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Introduction to Solid Organ Transplantation

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2.1 Historical Perspective

Organ transplantation has been the subject of ancient myths dating back to the twelfth century. The modern era of transplantation began in the early 1900s with the development of surgical techniques for constructing vascular anastomoses [1] leading to successful kidney transplantation in dogs in 1902 [2]. The first series of human kidney transplants were performed in the Ukraine beginning in 1933, but each of five attempted transplants failed [3, 4]. Around the same time, Kuss et al. [5], Servelle et al. [6], and Dubost et al. [7] reported technically successful transplantation of kidney allografts in humans, placing the organs heterotopically in the iliac fossa, similar to the technique used in the modern-day operation. However, all of these grafts failed over a short period of time. In 1954, Murray et al. [8, 9] performed a kidney transplant between identical twins and achieved long-term function. During the subsequent 10 years, more than 30 kidney transplants between identical twins were performed worldwide.

These early transplants between identical twins were successful because the donors and recipients were syngeneic, sharing the same immune system and thus eliminating the possibility of immunologically mediated rejection of the graft. In the 1940s, the seminal experiments of Medawar first delineated the immunologic basis for allograft rejection [10] and the need for immunosuppressive therapy to achieve successful transplantation using non-syngeneic grafts. By 1963, the first human liver transplantation was performed, using early forms of immunosuppression [11]. One year later, Barnard [12] performed the first successful human heart transplant. Shortly thereafter, techniques were developed for clinical heart–lung [13] and pancreas [14] transplantation.

Since those early days, remarkable strides have been made to increase the success of organ transplantation to prolong the lives of patients with end-stage organ disease. General advances in medical science, including improvements in surgical techniques and the development of effective antimicro-

bial agents, have undoubtedly played a role in this success story. However, the current success of organ transplantation has been related more directly to an improved understanding of the mechanisms of allograft rejection and the development of immunosuppressive drugs capable of preventing or treating rejection.

Although transplantation offers a survival advantage and improved quality of life for most patients with end-stage organ disease, the continued disparity between the supply of allografts from deceased donors and the growing demand for these organs represents the main limiting factor in field of transplantation today. In addition, while the mechanisms and treatments for acute forms of allograft rejection are well understood, our understanding of chronic forms of rejection remains limited, and organs continue to be lost from both immune and nonimmune causes. The remainder of this chapter will review the known mechanisms of allograft rejection, the drugs used to prevent and treat rejection, and current outcomes of organ transplant recipients.

2.2 Mechanisms of Allograft Rejection

Alloimmune reactions resulting in rejection of an allograft remain the major barrier to long-term survival of transplanted organs. Immunologic tolerance can be achieved with relative ease in small animals. However, the human immune system is complex, containing redundant pathways that make tolerance difficult to achieve. Thus, in the current era, allograft rejection remains the major threat to long-term survival of transplanted kidneys and the vast majority of transplant recipients require life-long treatment with immunosuppression drugs. Delineation of mechanisms leading to allograft rejection has been critical to the development of agents capable of preventing or treating rejection.

Mammalian immune responses evolved to protect the host from infectious pathogens and to provide discrimination of

self from nonself. An efficient response requires the recognition of pathogens and subsequent activation of key cells and soluble mediators of immunity [15, 16]. Similarly, immune responses resulting in the recognition and destruction of an allograft require cells with an ability to migrate, antigen-presenting cells (APCs), soluble mediators such as cytokines and effector cells that injure the graft.

2.2.1 Allorecognition

The major histocompatibility complex (MHC) is a set of cell surface molecules encoded by genes contained on chromosome 6 [17, 18]. The primary immunologic function of MHC gene products is to present fragments of foreign proteins, forming complexes that can be recognized by T lymphocytes through their antigen-specific receptors. Antigen presentation begins when an MHC complex binds a peptide antigen. MHC molecules are composed of a highly polymorphic polypeptide alpha chain and a monomorphic beta chain, consisting of beta2-microglobulin in the case of class I MHC. Allospecificity of class I MHC molecules, expressed constitutively on all nucleated cells, resides in the alpha chain, a polypeptide with a prominent groove or pocket that is the site where foreign proteins bind for presentation to T cells. Class II MHC molecules are expressed constitutively only on APCs, including macrophages, dendritic cells, and B cells. Adjacent portions of the highly variable alpha chain and a non-variable beta chain form a peptide groove. Highly variable amino acid residues located in the groove determine

the specificity of T cell antigen recognition. The same T cell receptor (TCR) can recognize either class I or class II MHC molecules, but restrictions are imposed by the engagement of the T cell surface molecule, CD4, to class II molecules and CD8 to class I molecules. Thus, CD4-positive T cells primarily engage peptides presented by class II MHC, while CD8-positive T cells engage peptides presented by class I MHC (see Figure 2-1a).

Immediately following vascularization of an allograft, donor antigens enter the systemic circulation via APCs and travel to the spleen and lymph nodes where naïve T cells are activated. At the same time, recipient cells enter the allograft. *Direct allorecognition* occurs either in the secondary lymphoid system or in the graft. In the lymphoid system, this occurs when the recipient's naïve lymphocytes are engaged with donor APCs that have traveled to the lymph nodes or spleen. In the graft, direct allorecognition occurs when donor APCs engage with recipient lymphocytes [19]. *Indirect allorecognition* occurs in the secondary lymphatic system when donor proteins or peptides are first processed by recipient APCs and presented to the TCR by the recipient's MHC on the surface of the APC (Figure 2-1b). In the graft, indirect allorecognition occurs when recipient APCs process donor peptides and engage recipient lymphocytes by presenting those processed peptides in the groove of the recipient MHC [19]. The direct pathway of allorecognition plays a dominant role in early T cell-mediated acute rejection episodes while the indirect pathway is believed to be more important in mediating chronic rejection.

