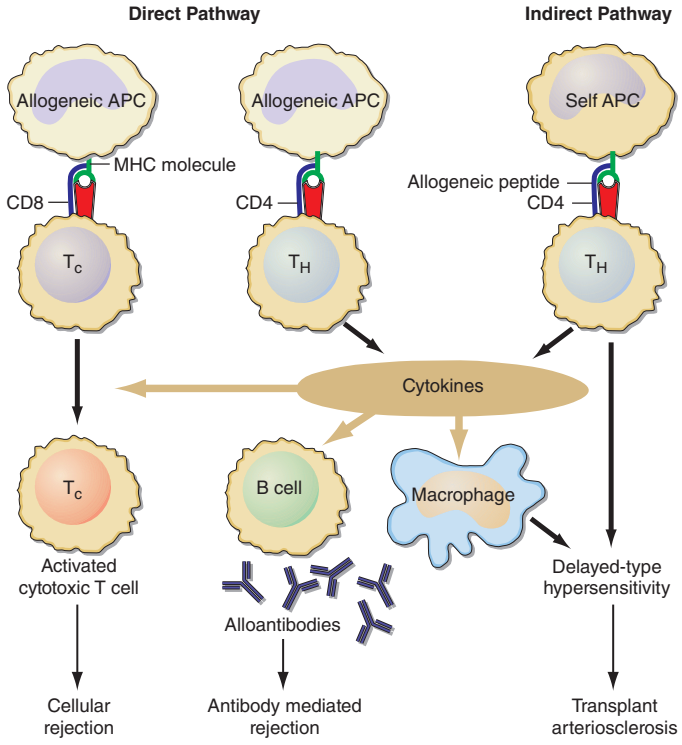

FIGURE 337-1 Recognition pathways for major histocompatibility complex (MHC) antigens. Graft rejection is initiated by CD4 helper T lymphocytes (T_H) having antigen receptors that bind to specific complexes of peptides and MHC class II molecules on antigen-presenting cells (APC). In transplantation, in contrast to other immunologic responses, there are two sets of T cell clones involved in rejection. In the direct pathway, the class II MHC of donor allogeneic APCs is recognized by CD4 T_H cells that bind to the intact MHC molecule, and class I MHC allogeneic cells are recognized by CD8 T cells. The latter generally proliferate into cytotoxic cells (T_C). In the indirect pathway, the incompatible MHC molecules are processed into peptides that are presented by the self-APCs of the recipient. The indirect, but not the direct, pathway is the normal physiologic process in T cell recognition of foreign antigens. Once T_H cells are activated, they proliferate and, by secretion of cytokines and direct contact, exert strong helper effects on macrophages, T_C, and B cells. *(From MH Sayegh, LH Turka: N Engl J Med, 338:1813, 1998. Copyright 1998, Massachusetts Medical Society. All rights reserved.)*

IMMUNOSUPPRESSIVE TREATMENT

Immunosuppressive therapy, as currently available, generally suppresses all immune responses, including those to bacteria, fungi, and even malignant tumors. In general, all clinically useful drugs are more selective to primary than to memory immune responses. Agents to suppress the immune response are classically divided into induction and maintenance agents and will be discussed in the following paragraphs. Those currently in clinical use are listed in Table 337-3.

INDUCTION THERAPY

Induction therapy is currently given to most kidney transplant recipients in the United States at the time of transplant to reduce the risk of early acute rejection and to minimize or eliminate the use of either steroids or calcineurin inhibitors and their associated toxicities. Induction therapy consists of antibodies that could be monoclonal or polyclonal and depletional or nondepletional.

Depleting Agents Peripheral human lymphocytes, thymocytes, or lymphocytes from spleens or thoracic duct fistulas are injected into horses, rabbits, or goats to produce antilymphocyte serum, from which the globulin fraction is then separated, resulting in antithymocyte globulin. Those polyclonal antibodies induce lymphocyte depletion, and the immune system may take several months to recover.

Monoclonal antibodies against defined lymphocyte subsets offer a more precise and standardized form of therapy. Alemtuzumab is directed to the CD52 protein, widely distributed on immune cells such as B and T cells, natural killer cells, macrophages, and some granulocytes.

Nondepleting Agents Another approach to more selective therapy is to target the 55-kDa alpha chain of the IL-2 receptor, which is expressed only on T cells that have been recently activated. This approach is used as prophylaxis for acute rejection in the immediate posttransplant period and is effective at decreasing the early acute rejection rate with few adverse side effects.

The next step in the evolution of this therapeutic strategy, which has already been achieved in the short term in small numbers of immunologically well-matched patients, is the elimination of all maintenance immunosuppression therapy.

MAINTENANCE THERAPY

All kidney transplant recipients should receive maintenance immunosuppressive therapies except identical twins. The most frequently used combination is triple therapy with prednisone, a calcineurin inhibitor, and an antimetabolite; mammalian TOR (mTOR) inhibitors can replace one of the last two agents. More recently, the U.S. Food and Drug Administration (FDA) approved a new costimulatory blocking antibody, belatacept, as a new strategy to prevent long-term calcineurin inhibitor toxicity.

Antimetabolites *Azathioprine*, an analogue of mercaptopurine, was for two decades the keystone to immunosuppressive therapy in humans, but has given way to more effective agents. This agent can inhibit synthesis of DNA, RNA, or both. Azathioprine is administered in doses of 1.5–2 mg/kg per day. Reduction in the dose is required because of leukopenia and occasionally thrombocytopenia. Excessive amounts of azathioprine may also cause jaundice, anemia, and alopecia. If it is essential to administer allopurinol concurrently, the azathioprine dose must be reduced. Because inhibition of xanthine oxidase delays degradation, this combination is best avoided.

Mycophenolate mofetil or *mycophenolate sodium*, both of which are metabolized to mycophenolic acid, is now used in place of azathioprine in most centers. It has a similar mode of action and a mild degree of gastrointestinal toxicity but produces less bone marrow suppression. Its advantage is its increased potency in preventing or reversing rejection.

Steroids *Glucocorticoids* are important adjuncts to immunosuppressive therapy. Among all the agents employed, prednisone has effects that are easiest to assess, and in large doses it is usually effective for the reversal of rejection. In general, 200–300 mg prednisone is given immediately before or at the time of transplantation, and the dose is reduced to 30 mg within a week. The side effects of the glucocorticoids, particularly impairment of wound healing and predisposition to infection, make it desirable to taper the dose as rapidly as possible in the immediate postoperative period. Many centers now have protocols for early discontinuance or avoidance of steroids because of long-term adverse effects on bone, skin, and glucose metabolism. For treatment of acute rejection, methylprednisolone, 0.5–1 g IV, is administered immediately upon diagnosis of beginning rejection and continued once daily for 3 days. Such "pulse" doses are not effective in chronic rejection. Most patients whose renal function is stable after 6 months or a year do not require large doses of prednisone; maintenance doses of 5–10 mg/d are the rule. A major effect of steroids is preventing the release of IL-6 and IL-1 by monocytes-macrophages.

Calcineurin Inhibitors *Cyclosporine* is a fungal peptide with potent immunosuppressive activity. It acts on the calcineurin pathway to block transcription of mRNA for IL-2 and other proinflammatory cytokines, thereby inhibiting T cell proliferation. Although it works alone, cyclosporine is more effective in conjunction with glucocorticoids and mycophenolate. Clinical results with tens of thousands of renal transplants have been impressive. Among its toxic effects (nephrotoxicity, hepatotoxicity, hirsutism, tremor, gingival hyperplasia,