

REVIEW ARTICLE

MECHANISMS OF DISEASE

Robert S. Schwartz, M.D., *Editor*

Rejection of the Kidney Allograft

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THE SCIENCE OF KIDNEY TRANSPLANTATION HAS PROGRESSED CONSIDERABLY in the past half-century largely because of an improved understanding of the role of the immune system in allograft rejection, the disentanglement of the molecular mechanisms underlying graft failure, and better management of immunosuppression.^{1,2} Rejection has always been the major obstacle. Transplantation of tissues or cells from a donor who differs genetically from the graft recipient induces an immune response in the recipient against alloantigens of the donor graft. If not controlled, this response will destroy the graft.

Recent discoveries have clarified how T lymphocytes, the principal agents of acute rejection, travel to and recognize the allograft. Important progress has also been made in understanding the influences of costimulatory molecules and cytokines and in elucidating how the innate immune system participates in graft rejection. In this review, we discuss the mechanisms underlying renal allograft rejection in the order of their clinical occurrence after transplantation.

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CLINICAL FEATURES OF ALLOGRAFT REJECTION

In the early 1960s, drug therapy for kidney-allograft recipients consisted of azathioprine and corticosteroids, but acute rejection, with fever and graft tenderness, was common. This clinical picture has virtually disappeared. The introduction of immunosuppression by means of powerful calcineurin inhibitors in the 1980s and better immunologic matching of recipients with donors changed the character of acute rejection. The overall risk of acute rejection within 1 year after transplantation is now less than 15%. Nevertheless, the rejection episodes that do occur are more severe than they were previously, and, disappointingly, the rates of graft survival beyond 5 years have remained largely unaltered.³

Although an increase in serum creatinine points to rejection, subclinical rejection may be apparent only on biopsy of the organ and, in the absence of renal dysfunction, can damage the allograft.⁴ The histologic findings on biopsy influence the prognosis and the choice of therapy.^{4,5} Rejection can be hyperacute (occurring within minutes), acute (occurring within days to weeks), late acute (occurring after 3 months), or chronic (occurring months to years after transplantation). It can also be classified according to pathophysiological changes (cellular-Interstitial, vascular, antibody-endothelial), severity (extent of histologic inflammation and injury, as scored and graded by means of the Banff schema^{6,7}), response to treatment (presence or absence of glucocorticoid resistance), presence or absence of renal dysfunction (indicating acute or subclinical rejection, respectively), and immunologic mechanisms (adaptive or innate immune system response).

The immunologic threat to the renal graft begins before transplantation and arises from the systemic effects of donor brain death or perioperative ischemia-reperfusion injury. Ischemia followed by reperfusion up-regulates the expression of

HLA antigens by the graft and causes the release of a cascade of chemokines, proinflammatory cytokines, and adhesion molecules within the graft. This increased display of HLA antigens intensifies the immune response and increases cellular infiltration of the graft, and both these responses increase the risk of rejection.^{8,9}

THE INNATE IMMUNE SYSTEM

Pathways of inflammation up-regulate innate injury molecules and aggravate the rejection process either directly or indirectly through the activation and recruitment of T lymphocytes. Injured tissues express ligands of the toll-like receptor system — damage-associated molecular-pattern (DAMP) molecules — and other innate danger molecules.¹⁰ Toll-like receptors normally detect pathogens, but they can also sense the presence of foreign-tissue molecules and can produce factors that cause the maturation and activation of dendritic cells. These cells have an important role in promoting acute rejection.⁹ Another element of innate immunity, the complement system, produces C3a and C5a, which directly activate intragraft T cells and antigen-presenting cells.¹¹⁻¹⁴ An increase in major-histocompatibility-complex (MHC) class I peptide-related sequence A (MICA) antigens on endothelial surfaces can activate natural killer cells and CD8 T cells. Moreover, there is an association between poor graft outcomes and sensitization to the highly polymorphic MICA antigens in HLA-matched transplants.^{15,16}

THE DONOR

Certain features of the donor — older age, presence of hypotension or hypertension, diabetes, renal impairment, donation after cardiac death, and prolonged ischemia of the graft due to a delay in shipping — influence the decision about whether to accept an organ from a deceased donor or to discard it.^{17,18} As compared with transplants from deceased donors, transplants obtained from a spouse, friend, or altruistic donor under optimal physiological conditions and with shorter ischemia times lead to excellent results, even when genetic and HLA differences are greater.¹⁹

ANTIBODY-MEDIATED REJECTION

Antibodies that can mediate rejection include those against HLA molecules, endothelial-cell antigens, and ABO blood-group antigens on endothelial cells and red cells. Most recipients do not have anti-

bodies against HLA molecules before transplantation unless they were sensitized by exposure to alloantigens through pregnancy, blood transfusion, or previous transplantation.

ANTIBODIES AGAINST BLOOD-GROUP ANTIGENS

Kidneys selected for transplantation are routinely assigned to recipients with a compatible blood group; however, ABO-incompatible kidneys have been successfully transplanted with the use of an experimental protocol that entails perioperative removal of antibodies from the recipient by means of plasmapheresis or immunoadsorption. After they have been removed, anti-blood-group antibodies can rise to pretreatment levels after transplantation, adhere to the microvasculature, and activate complement, yet they generally do not injure the endothelium. This anomaly has been attributed to “accommodation” within the kidney, but the mechanism responsible for this benign response is unknown.²⁰ In contrast, injury to the graft by anti-HLA antibodies is frequently insidious, and accommodation is uncommon.