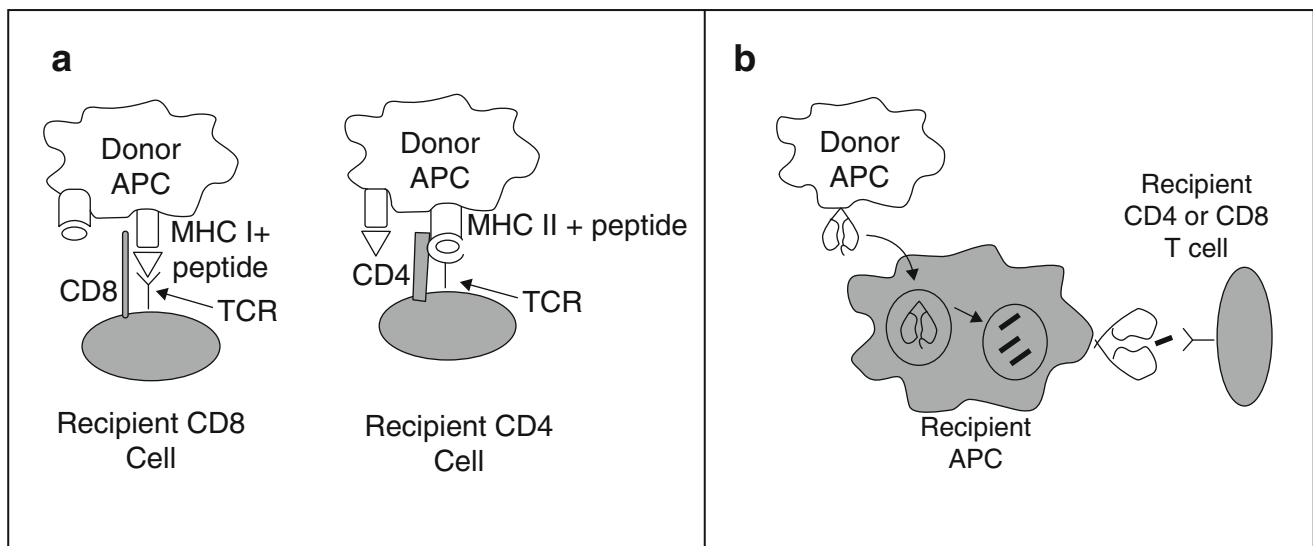


FIGURE 2-1. (a) Depiction of *direct allorecognition* in which a donor antigen-presenting cell (APC) presents peptide to the T cell receptor (TCR) within the context of donor major histocompatibility complex (MHC) molecule. *Left side*: presentation of a peptide within a class I MHC molecule to a CD8-positive T cell. *Right side*: presentation of a peptide within a class II MHC molecule to a CD4-positive T cell. (b) Depiction of *indirect allorecognition* in which an antigen is first processed by a recipient antigen-presenting cell (APC) and then presented within the context of a recipient major histocompatibility complex (MHC) molecule to either a CD4- or CD8-positive T cell. Reprinted from Am J Kidney Dis, 65(6), Donald E. Hricik, pp. 956–66, Copyright 2015, with permission from Elsevier.

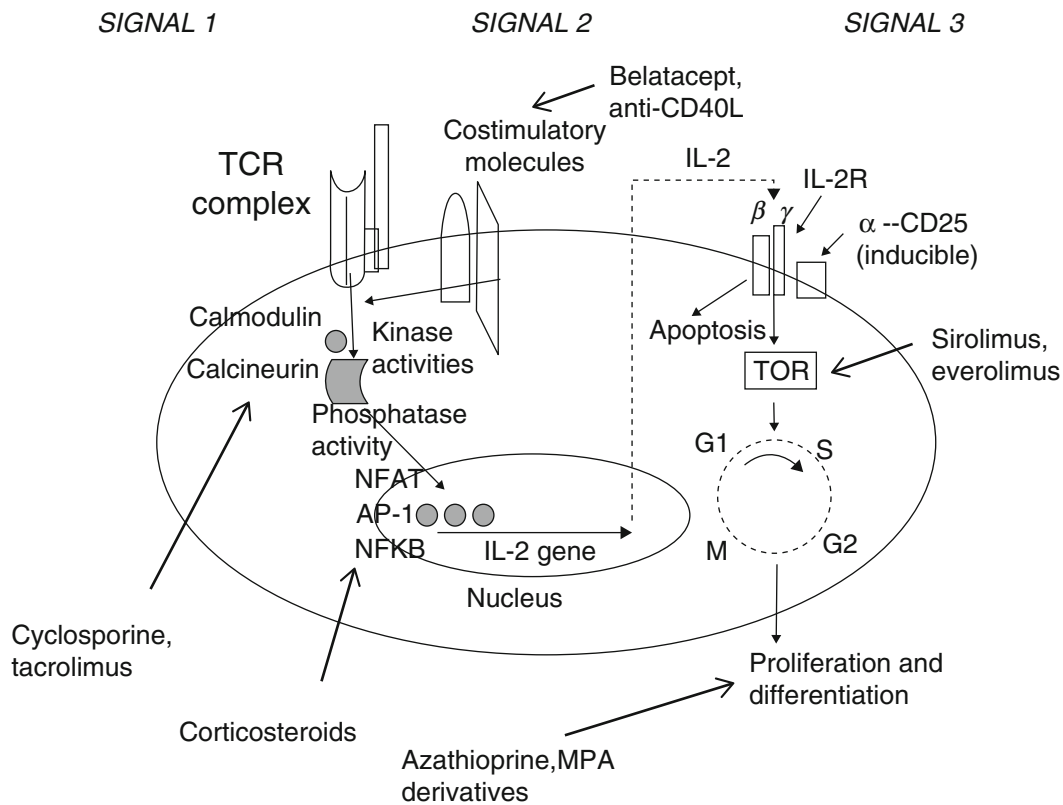


FIGURE 2-2. Schematic diagram of the three signals required for full activation and proliferation of T cells. Also shown are the sites of action of the major classes of maintenance immunosuppressive drugs. See text for details. Reprinted from Am J Kidney Dis, 65(6), Donald E. Hricik, pp. 956–66, Copyright 2015, with permission from Elsevier.

