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PATHOPHYSIOLOGY OF REJECTION

General Concepts

Rejection of any transplanted organ is primarily mediated by activation of alloreactive T cells and antigen-presenting cells such as B lymphocytes, macrophages, and dendritic cells. Acute allograft rejection is caused primarily by the infiltration of T cells into the allograft, which triggers inflammatory and cytotoxic effects on the graft. Complex interactions between the allograft and cellular cytokines, cell-to-cell interactions, CD4+ and CD8+ T cells, and B cells ultimately lead to chronic rejection and graft loss if adequate immunosuppression is not maintained. 12

The sequence of events that underlies graft rejection is recognition, via MHC class I and II antigens, of the donor's histocompatibility differences by the recipient's immune system, recruitment of activated lymphocytes, initiation of immune effector mechanisms, and finally graft destruction. The specifics of this immune cascade of organ rejection are discussed in Chapter 95. The complex nature of cytokine interactions makes it very difficult to design drugs with exclusive actions (Fig. 98–1).

Figure 98-1.
Stages of CD4 T-cell activation and cytokine production with identification of the sites of action of different immunosuppressive agents. Antigen major histocompatibility complex (MHC) II molecule complexes are responsible for initiating the activation of CD4 T cells. These MHC-peptide complexes are recognized by the T-cell recognition complex (TCR). A costimulatory signal initiates signal transduction with activation of second messengers, one of which is calcineurin. Calcineurin removes phosphates from the nuclear factors (NFAT-P) allowing them to enter the nucleus. These nuclear factors specifically bind to an interleukin (IL)-2 promoter gene facilitating IL-2 gene transcription. Interaction of IL-2 with the IL-2 receptor (IL-2R) on the cell membrane surface induces cell proliferation and production of cytokines specific to the T cell. (APC, antigen-presenting cells; MMF, mycophenolate mofetil.) (Reprinted from Ann Thorac Surg, Vol. 77, Mueller XM, Drug immunosuppressive therapy for adult heart transplantation. Part I. Immune response to allograft and mechanism of action of immunosuppressants, pages 354–362, Copyright © 2004, with permission from Elsevier.)

Rejection of the transplanted tissue can take place at any time following surgery and is classified clinically as hyperacute rejection, acute cellular rejection, and/or humoral or chronic rejection. \(^{13}\)
Efforts are made to allocate well-matched, according to human leukocyte antigens (HLA)-A, -B, and -DR, kidneys to minimize rejection and enhance survival rates. However, the benefit of having no recipient donor mismatches may be negated by excessive cold ischemia time (>36 hours) and donor age older than 60 years. HLA tissue matching is not performed routinely before transplantation for livers and hearts because organ availability is more limited and the optimal cold ischemia time is shorter. However, if the potential recipient's blood is reactive against a panel of random donor blood samples (i.e., panel reactive antibody [PRA] >10% to 20%), a negative T-cell crossmatch is required prior to transplantation. Transplanted organs must be matched for ABO blood group compatibility with the recipient as ABO mismatching will result. Liver transplantation may be carried out in emergency situations across ABO blood groups, but survival is lower.

**Hyperacute Rejection**

Hyperacute rejection may be evident within minutes of the transplantation procedure when preformed donor-specific antibodies are present in the recipient at the time of the transplant. Hyperacute rejection can also be induced by immunoglobulin G antibodies that bind to antigens on the vascular endothelium, such as class I MHC, ABO, and vascular endothelial cell antigens. Tissue damage can be mediated through antibody-dependent, cell-mediated cytotoxicity or through activation of the complement cascade. The ischemic damage to the microvasculature rapidly results in tissue necrosis.

Hyperacute rejection has become uncommon in kidney and heart transplants. A positive crossmatch presents a serious risk for graft failure even if hyperacute rejection does not occur. A negative lymphocytotoxicity crossmatch does not entirely rule out the possibility of hyperacute rejection because non-MHC antigens on the vascular endothelium can serve as targets of donor-specific antibodies. Early graft dysfunction is treated with supportive care and retransplantation if possible. The reason for the rarity of hyperacute rejection in liver transplantation is not fully understood, but the local release of cytokines may alter the immunologic reaction in the liver.

**Acute Cellular Rejection**

Acute rejection is most common in the first few months following transplantation but can occur at any time during the life of the allograft. Acute cellular rejection is mediated by alloreactive T-lymphocytes that appear in the circulation and infiltrate the allograft through the vascular endothelium. After the graft is infiltrated by lymphocytes, the cytotoxic cells specifically target and kill the functioning cells in the allograft. At the same time, local release of lymphokines attracts and stimulates macrophages to produce tissue damage through a delayed hypersensitivity-like mechanism. These immunologic and inflammatory events lead to nonspecific signs and symptoms including pain and tenderness over the graft site, fever, and lethargy.

**KIDNEY**

Acute rejection, which may affect up to 20% of patients during the first 6 months following transplantation, is evidenced by an abrupt rise in serum creatinine concentration of ≥30% over baseline. A specific histologic diagnosis can be obtained via biopsy of the allograft and is often
used to guide therapy for rejection. A biopsy specimen with a diffuse lymphocytic infiltrate is consistent with acute cellular rejection. After the diagnosis of rejection has been confirmed, the potential risks and benefits of specific antirejection therapies must be evaluated. Hypertension often worsens during an episode of rejection, and edema and weight gain are common as a result of sodium and fluid retention. Symptomatic azotemia may also develop in severe cases.