HYPERACUTE REJECTION

Rejection of the renal graft that occurs almost immediately after release of the vascular cross-clamps is classified as hyperacute. Instead of “pinking up” as a result of normal reperfusion, the kidney appears flaccid and mottled, reflecting the deposition of antibodies against HLA antigens expressed on the endothelium of the glomeruli and microvasculature. Activation of the classic complement cascade within the graft is followed by endothelial necrosis, platelet deposition, and local coagulation.²¹ In these cases, the initial organ transplantation procedure usually ends with removal of the graft. Improvements in cross-matching techniques that can better detect donor-specific antibodies before surgery have largely eliminated this problem.²²

ACUTE ANTIBODY-MEDIATED REJECTION

Antibody-mediated rejection often begins within days after transplantation (or within weeks, if antilymphocyte antibody therapy was given). The main feature is rapid graft dysfunction due to inflammation. An anamnestic response engendered by previous exposure to the relevant antigen rapidly generates high titers of complement-fixing antibodies.²² The main targets of these “recall” antibodies are MHC antigens displayed by the endothelium of the donor peritubular and glomeru-

lar capillaries. Agonistic angiotensin II type 1 (AT1)-receptor antibodies have also been associated with corticosteroid-resistant vascular rejection accompanied by malignant hypertension,²³ but their pathogenic role remains unclear.²⁴ The damaged endothelial cells release various injurious molecules: von Willebrand factor and P-selectin, which promote platelet aggregation; cytokines and chemokines, such as interleukin-1 α , interleukin-8, and chemokine (C-C motif) ligand 2 (CCL2), which cause leukocytes to adhere to glomeruli (glomerulitis) or to dilated peritubular capillaries (margination); and the chemoattractants C3a and C5a.²¹ C4d, a marker of classic complement activation, is frequently found in peritubular capillaries (Fig. 1).²¹ C5b triggers the assembly of the membrane-attack complex (C5b-C9), which causes localized endothelial necrosis and apoptosis, as well as detachment of endothelial cells from the basement membrane. Microthrombi, with hemorrhage and arterial-wall necrosis and infarction, occur in severe cases.²¹

Early diagnosis and treatment are essential for salvaging grafts undergoing acute antibody-mediated rejection. Treatments include removal of antibodies by plasmapheresis or immunoadsorption, high-dose pulses of glucocorticoids, intravenous immune globulin, and antiproliferative agents. Supplementary therapies include rituximab²⁵ or antilymphocyte antibody, if there is concurrent T-cell-mediated rejection.⁵ These treatments can be useful when given as prophylaxis to highly sensitized or ABO-mismatched recipients.²⁶ Eculizumab (a monoclonal antibody that inhibits the cleavage of C5) and bortezomib (a proteasome inhibitor that can inhibit plasma cells) are new, investigational agents that have shown promise in preliminary studies of antibody-mediated acute rejection, but the results require confirmation.^{27,28} Detection of potentially harmful antibodies before transplantation should prompt a search for an alternative donor or an aggressive approach to post-transplantation management.

T-CELL-MEDIATED REJECTION

ANTIGEN PRESENTATION

The most common form of acute allograft rejection is initiated when donor alloantigens are presented to the T lymphocytes of the recipient by antigen-presenting cells (APCs). Immature dendritic cells within the graft carry donor antigens from the transplanted organ to the recipient's

draining lymph nodes and spleen; during their journey, these antigens mature into APCs.²⁹ The recipient's antigen-presenting dendritic cells also participate and circulate through the graft. The APCs then home to lymphoid organs, where they activate the recipient's T cells. These T cells differentiate into various subgroups and return to the graft, where they take part in destroying the transplanted organ.

Dendritic cells and macrophages present antigen to T cells efficiently, but B cells can also function in this way by capturing and presenting antigens with the use of their surface immunoglobulins and MHC class II molecules. Even tubular epithelial and endothelial cells can present antigen to activated T cells.^{30,31} Sensitization can occur in the periphery or in tertiary lymphoid organs that develop within the transplanted kidney.³²

THE MAJOR HISTOCOMPATIBILITY COMPLEX

Figure 2 shows the principal features of the MHC, which contains the HLA genes. These highly polymorphic genes encode glycoproteins (MHC molecules) that enable the APCs to display fragments of antigens (peptides) to receptors on T cells. Most of the MHC molecules are either class I or class II. A major functional difference between them is that class I molecules present peptides derived from internal proteins (e.g., viral proteins) to cytotoxic CD8 T cells, whereas class II molecules present peptides derived from extracellular proteins (e.g., bacterial proteins) to CD4 T cells.

The MHC encodes the HLA system,³³ and mismatches between donor and recipient HLA increase the risk of rejection. Grafts from HLA-identical siblings survive much longer than HLA-mismatched grafts from siblings or unrelated donors. Differences of only a few amino acids within the peptide-binding site of MHC may be sufficient to provoke graft rejection.

RECOGNITION OF ALLOANTIGENS BY T CELLS

Normally, only a small proportion of the T-cell population responds to a specific antigen (approximately 1 cell in 10⁵ to 10⁶ T cells). In contrast, the responding proportion in transplantation is 1 to 10%.^{34,35} Some of these responding T cells are antigen-experienced and have low thresholds for cross-reactive activation by MHC antigens.