2.2.2 T Cell Activation and Differentiation

The TCR consists of two polypeptide chains, alpha and beta, that are linked to each other. The TCR is linked to another group of cell surface molecules known as CD3, a complex that consists of several covalently bound peptide chains. When the TCR binds to an MHC-presented antigen, there is a conformational change in CD3 that activates intracellular signal pathways, including tyrosine kinases located on the intracytoplasmic tails of the CD3 peptides as well as on the CD4 and CD8 accessory molecules. This antigen-driven signal, transduced by the TCR–CD3 complex to the T cell cytoplasm, has been called “signal one” (see Figure 2-2). It is essential but not sufficient alone for full activation of T cells.

A second antigen-independent signal (“signal 2”), provided through additional accessory molecules resulting in “co-stimulation” of the T cell, is necessary for full activation of the T cell [20] (see Figure 2-2). Although the family of known co-stimulatory ligands is large, the two most important are ligands between the T cell surface molecules, B28 and CD154 (CD40 ligand), and the APC surface molecules B7 and CD40, respectively. Without co-stimulation, the provision of signals through the TCR alone leads to clonal and antigen-specific anergy. The T cell does not produce cyto-

kines and does not divide, but instead becomes unresponsive to appropriate stimulation or undergoes apoptosis.

With adequate co-stimulation, T cell activation continues, and signals are transduced to the nucleus. Phosphorylation of tyrosine residues on several proteins occurs as an immediate consequence of TCR activation. The immediate effect is the appearance of newly phosphorylated tyrosine residues on a number of proteins, leading to the generation of the second messengers such as inositol 1,4,5-triphosphate (IP3) that stimulates the release of ionized calcium from intracellular stores. Released calcium interacts with the calcium-dependent regulatory protein, calmodulin. These calcium–calmodulin complexes activate other kinases and phosphatases. One of these is calcineurin, a phosphatase that plays a key role in the activation of factors required for IL-2 gene transcription.

The transcription of IL-2 and other cytokines ultimately drive cell cycle progression (“signal 3”) with help from a series of kinases, including those that act in the target-of-rapamycin (TOR) pathway (see Figure 2-2). The final results of activation are the proliferation of CD4-positive helper T cells and the maturation of CD8-positive cytotoxic T cells. Activated T cells ultimately differentiate into a number of other phenotypes including memory cells that can respond

quickly and robustly to the initially presented antigen many years after the initial presentation, and regulatory T cells that can suppress immune responses and promote tolerance.

2.2.3 Effector Mechanisms

The mammalian immune system can be divided into innate and adaptive components. *Innate immunity* is mediated by several nonpolymorphic proteins (e.g., defensins, cytokines, toll-like receptors, and complement) and cells (e.g., macrophages, dendritic cells, natural killer cells, and neutrophils) that immediately contain and eliminate infectious agents. There has been recent interest in the concept that these innate responses may interact with alloimmune mechanisms, forming a potential link between nonspecific injury (e.g., ischemia reperfusion injury or infections) and allograft rejection.

In contrast, T cells and B cells provide finely tuned specificity mediated by highly polymorphic receptors and antigen-induced clonal expansion. This *adaptive immunity* develops only days to weeks after antigen exposure. The complement system serves as an interface between innate and adaptive immunity [21]. The terminal components of complement are important effectors of graft destruction, leading to membrane injury, neutrophil infiltration, and damage to epithelial and endothelial cells. However, the complement system also is involved in T and B cell stimulation.

The Fas/Fas ligand (FasL) pathway is an important effector mechanism leading to destruction of an allograft. Fas is expressed ubiquitously on parenchymal cells, while FasL is induced upon activation of CD4-positive T cells. Cross-linking of Fas with FasL leads to activation of caspase 8 and propagation of a death signal that culminates in apoptosis.

The activation of caspase enzymes leading to irreversible cell injury with DNA fragmentation can occur independently of cell surface receptors. In addition, CD8-positive T cells express cytotoxic molecules that are lethal to cells. One of these, granzyme B, gains access to the cell by a pore structure created by perforin, another product of the CD8-positive cytotoxic T cell. Entry of granzyme B into the target cell cytoplasm ultimately leads to target cell death through apoptosis. Natural killer cells are effector cells that also produce perforin and granzyme B. In addition, they produce interferon gamma, thus promoting inflammation.

2.2.4 Role of B Cells

With the help of T cells, bone marrow-derived B cells can differentiate into plasma cells that ultimately produce antibodies specific for the original peptide antigen presented to the T cell. Several growth factors required for this differentiation have been identified recently and may ultimately serve as therapeutic targets. Mature B cells are found mainly

in lymphoid follicles, in bone marrow, and in low numbers in the circulation. Differentiated plasma cells generate antibodies that can act by fixing complement or by opsonizing cells that are then killed by cell-mediated lympholysis. As noted above, B cells also serve as excellent APCs.

