa F, Jankovic D, Sher A, Matzinger P. Successful T cell priming in B cell-deficient mice. Journal of Experimental Medicine. 1995;**182**(4):915-922

[60] Sarwal M, Chua MS, Kambham N, Hsieh SC, Satterwhite T, Masek M, et al. Molecular heterogeneity in acute renal allograft rejection identified by DNA microarray profiling. The New England Journal of Medicine. 2003;**349**(2):125-138

[61] Hippen BE, DeMattos A, Cook WJ, Kew CE, Gaston RS. Association of CD20+ infiltrates with poorer clinical outcomes in acute cellular rejection of renal allografts. American Journal of Transplantation. 2005;**5**(9):2248-2252

[62] Tsai EW, Rianthavorn P, Gjertson DW, Wallace WD, Reed EF, Ettenger RB. CD20+ lymphocytes in renal allografts are associated with poor graft survival in pediatric patients. Transplantation. 2006;**82**(12):1769-1773

[63] Zarkhin V, Kambham N, Li L, Kwok S, Hsieh SC, Salvatierra O, et al. Characterization of intra-graft B cells during renal allograft rejection. Kidney International. 2008;**74**(5):664-673

[64] Bagnasco SM, Tsai W, Rahman MH, Kraus ES, Barisoni L, Vega R, et al. CD20-positive infiltrates in renal allograft biopsies with acute cellular rejection are not associated with worse graft survival. American Journal of Transplantation. 2007;**7**(8):1968-1973

[65] Kirk AD, Hale DA, Mannon RB, Kleiner DE, Hoffmann SC, Kampen RL, et al. Results from a human renal allograft tolerance trial evaluating the humanized CD52-specific monoclonal antibody alemtuzumab (CAMPATH-1H). Transplantation. 2003;**76**(1):120-129

[66] Cao Q, Harris DC, Wang Y. Macrophages in kidney injury, inflammation, and fibrosis. Physiology (Bethesda, Md.). 2015;**30**(3):183-194

[67] Lee S, Huen S, Nishio H, Nishio S, Lee HK, Choi BS, et al. Distinct macrophage phenotypes contribute to kidney injury and repair. Journal of the American Society of Nephrology. 2011;**22**(2):317-326

[68] Halloran PF, Afrouzian M, Ramassar V, Urmson J, Zhu LF, Helms LM, et al. Interferon-gamma acts directly on rejecting renal allografts to prevent graft necrosis. The American Journal of Pathology. 2001;**158**(1):215-226

[69] Halloran PF, Miller LW, Urmson J, Ramassar V, Zhu LF, Kneteman NM, et al. IFN-gamma alters the pathology of graft rejection: Protection from early necrosis. Journal of Immunology. 2001;**166**(12):7072-7081

[70] Afrouzian M, Ramassar V, Urmson J, Zhu LF, Halloran PF. Transcription factor IRF-1 in kidney transplants mediates resistance to graft necrosis during rejection. Journal of the American Society of Nephrology. 2002;**13**(5):1199-1209

[71] Terasaki PI. A personal perspective: 100-year history of the humoral theory of transplantation. Transplantation. 2012;**93**(8):751-756

[72] Kissmeyer-Nielsen F, Olsen S, Petersen VP, Fjeldborg O. Hyperacute rejection of kidney allografts, associated with pre-existing humoral antibodies against donor cells. Lancet. 1966;**2**(7465):662-665

[73] Patel R, Terasaki PI. Significance of the positive crossmatch test in kidney transplantation. The New England Journal of Medicine. 1969;**280**(14):735-739

[74] Loupy A, Viglietti D, Mengel M. Complement inhibition in HLA-incompatible kidney transplants: Persisting antibody-mediated injury despite marked decrease of clinical ABMR. The New England Journal of Medicine. 2015;**15**(5):1139-1140

[75] Everly MJ. Incidence and hazards of alloantibodies in renal transplantation. Clinical Transplants. 2013;313-317

[76] Butler CL, Valenzuela NM, Thomas KA, Reed EF. Not all antibodies are created equal: Factors that influence antibody mediated rejection. Journal of Immunology Research. 2017;**2017**:7903471

[77] Wang H, Arp J, Liu W, Faas SJ, Jiang J, Gies DR, et al. Inhibition of terminal complement components in presensitized transplant recipients prevents antibody-mediated rejection leading to long-term graft survival and accommodation. Journal of Immunology. 2007;**179**(7):4451-4463

[78] Valenzuela NM, McNamara JT, Reed EF. Antibody-mediated graft injury: Complement-dependent and complement-independent mechanisms. Current Opinion in Organ Transplantation. 2014;**19**(1):33-40

[79] Akiyoshi T, Hirohashi T, Alessandrini A, Chase CM, Farkash EA, Neal Smith R, et al. Role of complement and NK cells in antibody mediated rejection. Human Immunology. 2012;**73**(12):1226-1232

[80] Csencsits K, Burrell BE, Lu G, Eichwald EJ, Stahl GL, Bishop DK. The classical complement pathway in transplantation: Unanticipated protective effects of C1q and role in inductive antibody therapy. American Journal of Transplantation. 2008;**8**(8):1622-1630

[81] Jane-Wit D, Manes TD, Yi T, Qin L, Clark P, Kirkiles-Smith NC, et al. Alloantibody and complement promote T cell-mediated cardiac allograft vasculopathy through noncanonical nuclear factor-κB signaling in endothelial cells. Circulation. 2013;**128**(23):2504-2516

[82] Venner JM, Hidalgo LG, Famulski KS, Chang J, Halloran PF. The molecular landscape of antibody-mediated kidney transplant rejection: Evidence for NK involvement through CD16a Fc receptors. American Journal of Transplantation. 2015;**15**(5):1336-1348

[83] Valenzuela NM, Hickey MJ, Reed EF. Antibody subclass repertoire and graft outcome following solid organ transplantation. Frontiers in Immunology. 2016;**7**:433

IntechOpen