The recipient's T lymphocytes can sense alloantigens displayed by either the donor's APCs (the direct pathway) or the recipient's APCs (the indi-

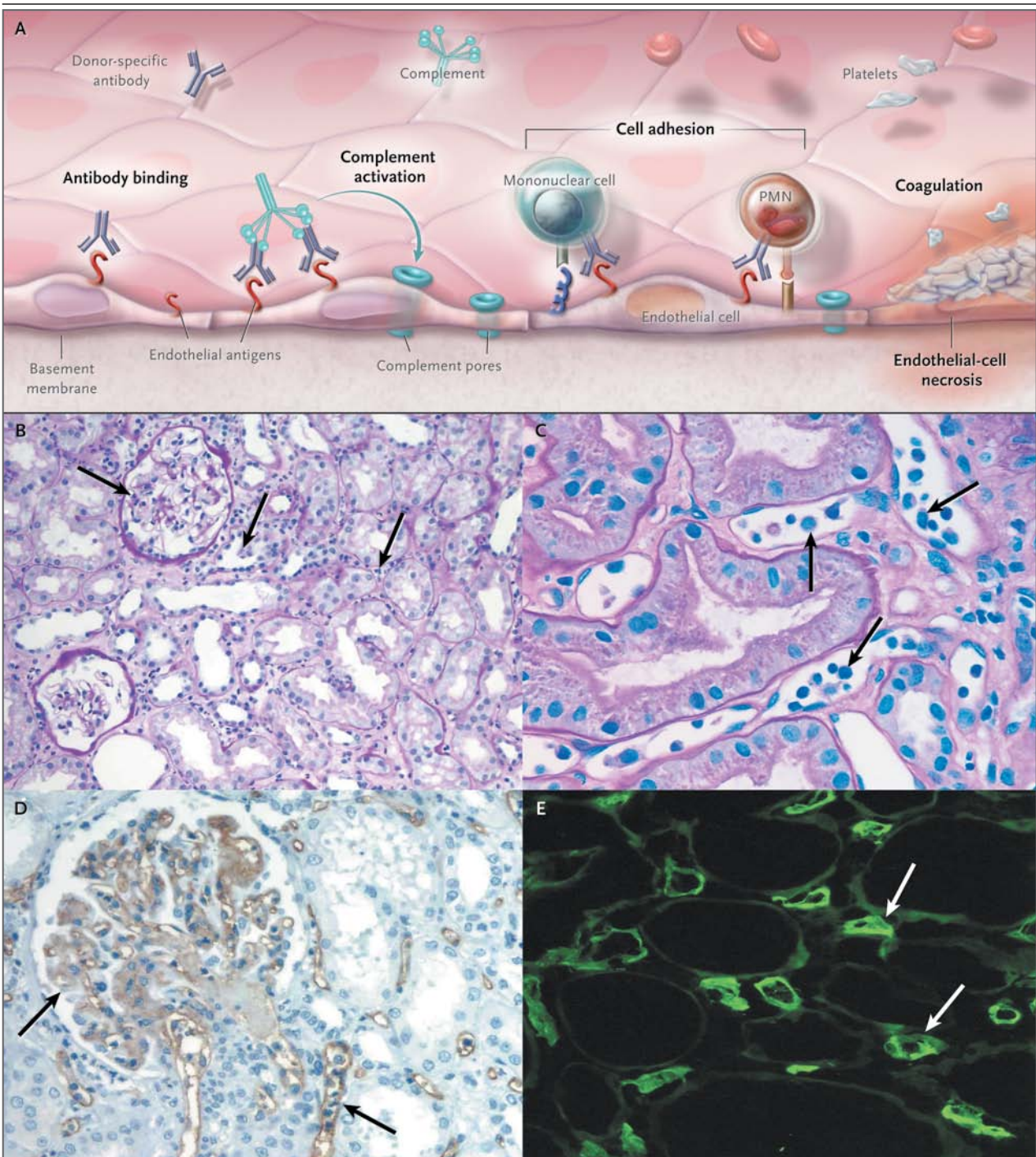
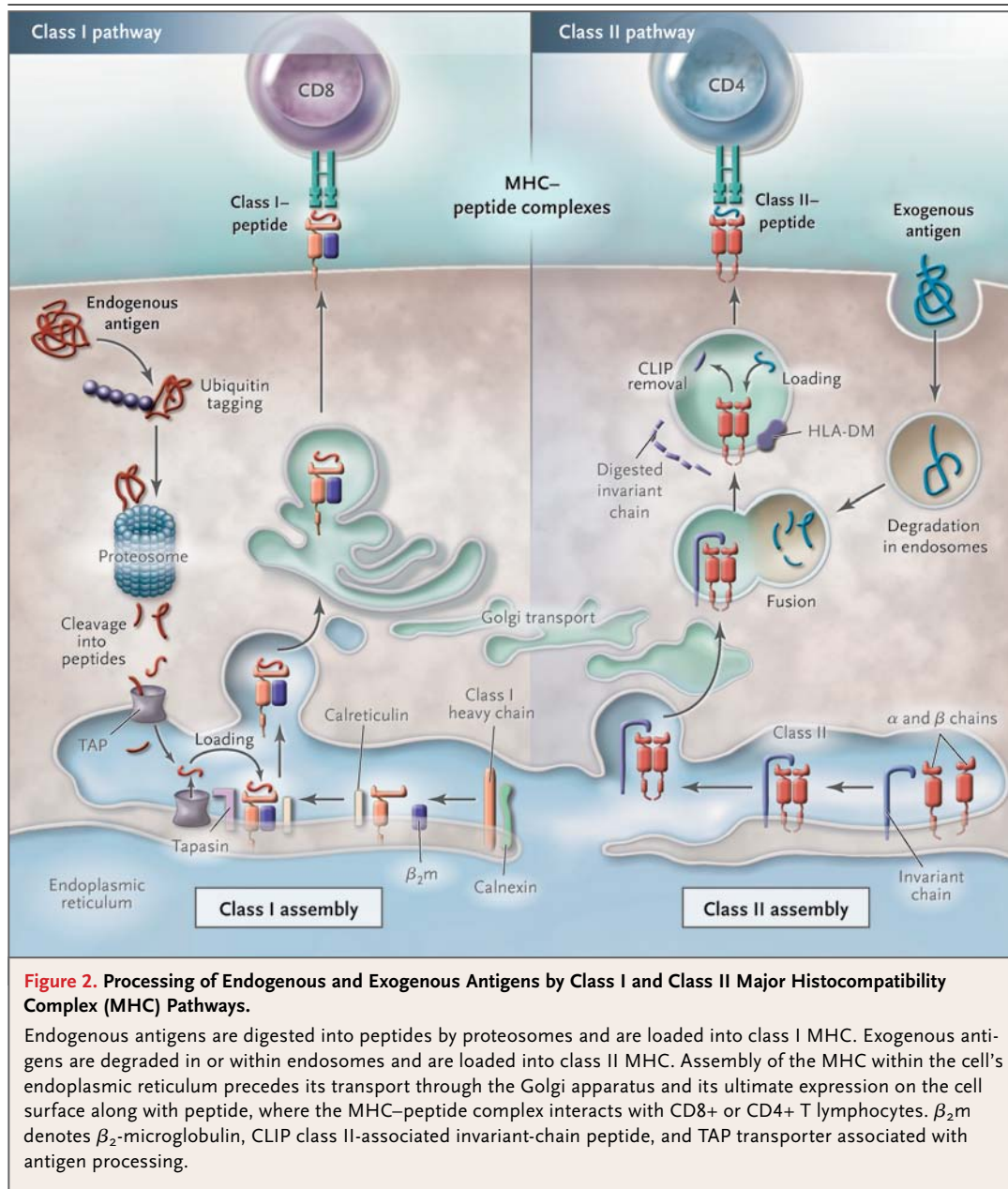