Recently, alloantibodies have been identified as major effectors of both acute and chronic graft injury. Alloantibodies are primarily directed against HLA antigens. However, a number of less common alloantibodies to non-HLA antigens (e.g., endothelial or epithelial antigens) have been identified and occasionally cause graft injury. Preformed antibodies to HLA antigens most commonly occur in patients who have had previous transplants, blood transfusions, or pregnancy. Less commonly, they develop cross-reactively after exposure to vaccines, viruses, or other pathogens. Preformed anti-HLA antibodies are measured by a variety of cross-matching techniques. Mixing recipient serum with the cells or HLA antigens of a specific donor performs a donor-specific cross-match. When the serum of a potential transplant recipient is “cross-matched” with cells from a large panel of potential donors, the test is referred to as a panel of reactive antibodies (PRA). Patients with high PRA (i.e., preformed anti-HLA antibodies against a large number of potential donors) are said to be “sensitized” and generally exhibit graft outcomes that are inferior to non-sensitized patients. In theory, only donor-specific antibodies (DSAs) are responsible for graft injury [22]. Transplantation is usually avoided in patients with pre-existing DSAs. However, very low titers may escape detection by even the most sensitive of cross-matching techniques. Moreover, *de novo* DSAs develop in as many as 15 % of kidney transplant recipients during the first posttransplant year, increase in frequency with the passage of time, and are now recognized as a major cause of late graft injury and graft loss.

2.3 Types of Allograft Rejection

Allograft rejection can be classified based on clinicopathologic criteria into hyperacute, acute, and chronic forms. However, the pathologic findings obviously vary from one organ to another. This is especially true of chronic rejection which, for example, is manifested in kidney transplant recipients as some combination of interstitial fibrosis, tubular atrophy, and/or transplant glomerulopathy, in heart transplant recipients as coronary vasculopathy, and in lung transplant recipients as bronchiolitis obliterans. Lung transplantation is unique in that chronic rejection can be defined histologically but is most often diagnosed by functional parameters such as changes in forced expiratory velocity (FEV) over time. Hyperacute rejection occurs in recipients with high titers of preformed DSAs and is a rare occurrence in the era of modern, highly sensitive cross-matching techniques.

A complete description of the pathology of acute and chronic rejection in each organ is beyond the scope of this review. Pathologic scoring systems for acute rejection have been best developed in kidney [23, 24], heart [25] transplantation. For kidney transplants, use of the Banff criteria for grading rejection has become the standard of practice [23, 24]. Most centers prefer to obtain a biopsy of the organ to facilitate treatment decisions in patients with suspected rejection, although some centers do not routinely perform pancreas transplant biopsies, mostly due to concerns about bleeding. Acute forms of rejection are usually divided into cellular and humoral types, but there are sometimes components of both cellular and antibody-mediated damage in a single tissue specimen.

Cases of acute cellular rejection that are deemed to be clinically or histologically mild are often treated initially with large “pulse” doses of corticosteroids. Patients who do not respond to pulse steroid therapy and those with clinically or histologically severe rejection are treated with antilymphocyte preparations. Algorithms for treating acute antibody-mediated rejection are less well established and vary widely from center to center. Therapeutic strategies have been best defined in kidney and heart transplantation. Traditional antilymphocyte antibodies are often employed to treat antibody-mediated rejection, based on the concern for simultaneous cellular rejection. However, treatment with plasmapheresis, anti-CD20 antibodies (i.e., rituximab), and/or IVIg is now commonly used as either primary or adjunctive therapy for humoral rejection. Chapter 3 contains a more detailed discussion of drug therapy for treatment of acute rejection.

2.4 Immunosuppressive Therapy

In this section, we will focus on the mechanisms of action of commonly used classes of immunosuppressive agents, based on our understanding of how they inhibit alloimmune responses detailed in the previous section. Chapter 3 includes a more complete discussion of clinical use of these drugs.

2.4.1 Antibodies Used for Induction Therapy

In the USA, available T cell-depleting antibodies include two polyclonal agents generated in either rabbits (rabbit antithymocyte globulin, Thymoglobulin®) or horses (ATGAM®) [26]. Rabbit ATG is currently the most popular polyclonal antibody used in the USA. However, it is technically prescribed off-label for induction therapy, being approved by the Food and Drug Administration (FDA) only for the *treatment* of acute rejection. The exact mechanisms accounting for the effectiveness of rabbit ATG (or ATGAM®) are not entirely understood. These preparations include antibodies against numerous T cell markers including CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, HLA-DR, and

HLA class I heavy chains. Treatment is generally associated with profound lymphopenia. The agent is effective in suppressing the cellular immune responses against a variety of antigenic stimuli, but may be less reliable in preventing antibody-mediated acute rejection. Alemtuzumab (Campath®) is an anti-CD52 humanized monoclonal antibody that binds to all T and B lymphocytes as well as most macrophages, monocytes, and natural killer cells. It is FDA approved only for the treatment of lymphoma and is used off-label for induction therapy in transplant recipients [27]. The agent causes significant leukopenia, probably via antibody-mediated lysis of lymphocytes, resulting in T cell depletion that lasts much longer than that observed with the polyclonal agents (often detectable for more than 1 year).

The only nondepleting antibody available in the USA currently is basiliximab (Simulect®) [26]. This chimeric monoclonal antibody is directed against the α chain of the interleukin-2 (IL-2) receptor (also known as CD25). Binding to this receptor inhibits the proliferative signals normally mediated by IL-2 (see Figure 2-2) without causing profound depletion of lymphocytes.

