region that encodes the strong, or major, transplantation antigens, and this region on the human sixth chromosome is called *HLA*. HLA antigens have been classically defined by serologic techniques, but methods to define specific nucleotide sequences in genomic DNA are increasingly being used. Other "minor" antigens may play crucial roles, in addition to the ABH(O) blood groups and endothelial antigens that are not shared with lymphocytes. The Rh system is not expressed on graft tissue. Evidence for designation of HLA as the genetic region that encodes major transplantation antigens comes from the success rate in living related donor renal and bone marrow transplantation, with superior results in HLA-identical sibling pairs. Nevertheless, 5% of HLA-identical renal allografts are rejected, often within the first weeks after transplantation. These failures represent states of prior sensitization to non-HLA antigens. Non-HLA minor antigens are relatively weak when initially encountered and are, therefore, suppressible by conventional immunosuppressive therapy. Once priming has occurred, however, secondary responses are much more refractory to treatment.

DONOR SELECTION

Donors can be deceased or volunteer living donors. When first-degree relatives are donors, graft survival rates at 1 year are 5–7% greater than those for deceased-donor grafts. The 5-year survival rates still favor a partially matched (3/6 HLA mismatched) family donor over a randomly selected cadaver donor. In addition, living donors provide the advantage of immediate availability. For both living and deceased donors, the 5-year outcomes are poor if there is a complete (6/6) HLA mismatch.

The survival rate of living unrelated renal allografts is as high as that of perfectly HLA-matched cadaver renal transplants and comparable to that of kidneys from living relatives. This outcome is probably a consequence of both short cold ischemia time and the extra care taken to document that the condition and renal function of the donor are optimal before proceeding with a living unrelated donation. It is illegal in the United States to purchase organs for transplantation.

Living volunteer donors should be cleared of any medical conditions that may cause morbidity and mortality after kidney transplantation. Concern has been expressed about the potential risk to a volunteer kidney donor of premature renal failure after several years of increased blood flow and hyperfiltration per nephron in the remaining kidney. There are a few reports of the development of hypertension, proteinuria, and even lesions of focal segmental sclerosis in donors over long-term follow-up. It is also desirable to consider the risk of development of type 1 diabetes mellitus in a family member who is a potential donor to a diabetic renal failure patient. Anti-insulin and anti-islet cell antibodies should be measured and glucose tolerance tests should be performed in such donors to exclude a prediabetic state. Selective renal arteriography should be performed on donors to rule out the presence of multiple or abnormal renal arteries, because the surgical procedure is difficult and the ischemic time of the transplanted kidney is long when there are vascular abnormalities. Transplant surgeons are now using a laparoscopic method to isolate and remove the living donor's kidney. This operation has the advantage of less evident surgical scars, and, because there is less tissue trauma, the laparoscopic donors have a substantially shorter hospital stay and less discomfort than those who have the traditional surgery.

Deceased donors should be free of malignant neoplastic disease, hepatitis, and HIV due to possible transmission to the recipient, although there is increasing interest in using hepatitis C– and HIV-positive organs in previously infected recipients. Increased risk of graft failure exists when the donor is elderly or has renal failure and when the kidney has a prolonged period of ischemia and storage.

In the United States, there is a coordinated national system of regulations, allocation support, and outcomes analysis for kidney transplantation called the Organ Procurement Transplant Network. It is now possible to remove deceased-donor kidneys and maintain them for up to 48 h on cold pulsatile perfusion or with simple flushing and cooling. This approach permits adequate time for typing, cross-matching, transportation, and selection problems to be solved.

PRESENSITIZATION

A positive cytotoxic cross-match of recipient serum with donor T lymphocytes indicates the presence of preformed donor-specific anti-HLA class I antibodies and is usually predictive of an acute vasculitic event termed *hyperacute rejection*. This finding, along with ABO incompatibility, represents the only absolute immunologic contraindication for kidney transplantation. Recently, more tissue typing laboratories have shifted to a flow cytometric–based cross-match assay, which detects the presence of anti-HLA antibodies that are not necessarily detected on a cytotoxic cross-match assay and may not be an absolute contraindication to transplantation. The known sources of such sensitization are blood transfusion, a prior transplant, pregnancy, and vaccination/infection. Patients sustained by dialysis often show fluctuating antibody titers and specificity patterns. At the time of assignment of a cadaveric kidney, cross-matches are performed with at least a current serum. Previously analyzed antibody specificities and additional cross-matches are performed accordingly. Flow cytometry detects binding of anti-HLA antibodies of a candidate's serum by a recipient's lymphocytes. This highly sensitive test can be useful for avoidance of accelerated, and often untreatable, early graft rejection in patients receiving second or third transplants.

For the purposes of cross-matching, donor T lymphocytes, which express class I but not class II antigens, are used as targets for detection of anti–class I (HLA-A and -B) antibodies that are expressed on all nucleated cells. Preformed anti–class II (HLA-DR and -DQ) antibodies against the donor also carry a higher risk of graft loss, particularly in recipients who have suffered early loss of a prior kidney transplant. B lymphocytes, which express both class I and class II antigens, are used as targets in these assays.

Some non-HLA antigens restricted in expression to endothelium and monocytes have been described, but clinical relevance is not well established. A series of minor histocompatibility antigens do not elicit antibodies, and sensitization to these antigens is detectable only by cytotoxic T cells, an assay too cumbersome for routine use.

Desensitization before transplantation by reducing the level of anti-donor antibodies using plasmapheresis and administration of pooled immunoglobulin, or both, has been useful in reducing the risk of hyperacute rejection following transplantation.

IMMUNOLOGY OF REJECTION

Both cellular and humoral (antibody-mediated) effector mechanisms can play roles in kidney transplant rejection.

Cellular rejection is mediated by lymphocytes that respond to HLA antigens expressed within the organ. The CD4+ lymphocyte responds to class II (HLA-DR) incompatibility by proliferating and releasing pro-inflammatory cytokines that augment the proliferative response of the immune system. CD8+ cytotoxic lymphocyte precursors respond primarily to class I (HLA-A, -B) antigens and mature into cytotoxic effector cells that cause organ damage through direct contact and lysis of donor target cells. Full T cell activation requires not only T cell receptor binding to the alloantigens presented by self or donor HLA molecules (indirect and direct presentation, respectively), but also engaging costimulatory molecules such as CD28 on T cells and CD80 and CD86 ligands on antigen-presenting cells (Fig. 337-1). Signaling through both of these pathways induces activation of the kinase activity of calcineurin, which, in turn, activates transcription factors, leading to upregulation of multiple genes, including interleukin 2 (IL-2) and interferon gamma. IL-2 signals through the target of rapamycin (TOR) to induce cell proliferation in an autocrine fashion. There is evidence that non-HLA antigens can also play a role in renal transplant rejection episodes. Recipients who receive a kidney from an HLA-identical sibling can have rejection episodes and require maintenance immunosuppression, whereas identical twin transplants require no immunosuppression. There are documented non-HLA antigens, such as an endothelial-specific antigen system with limited polymorphism and a tubular antigen, which can act as targets of humoral or cellular rejection responses, respectively.