Figure 1. Acute Antibody-Mediated Rejection.

Antibodies against donor antigens bind to antigens expressed on endothelial cells in the graft vessel (Panel A). The subsequent complement activation and cell adhesion result in endothelial-cell necrosis, followed by platelet deposition and coagulation. PMN denotes polymorphonuclear cell. The corresponding histologic changes are shown in Panels B through E. Mononuclear cells adhere to the endothelium of the glomeruli (Panel B, arrows; periodic acid–Schiff stain) and the peritubular capillaries (shown at higher magnification in Panel C, arrows; periodic acid–Schiff stain). This process is accompanied by C4d deposition in the glomeruli and peritubular capillaries (Panel D, arrows; C4d immunohistochemical stain) and in the peritubular capillaries between ghost outlines of the renal tubules (Panel E, arrows; C4d immunofluorescent stain).

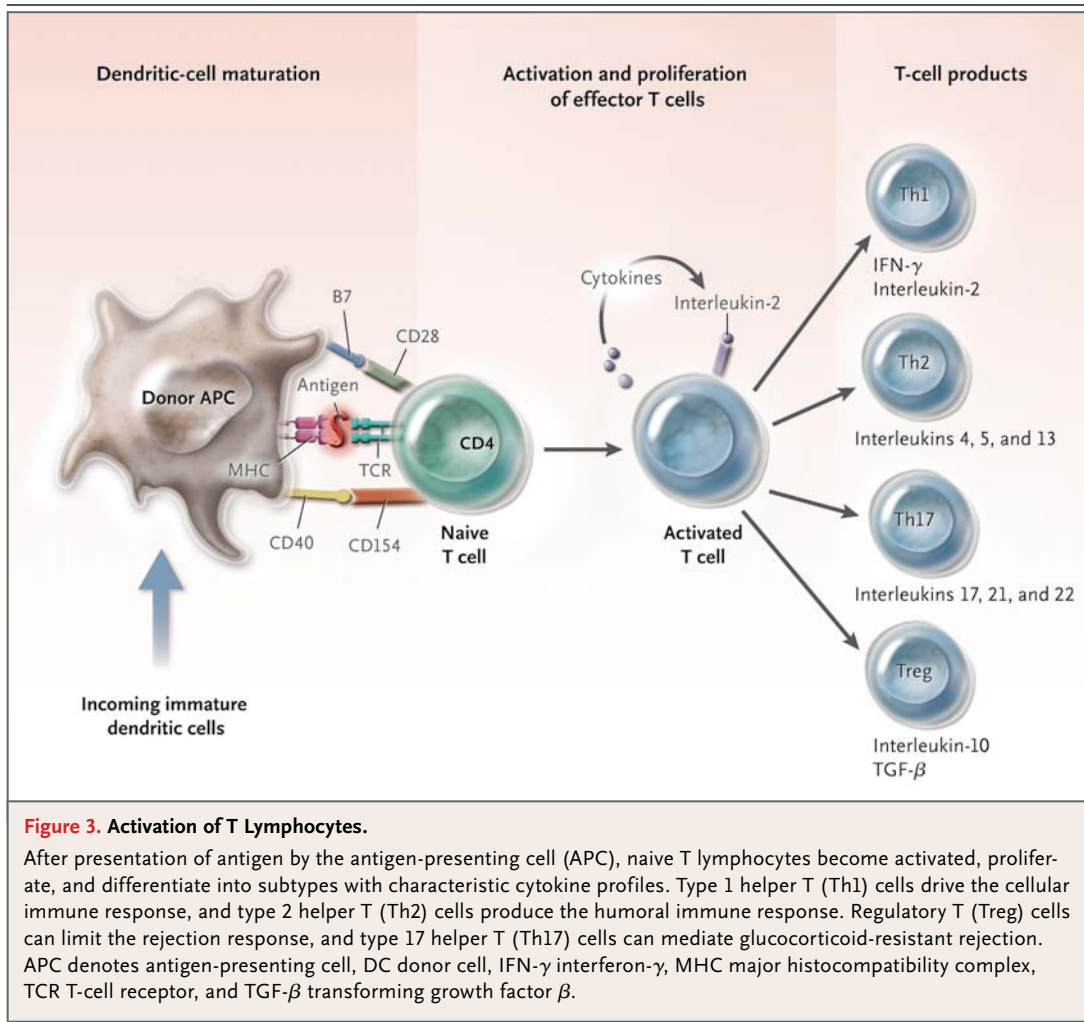


rect pathway, which resembles the pathway involved in the recognition of foreign antigens).³⁶ Initially, only a few T cells recognize antigens indirectly, but the indirect pathway becomes increasingly important in long-term immune injury to the graft, after the donor's APCs have disappeared.³⁷ The recipient's APCs can also take up membrane fragments of other cells; these fragments contain MHC molecules bearing "predigested" peptides derived from the donor's MHC glycoproteins (the semidirect pathway).^{38,39} APCs

can present such MHC-peptide complexes to CD4 T cells, which in turn activate CD8 T cells.

T-CELL SUBGROUPS

Subgroups of helper T cells have distinct cytokine profiles.⁴⁰⁻⁴³ Figure 3 shows the main features of these cells. The concept that type 1 helper T (Th1) cells mediate rejection whereas type 2 helper T (Th2) cells promote tolerance now appears to be simplistic, since Th2 cells alone can reject grafts, using pathways that involve eosinophils. Although



CD4 T cells produce inflammatory cytokines (interferon- γ and interleukin-2, which drive a cellular response, and interleukin-4, interleukin-5, and interleukin-13, which produce a humoral response), and CD8 T cells mediate cytotoxicity, their effector functions overlap.⁴⁴