2.4.2 Maintenance Immunosuppression

Corticosteroids have multiple effects on alloimmune pathways [28–30]. These agents alter the distribution of lymphocytes, leading to their sequestration in the reticuloendothelial system. They also inhibit the proliferation and function of lymphocytes by blocking the expression of various cytokines. In addition, corticosteroids inhibit transcription factors such as activating protein-1 (AP-1) and nuclear factor- κ B. As a consequence, these agents inhibit the production of IL-1 (a primary stimulus for helper T cell activation) and IL-6 (a major inducer of B cell activation), thus inhibiting both the cellular and humoral arms of the alloimmune response.

Calcineurin inhibitors include cyclosporine, a small cyclic polypeptide of fungal origin and tacrolimus, a macrolide antibiotic compound [31, 32]. Multiple formulations and generic version of these drugs are now available. Within the cytoplasm of the lymphocyte, cyclosporine binds to cyclophilin, while tacrolimus binds to FK-binding protein (FKBP). Both the cyclosporine-cyclophilin and tacrolimus-FKBP compounds bind to and inhibit calcineurin, preventing its normal function and thereby blocking T cell activation (see Figure 2-2). Thus the two agents are similarly efficacious in preventing rejection. However, they exert considerably different side effect profiles (see Chap. 3).

Antiproliferative agents include azathioprine and various derivatives of mycophenolic acid (MPA), including the original agent, mycophenolate mofetil, a prodrug that is metabolized to MPA. Azathioprine is a metabolite of 6-mercaptopurine. It is processed into purine analogs that inhibit both the de novo and salvage pathways of purine

synthesis. This inhibits the synthesis of RNA and DNA, thus blocking gene replication and cell proliferation [33]. MPA (derived either from mycophenolate mofetil or available as enteric-coated mycophenolate sodium) is a reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), a rate-limiting enzyme in the synthesis of purines [34]. Like azathioprine, it works by inhibiting nucleic acid synthesis. However, the effect is relatively selective for lymphocytes because IMPDH plays a preeminent role in the de novo pathway for purine synthesis and lymphocytes do not have an effective salvage pathway that is present in most other rapidly dividing cells.

TOR inhibitors include sirolimus and everolimus [35, 36]. These drugs bind to FKBP in the cytoplasm but have no effects on calcineurin and instead inhibit TOR, an important regulatory kinase that normally mediates cell cycle progression (see Figure 2-2). Inhibition of TOR affects both lymphocytes and mesenchymal cells. The TOR pathway also mediates angiogenic effects so that TOR inhibitors exhibit unique anti-angiogenic properties.

Belatacept is currently the only available *co-stimulation blocker*. The drug is fusion protein that blocks T cell co-stimulation (“signal 2”) mediated by the B7-CD28 ligand described above. As described in Chap. 3, the agent was developed largely as a replacement for calcineurin inhibitors [37].

2.5 Current Outcomes in Solid Organ Transplantation

This section will focus on the characteristics, outcomes, and long-term morbidities of solid organ transplant recipients in the United States. Most of the data comes directly from the 2013 Annual Data Report of the Organ Procurement and Transplantation Network (OPTN)/Scientific Registry of Transplant Recipients (SRTR) [38].

2.5.1 Kidney Transplantation [39]

The most common current causes of end-stage renal disease resulting in the need for kidney transplantation are diabetes mellitus (29.3 %), hypertension (21.8 %), and glomerulonephritis (18.3 %). Since 2002, the number of candidates on the deceased donor waiting list almost doubled from approximately 50,000 to 96,000 in 2013. In 2013, 16,901 kidney transplants were performed in the USA (11,448 from deceased donors and 5433 from living donors). By comparison, 15,197 transplants were performed in 2003. Despite this modest overall growth in transplant volume, living donation rates decreased almost 40 % during the same decade. Paired and other unrelated donations have increased since 2007, but not enough to compensate for the general decline in living donation. During the past decade, the number of recipients

TABLE 2-1. Donor characteristics used in calculating the kidney donor profile index (KDPI)

• Age
• Height
• Weight
• Ethnicity
• History of hypertension
• History of diabetes mellitus
• Stroke as the cause of death
• Serum creatinine
• Presence or absence of hepatitis C
• Type of donor: brain dead versus donor after cardiac death

aged 50 years or older has increased. The use of donors after cardiac death (DCD) increased from approximately 4 % of all deceased donors in 2003 to more than 15 % of deceased donors in 2013.

Until recently, allocation of kidneys from deceased donors was prioritized using a point system, with points awarded for several variables including time on the waiting list, prior organ donation, HLA matching, and sensitization based on calculated PRA levels of >80 % [40]. The allocation system was revised in December 2014. In the new system, deceased donors will be scored on a cumulative percentage scale of 0–100 % using a kidney donor profile index (KDPI) based on ten donor characteristics shown in Table 2-1 [41]. The best 20 % of kidneys (KDPI of 0–20 %) are now preferentially allocated to the best 20 % of candidates based on estimated posttransplant survival and thus will virtually always be offered to candidates under the age of 50 years. The influence of KDPI scores on 1- and 2-year allograft survival rates is depicted in Figure 2-3. More priority will be given to sensitized patients in the new system. In addition, for patients who started dialysis before being approved for wait listing, waiting time will start at the time that dialysis was initiated. The impact of these new changes in the allocation system will be scrutinized heavily in the next few years.

During the past decade, death-censored graft survival for both deceased and living donor kidney recipients steadily increased at 1, 5, and 10 years. Death-censored graft survival at 90 days posttransplant is now approximately 97 % for deceased donors and 99 % for living donors. For patients transplanted between 2007 and 2011, the cumulative 24-month incidence of a first acute rejection episode was approximately 14 % for deceased donor recipients and approximately 12 % for living donor recipients.