LIVER

The liver is more likely to promote immunologic tolerance than the other vascularized organs. Approximately 18% of liver transplantation recipients will experience a rejection episode in the first post-transplant year. The clinical signs of acute cellular rejection include leukocytosis and a change in the color or quantity of bile for those who still have an external drainage tube in place. A serum bilirubin 50% over baseline or increases in hepatic transaminases to values more than three times the upper limit of normal, are sensitive markers of rejection. Although a liver biopsy provides definitive evidence of the diagnosis of rejection, a prompt response to antirejection medication has also proven useful as a means to differentiate rejection from other causes of hepatic dysfunction.

HEART

More than 60% of heart transplantation recipients will experience at least one episode of acute rejection during the first year, with 90% of all rejections occurring within the first 6 months. 14 Because rejection of the cardiac allograft is not necessarily accompanied by overt clinical signs or symptoms and because the incidence of acute rejection is highest during this time period, endomyocardial biopsies are often performed at regularly scheduled intervals following transplantation. 15 A typical biopsy schedule would be weekly for the first postoperative month, biweekly for the next 2 months, and monthly to bimonthly through the remainder of the first post-transplant year. Nonspecific symptoms, including low-grade fever, malaise, mild reduction in exercise capacity, heart failure, or atrial arrhythmias may also be evident and if present are reflective of a more severe rejection episode.

Antibody-Mediated Rejection

Antibody-mediated rejection (AMR), sometimes referred to as vascular or humoral rejection, is characterized by the presence of antibodies directed against HLA antigens present on the donor vascular endothelium. It can be characterized by capillary deposition of immunoglobulins, complement, and fibrinogen on immunofluorescence staining. Circulating immune complexes often precede humoral rejection. This form of rejection is less common than cellular rejection and generally occurs in the first 3 months after transplantation. It is associated with an increased fatality rate and appears to be more common when antilymphocyte antibodies are used for rejection prophylaxis. An increased risk of humoral rejection is associated with female gender, elevated PRA, cytomegalovirus seropositivity, a positive crossmatch, and prior sensitization to OKT3 (muromonab CD3). 16 Strategies to reverse humoral rejection include plasmapheresis, often in combination with intravenous immunoglobulin, high-dose intravenous corticosteroids, antithymocyte globulin, cyclophosphamide, rituximab, and mycophenolate
Chronic Rejection

Chronic rejection is a major cause of graft loss. It presents as a slow and indolent form of acute cellular rejection, in which the involvement of the humoral immune system and antibodies against the vascular endothelium appear to play a role. Persistent perivascular and interstitial inflammation is a common finding in kidney, liver, and heart transplantation. As a result of the complex interaction of multiple drugs and diseases over time, it is difficult to delineate the true nature of chronic rejection. Unlike acute rejection, chronic rejection is not reversible with any immunosuppressive agents currently available.

**KIDNEY**

Advances in the management of acute rejection during the last decade have increased the duration of functioning grafts from living and cadaveric donors by more than 70%. Chronic allograft nephropathy remains the most common cause of graft loss in the late post-transplantation period (>1 year). The histopathologic characteristics of chronic allograft nephropathy include vascular intimal hyperplasia, tubular atrophy, interstitial fibrosis, and chronic glomerulopathy. Structural changes are seen in as many as 40% of kidney transplantation patients 1 year after transplantation and may present as early as 3 months. Hypertension, proteinuria, and a progressive decline in renal function represent the classic clinical triad of chronic allograft nephropathy. Factors that contribute to the development of chronic allograft nephropathy include calcineurin inhibitor nephrotoxicity, polyomavirus infection, hypertension, donor-related factors including ischemia time and undetected kidney disease in the donor kidney, and recurrence of the primary kidney disease in the recipient.

**LIVER**

Approximately 3 to 5% of transplant livers are affected by chronic rejection, which is characterized by an obliterator arteriopathy and the gradual loss of bile ducts, often referred to as the vanishing bile duct syndrome. Initially patients experience an asymptomatic rise in the alkaline phosphatase and \( \gamma \)-glutamyl transpeptidase. As levels of bilirubin increase, patients become jaundiced and may experience itching.

**HEART**

Cardiac allograft vasculopathy, characterized by accelerated intimal thickening or development of atherosclerotic plaques, is the leading cause of graft failure and death in heart transplant recipients. Endothelial injury, caused by both cell-mediated and humoral responses, is the first step in the process. Vasculopathy is restricted to the transplanted allograft. Routine surveillance with coronary angiography, intravascular ultrasound, or other procedures can aid in the diagnosis of vasculopathy. Evidence of cardiac allograft vasculopathy can be seen in as many as 14% of patients within 1 year of transplantation and in as many as 50% of patients within 5 years. While chronic rejection of the kidney or liver allograft is generally not amenable to treatment, 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA) reductase inhibitors and ACEIs...
have been used to decrease the incidence of vasculopathy in the heart allograft. More recently, sirolimus and everolimus have been shown to reduce the incidence and slow progression of cardiac allograft vasculopathy. Percutaneous transluminal coronary angioplasty and coronary artery bypass grafting have been used in severe cases of vasculopathy; these procedures, however, are limited by significantly increased mortality compared with the general population.