Regulatory T (Treg) cells that express the transcription factor forkhead box P3 (FOXP3) underlie some types of immune tolerance in animal models; however, in humans their numbers increase during acute allograft rejection. Whether these cells proliferate to restrain the immune response or as a consequence of T-cell activation is unknown.⁴⁵ In rare cases of tolerance in which patients discontinue immunosuppressive therapy yet retain a functioning graft, there are Treg cells in the graft. Other studies have shown that the number of Treg cells correlates with markers of

T-cell rejection, including interstitial inflammation, tubulitis, and cytotoxic gene expression, but not with the graft outcome, suggesting that FOXP3-positive cells aid in stabilizing inflammation within the graft.^{45,46}

COSTIMULATION

T-cell activation requires signals other than those engendered by the MHC-peptide complex, termed costimulatory signals. T cells become anergic when presented with an antigen in the absence of these signals, and agents that block these signals are under development. The chief sources of these signals are APCs and surrounding tissues.⁴⁷ Among the costimulatory molecules displayed by APCs are CD80 (B7-1) and CD86 (B7-2); these two B7 molecules are ligands for two T-cell-membrane receptors, CD28 and CTLA-4. Binding of either

CD80 or CD86 to CD28 stimulates the T cell, whereas binding of B7 ligands to CTLA-4 incites an inhibitory signal. Other costimulatory molecules include CD40, CD154 (the CD40 ligand), and the T-cell immunoglobulin and mucin (TIM) subgroup, in which TIM3, a ligand on APCs, interacts with TIM1 on Th1 cells.⁴⁷⁻⁴⁹

Early clinical trials of agents that block costimulation were disappointing; anti-CD154 antibodies are prothrombotic, and the initial CTLA-4-immunoglobulin compounds had suboptimal efficacy. Belatacept, a fusion protein containing CTLA-4 and the Fc fragment of IgG1, blocks T-cell stimulation engendered by the CD80-CD28 and CD86-CD28 pathways. Clinical trials are assessing this more potent inhibitor as a potential replacement for nephrotoxic calcineurin inhibitors.⁵⁰

T-CELL MOVEMENT IN THE ALLOGRAFT

T cells use adhesion molecules, including leukocyte-function-associated antigen 1 (LFA-1), to roll along and tether to endothelium, migrate across peritubular capillaries,⁸ and enter the graft (Fig. 4). Fingolimod, a small molecule that blocks the egress of T cells from lymph nodes, and anti-LFA-1 agents block such T-cell movement,^{51,52} but until now they have had a limited clinical effect in transplantation.