Trends in the major components of immunosuppression protocols since 2003 have been characterized by a steady increase in the use of T cell-depleting antibodies for induction therapy, use of tacrolimus as the preferred calcineurin inhibitor, and use of mycophenolate derivatives in favor of TOR inhibitors (see Figure 2-4). Approximately 35 % of patients are not taking corticosteroids 1 year after transplantations but the SRTR data suggests that the use of steroid-free regimens has not changed appreciably since 2007.

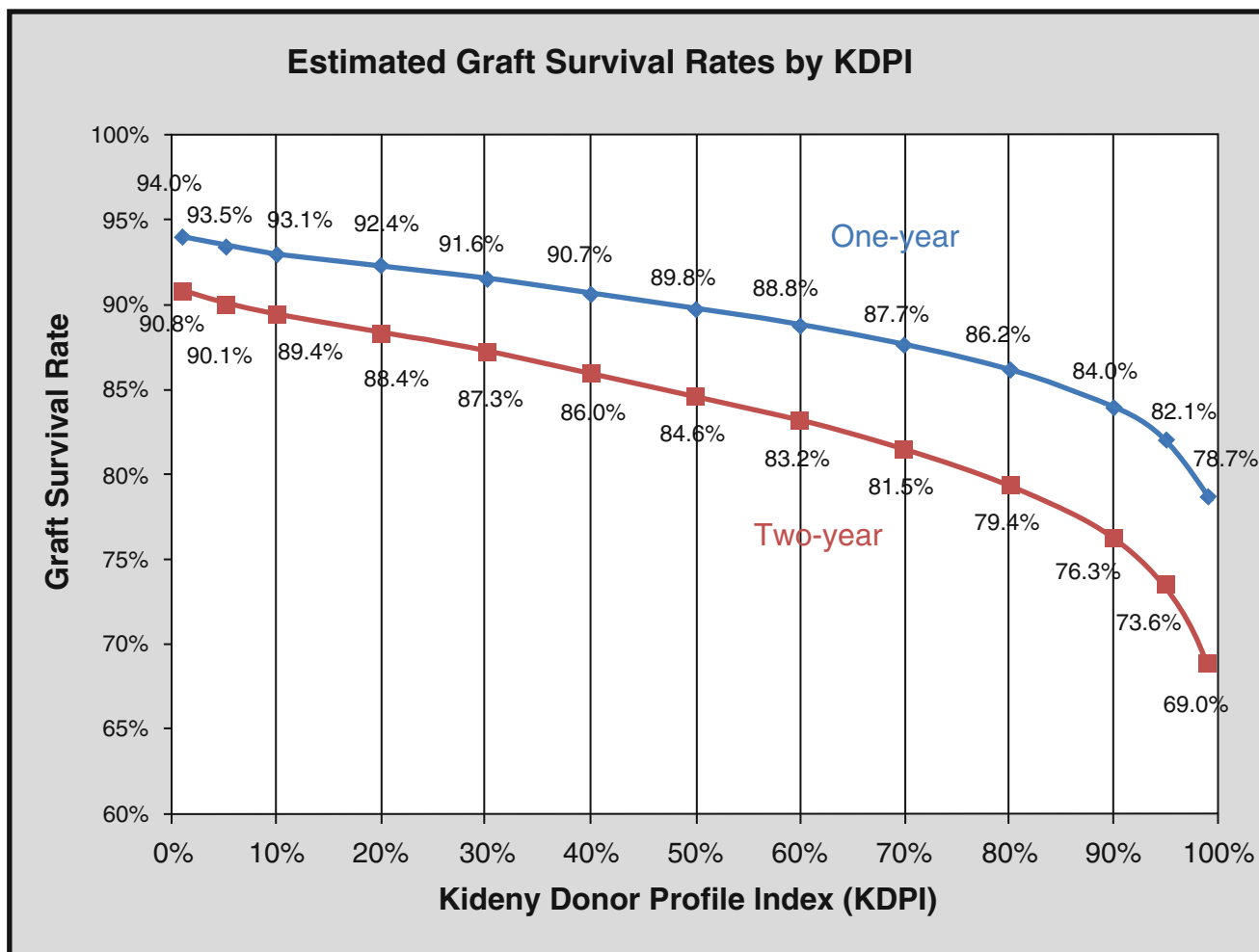


FIGURE 2-3. Influence of kidney donor profile index (KDPI) scores on 1- and 2-year graft survival rates in kidney transplant recipients. Kidney Transplantation Committee, Organ Procurement and Transplantation Network, "Proposal to Substantially Revise The National Kidney Allocation System," http://optn.transplant.hrsa.gov/PublicComment/pubcommentprosub_311.pdf. Accessed October 30, 2015.