Interstitial mononuclear cells, including CD4 and CD8 T cells, and inflammatory cytokines and chemokines accumulate in sites of acute cellular rejection (Fig. 1).^{53,54} The deletion of genes for anti-inflammatory cytokines such as interleukin-10 and transforming growth factor β accelerates graft rejection in mice, but, paradoxically, deletion of the genes for interferon- γ or its receptor exacerbates acute rejection.⁵⁵

Other cells and pathways have a role in acute rejection. The expression of B-cell genes and CD20 increases in severe cellular rejection,⁵⁶ and eosinophilic infiltrates occur in glucocorticoid-resistant rejection. Activated macrophages, which secrete substantial quantities of proinflammatory cytokines (interleukin-1, interleukin-12, and interleukin-18), tumor necrosis factor α (TNF- α), and interferon- γ , impair the function of the graft and intensify T-cell-mediated rejection.^{55,57}

Allografts undergoing rejection produce chemokines, and some of the cells that infiltrate the injured graft bear chemokine receptors.^{58,59} In studies in animals, the induced deficiency of chemokines, their receptors, or both impairs the re-

jection of allografts and may also influence the character of the inflammatory infiltrates within the graft.⁵⁹

EFFECTOR T CELLS

T cells mediate allograft injury directly through contact with tubular epithelial cells (cell-mediated cytotoxicity) and through the effects of locally released cytokines. They also injure the graft indirectly by activating inflammatory or vascular endothelial cells. CD8 T cells release perforin, which perforates target-cell membranes, and granzymes A and B, which enter cells and induce caspase-mediated apoptosis. The Fas ligand on cytotoxic T cells activates Fas, a receptor on cells of the graft, and this interaction also induces caspase-mediated apoptosis.⁶⁰ CD4 T cells can attack grafted cells expressing minor MHC antigens⁶¹ and can also secrete TNF- α and tumor necrosis factor β (TNF- β), which bind to TNF receptors on endothelial or tubular cells, causing them to undergo apoptosis.⁶² In animals, blockade of TNF by antibody or knockout of TNF-receptor genes prolongs allograft survival.⁶³

In grafts undergoing acute rejection, T lymphocytes infiltrate and proliferate within the interstitial space, whence they invade renal tubules, causing tubulitis (Fig. 4). Inflammatory cytokines produced by interstitial T cells activate tubular epithelial cells, which in turn attract more T lymphocytes by secreting chemokines (e.g., CCL2, CCL5, and CX3CL1).⁶⁴ Invading CD8 T lymphocytes, which have immunologic specificity for the allograft, cross the basement membrane of the tubule, where they proliferate and induce apoptosis of tubular cells (Fig. 4). Sublethally injured tubular cells can also transform from their native epithelial phenotype into primitive mesenchymal myofibroblasts, promoting interstitial fibrosis.⁶⁵ Necrosis of tubular epithelial cells and basement-membrane rupture cause urinary leakage, graft dysfunction, and progressive tubular atrophy.⁶⁶

OTHER PATTERNS OF REJECTION

VASCULAR REJECTION

The histologic characteristics of vascular rejection (also termed arteritis or endarteritis) include the infiltration of vessels by mononuclear cells, endothelial-cell apoptosis, and the synthesis of matrix proteins and collagens by intimal myofibroblasts (Fig. 4). CD4 and CD8 T cells and mac-

rophages invade the subendothelium and intima of muscular arteries by means of intercellular adhesion molecule 1 (ICAM-1) or vascular-cell adhesion molecules (VCAM) on activated endothelium and by means of chemokine (e.g., CCL4, CCL5, and CXCL8) gradients.⁶⁷ Experimental evidence suggests that anti-MHC antibodies, T-cell-mediated immunity to minor MHC antigens, natural killer cells, and interferon- γ all play a role in the invasion of vessels.⁶⁸ Vascular rejection is a severe condition that does not respond to glucocorticoid therapy and instead requires potent anti-lymphocyte-antibody therapy (muromonab-CD3 [Orthoclone OKT3, Ortho Biotech] or antithymocyte globulin).⁵

LATE ACUTE REJECTION

Late acute allograft rejection is often severe and difficult to reverse, with a high risk of subsequent graft loss. Its main features are active immune inflammation and chronic tubulointerstitial damage, which frequently involves graft-directed antibody.⁶⁸ It can develop in graft recipients with high-grade immunity against the transplant or in those who receive reduced amounts of immunosuppressive therapy because of cancer, prior severe infection, or noncompliance.

CHRONIC REJECTION

Chronic allograft rejection — ongoing immune injury to the graft — is due to a failure to maintain sufficient immunosuppression to control residual antigrraft lymphocytes or antibodies. Its features include a progressive decline in renal function, invasion of the renal parenchyma by T cells, and persistent infiltration of the interstitium by T cells and macrophages. Occasionally, one also sees smooth-muscle proliferation and hyperplasia in vessels, forming a neointima; focal destruction of internal elastic lamina; and finally, vascular occlusion⁷ (Fig. 4).

In chronic antibody-mediated rejection, undetected preexisting donor-specific antibodies or antibodies generated after transplantation deposit on the capillary endothelium.²¹ Endothelial injury to glomerular and peritubular capillaries causes cellular hypertrophy, subendothelial deposition of fibrillary material, expansion and duplication of the glomerular basement membrane, or mesangial-cell interposition (seen on histologic examination as double contours), and this is designated transplant glomerulopathy (Fig. 5). Complement (C4d) deposition in the peritubular capil-

Figure 4 (facing page). Acute T-Cell–Mediated Rejection.

Cellular rejection and transport of cells into the transplant are shown (Panel A). After the initial tethering, rolling, and arrest of effector T lymphocytes (which bind selectins and integrins on endothelial cells), lymphocytes and other immune cells enter the interstitial compartment and invade tubules, causing local tissue destruction. The histologic features of T-cell–mediated rejection include a dense interstitial lymphocytic infiltration (Panel B, arrow; periodic acid–Schiff stain), with mononuclear cells crossing the tubular basement membrane (pink) into the renal tubules, resulting in tubulitis (Panel C, arrow; periodic acid–Schiff stain). In acute vascular rejection, mononuclear cells adhere to the endothelium of small muscular arteries (Panel D, arrow; hematoxylin and eosin). In chronic vascular rejection, neointimal thickening (Panel E, arrow; Masson trichrome stain) due to myofibroblasts leads to complete vascular occlusion. ICAM-1 denotes intercellular adhesion molecule 1, LFA-1 leukocyte-function–associated antigen, VCAM-1 vascular-cell adhesion molecule 1, and VLA-4 very late antigen 4.

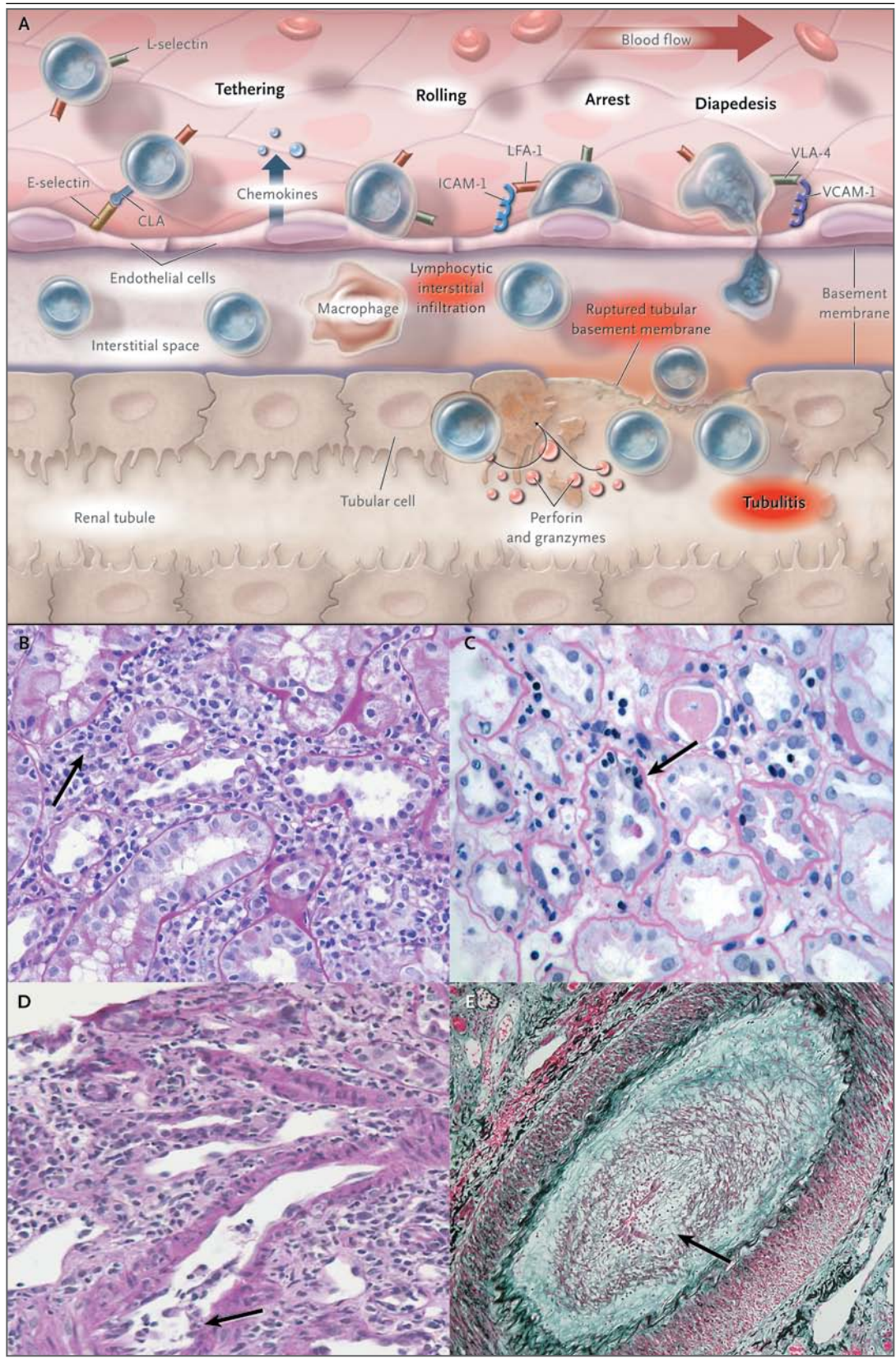
laries and basement-membrane multilamination may also occur.²¹

FUTURE DIRECTIONS

Despite technical advances and improvements in management, the alloimmune response remains the primary obstacle to successful kidney transplantation. Rejection of the graft entails much more than T-cell responses. Other elements include the innate immune system of natural killer cells, macrophages, and complement; the adaptive immune system of antigen-specific T lymphocytes and B cells; and cells intrinsic to the graft, such as endothelium. Antibody-mediated rejection is increasingly recognized as a contributor to late graft injury.