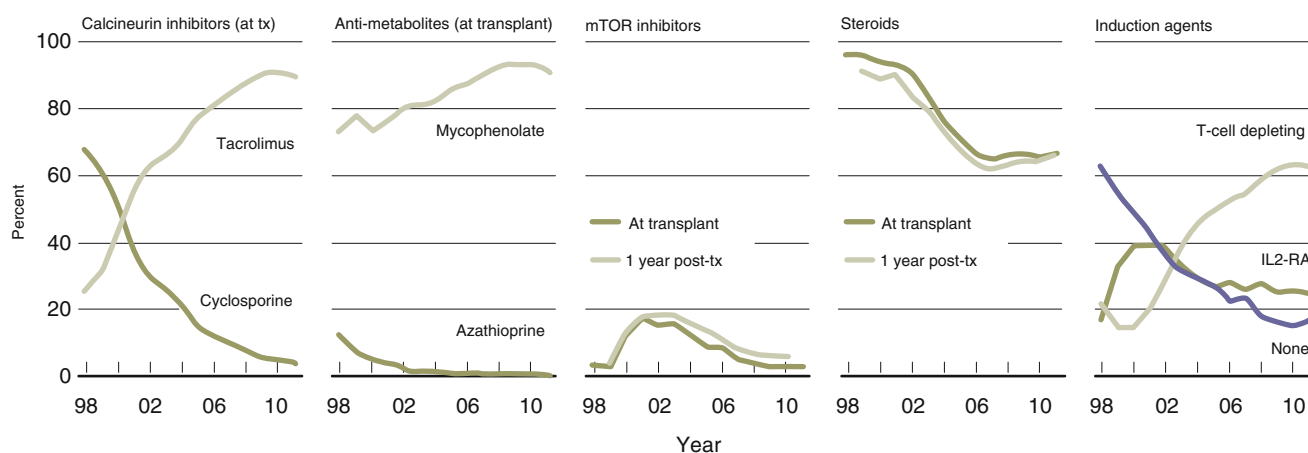


FIGURE 2-4. Trends in the use of immunosuppressant drug classes between 1998 and 2011 at the time of hospital discharge from the transplant operation (*dark lines*) and at 1 year post transplant (*light lines*). United States Renal Data System. 2014 USRDS annual data report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2014. The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government.

The incidence of new onset diabetes mellitus during the first year after kidney transplant has decreased from approximately 12% in 2005 to 5% in 2013. By 5 years posttransplant, 0.6% of adult transplant recipients have developed posttransplant lymphoproliferative disease. Renal function at 1 year has improved steadily. Currently, almost half of patients with functioning allografts at 6 months have an estimated glomerular filtration rate of 60 mL/min/1.73 m² or higher.

2.5.2 Liver Transplantation [42, 43]

Currently, the most common diseases resulting in the need for liver transplantation are hepatitis C (25%), malignancy (usually hepatocellular carcinoma, 19.4%), and alcoholic cirrhosis (18.4%). The recent availability of safe and highly effective antiviral drugs capable of treating and eradicating hepatitis C will likely change this pattern in the future. In 2013, 5921 adult liver transplants were performed in the USA, including 211 from living donors. At the end of that year, just over 15,000 candidates were registered on the waiting list for live transplants. Waitlist mortality and morbidity remain problematic in liver transplantation. In 2013, 1767 patients died while waiting for a transplant and another 1223 were removed from the list being deemed too ill to undergo the procedure. Allocation of livers continues to be driven by use of the model for end-stage liver disease (MELD) scores, using a system that assigns livers to candidates with the most advanced disease [43, 44]. The MELD score is currently based on measurements of serum creatinine, serum bilirubin, and the international normalized ratio (INR) (see Table 2-2).

The proportion of liver transplant patients receiving a simultaneous liver and kidney transplant rose from 6.7% in 2010 to 8.1% in 2013. This proportion may decrease over time as a consequence of the Share 35 policy that went into effect in the USA in 2013. That policy requires regional sharing of livers to candidates with MELD scores equal to or greater than 35. In the first several months after instituting the policy median waiting time for such patients fell dramatically from 14 months to 1.4 months [43]. The shorter waiting times may reduce the need for simultaneous kidney transplant by decreasing the frequency of prolonged hepatorenal syndrome.

By mid-2013, 59,500 US liver transplant recipients were alive with functioning grafts. Since 1991, 1-year graft sur-

vival has steadily improved from approximately 74% to approximately 90% in the most recent cohort. The use of antibodies for induction therapy in liver recipients has increased only slightly in the past decade. More than 70% of liver transplant recipients receive no induction therapy at all. Tacrolimus and mycophenolate derivatives are the most commonly used maintenance agents. Steroid withdrawal is more common after liver than after kidney transplantation. Only 40% of liver transplant patients remain on corticosteroids 1 year after transplantation. Recurrence of hepatitis C remains a problem and accounts for graft survival being poorest among the subset of liver transplant recipients with this underlying disease. Again, the recent introduction of newer antiviral agents promises to change these statistics in the next several years.

2.5.3 Pancreas Transplantation [45]

Pancreas transplantation is indicated primarily for patients with type 1 diabetes mellitus, but also for selected type 2 diabetics who are not obese, and who have relatively low insulin requirements. Virtually all pancreas transplants are recovered from deceased donors. Most commonly, pancreas transplantation is performed together with a kidney transplant in diabetic patients with end-stage renal failure (simultaneous pancreas and kidney, SPK) and less commonly is performed alone (pancreas transplant alone, PTA) or after a previous kidney transplant (pancreas after kidney, PAK) [46]. The major indication for a PTA is hypoglycemic unawareness.

The total number of pancreas transplants performed in United States has steadily decreased in the last decade. The reasons for this decline are not clear but possibly reflect relatively high rates of technical failure, surgical complications from the procedure [47], or improved outcomes with medical therapy alone for this special population. Just under 1500 total pancreas transplants were performed in 2002, dropping to just over 1000 transplants in 2013. The decline in volume has been more pronounced for SPK and PAK transplants than for PTA transplants. Historically PTAs were performed less commonly than SPKs or PAKs. Interestingly, in 2013, transplant rates for PAK and PAT were virtually equivalent but only about 100 transplants were performed in each of those categories. The allocation of pancreas transplants has traditionally been subject to regional variances. Current efforts are UNOS are aimed at creating a national pancreas allocation system in which candidates for SPK, PAK, or PTA will combine to form a single match run list [45]. If implemented, this system would assure that SPK candidates will not have to compete against nondiabetic kidney transplant candidates.