Current therapies are focused on the initial stages of T-cell activation, and this strategy has minimized early acute rejection. However, we need to improve our understanding of the mechanisms underlying chronic graft dysfunction and develop better treatments to prevent loss of the graft. Protocols that are designed to induce immunologic tolerance and the transplantation of organs in highly sensitized patients (those previously exposed to alloantigens) are also likely to alter the nature and presentation of rejection.

Tests based on the genetic signatures of lymphocytes or proteomic or metabolomic patterns, with the use of urine or blood samples, hold promise for monitoring the status of the graft. For



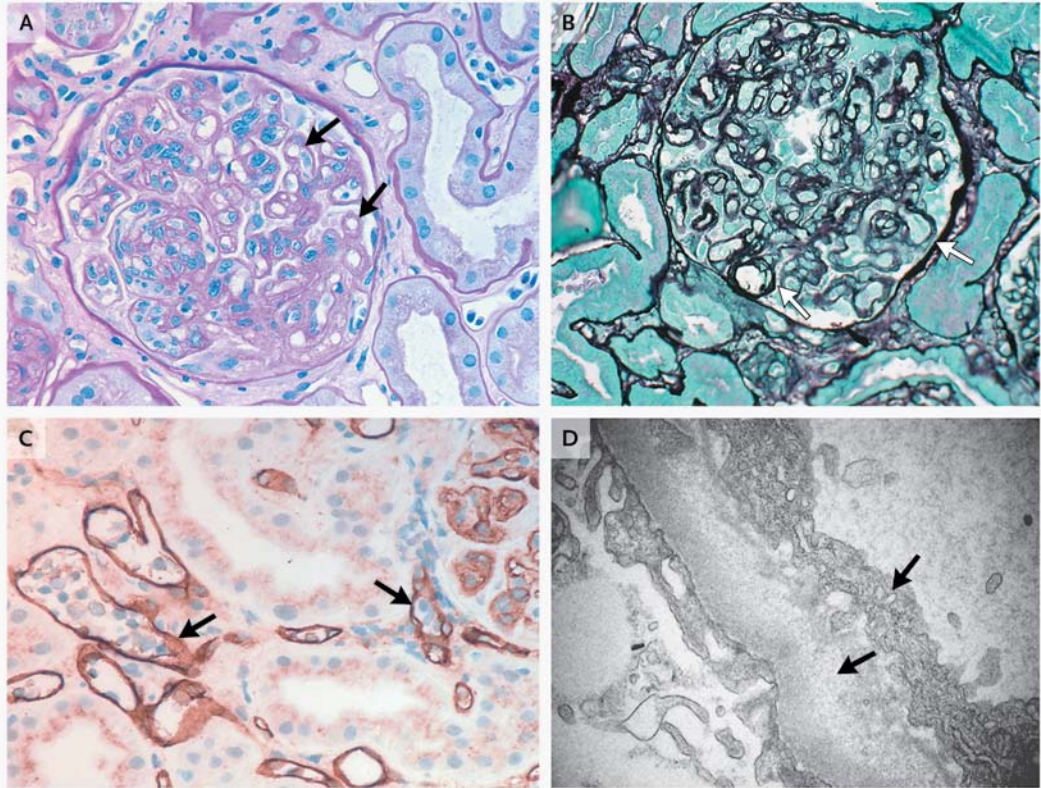


Figure 5. Chronic Antibody-Mediated Rejection.

Antibody-mediated rejection results in transplant glomerulopathy, with thickened glomerular capillaries (Panel A, arrows; periodic acid–Schiff stain) and double contours (Panel B, arrows; Masson green and silver stain), accompanied by C4d in peritubular capillaries containing mononuclear cells (Panel C, arrows; C4d immunohistochemical stain) and flocculent subendothelial material below an activated endothelial cell of the glomerular capillary (Panel D, arrows; electron microscopy).

kidney grafts, levels of mRNA in the urine that correspond to perforin, granzyme B, FOXP3, or other molecules appear to be more predictive of rejection than levels of mRNA from circulating mononuclear cells.⁶⁹ Enzyme-linked immunosorbent spot assays that measure activated lymphocytes and assays of mitogen-stimulated CD4 T-cell reactivity can quantify the risks of infection and rejection.^{70,71} However, the diagnostic overlap and limited number of independent studies validating their usefulness obscure the clinical value of these tests.^{45,72,73} The transplant biopsy remains the principal diagnostic tool, although supplementation by microarray transcriptome analysis could improve diagnostic classification and prognostication.^{56,74}

Another barrier to progress in this area is our limited knowledge of the mechanisms underly-

ing the down-regulation or silencing of the immune response. We do not know why in rare cases recipients appear to naturally tolerate an allograft, which functions without immunosuppression. An understanding of the mechanisms discussed in this review will allow the development of immunologically specific ways to prevent rejection and eliminate the need for toxic immunosuppressive therapies.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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