Immunosuppressive practice for recipients of pancreas transplants has changed little in the past 5 years. T cell-depleting induction was used in approximately 80% of all transplants in 2013. For maintenance, tacrolimus was used in

TABLE 2-2. Calculation of the model for end-stage liver disease (MELD) score

- MELD score = $0.957 \times \log_e(\text{serum creatinine, mg/dL})^a + 0.378 \times \log_e(\text{serum bilirubin, mg/dL}) + 1.120 \times \log_e(\text{INR}) + 0.643$
- Multiply score by 10 and round to nearest whole number. Laboratory values <1.0 are set to 1.0

^aThe maximum serum creatinine allowed in the MELD equation is 4.0 mg/dL. For patients on dialysis, the serum creatinine is automatically entered as 4.0 mg/dL

approximately 92% and mycophenolate in 90% of recipients. Steroids were used in 65% initially and in 75% of recipients at 1 year post transplant.

Due to lack of a uniform definition for pancreas transplant failure (variably defined as re-initiation of insulin, initiation of oral hypoglycemic medications, or undetectable C-peptide), the outcomes of pancreas transplant graft survival are not as standardized as those for kidney graft failure. With this limitation, graft failure rates within the first 3 months posttransplant (often described as technical losses) have decreased steadily over the past decade from 12.4% in 2002–2003 to 7.6% in 2012–2013. Rates were lowest among SPK recipients (2.5% for kidney, 4.9% for pancreas) and comparable for PTA and PAK (10.4% and 9.9%, respectively). Unadjusted actual 1- and 5-year pancreas graft survival for the transplants performed in 2008 were 74.3 and 50.6% for PTA, 85.8 and 74.3% for SPK, and 78.7 and 62.0% for PAK. It has been postulated that better graft survival for SPK compared to PAK and PTA is due to a relatively low incidence of rejection in this group and/or earlier recognition and treatment of rejection. This may reflect the presence of the kidney transplant, which is more amenable for a percutaneous biopsy than a pancreas transplant, and can be used as a surrogate marker for rejection in the pancreas.

The incidence of first acute pancreas rejection at 1 and 2 years was 22.1 and 27.8% for PTA, 16.0 and 20.4% for SPK, and 17.4 and 22.5% for PAK. Overall incidence of posttransplant lymphoproliferative disorder at 5 years was 2.6% for PTA, 1.0% for SPK, and 0.9% for PAK, and the incidence was higher among recipients negative for EBV (6.4% for PTA and 3.6% for SPK). The number of patients living with a functioning pancreas transplant has doubled between 2002 and 2013 from approximately 7000 to 14,000.

2.5.4 Heart Transplantation [48]

About 2500 heart transplants were performed in 2013, compared to 2100 in 2002. Cardiomyopathy is the most common indication for heart transplant, followed by coronary artery disease. The number of patients waiting for heart transplant steadily increased from 2800 in 2002 to 3200 in 2013. The waiting time for heart transplant overall has not changed significantly within this time period. In 2003, 14.8% of candidates spent 5 or more years on the waiting list, compared with only 5.4% in 2013. Heart transplants are allocated based on a UNOS scoring system (see Table 2-3). The proportion of candidates maintained on ventricular assist devices (VADs) at the time of wait listing increased dramatically, from 7.5% in 2003 to 27.4% in 2013. Because of steady improvements in VAD technology, some patients are maintained on these devices for long periods of time, either as a bridge or even as an alternative to transplantation [49].

More than half of heart transplants in the USA are performed without any induction agents, and the remainder are

TABLE 2-3. Heart transplant candidate listing status

UNOS waiting list status (in order of priority)	Patient/management description
1A	(a) Mechanical circulatory support, excepting VADs, ^a but including an artificial heart, extracorporeal membrane oxygenator, or intra-aortic balloon pump (b) Mechanical circulatory support within LVAD or RVAD, with complications (c) Continuous mechanical ventilation (d) Continuous infusion of high-dose intravenous inotropic agent with continuous invasive hemodynamic monitoring
1B	(a) RVAD and/or LVAD, uncomplicated (b) Continuous infusion of intravenous inotropic agent
2	Awaiting heart transplant but not meeting 1A or 1B criteria
7	Temporarily unsuitable to undergo transplantation (i.e., HOLD status)

^aVAD ventricular assist device, L left, R right.

done with either IL-2 blocking- or T cell-depleting antibodies. More than 90% of the patients are on a combination of tacrolimus, MPA derivatives, and corticosteroids. One-, 3-, and 5-year survival rates in patients who underwent heart transplant between 2006 and 2008 were 88.1%, 81.3%, and 75.3%, respectively. Survival was slightly lower for recipients with prior VADs than for those without VADs. The number of heart transplant survivors continued to increase over time with 27,120 heart transplant recipients being alive with a functioning graft in 2013.

Rejection remains an important cause of morbidity after heart transplant with a current cumulative incidence of acute rejection at 1 year of 23.6%. Rejection may be recognized more frequently in heart transplantation than in other organ transplants owing to the common practice of performing serial protocol biopsies, especially in the first posttransplant year. Cytomegalovirus (CMV) infection has been strongly linked to cardiac allograft vasculopathy [50]. The leading causes of death during year 1 posttransplant are infection, cardiovascular/cerebrovascular disease, and graft failure. After year 1, however, cardiovascular/cerebrovascular disease becomes the more common cause of death, followed by infection and graft failure.

2.5.5 Lung Transplantation [51]

Lung transplantation is being performed increasingly for critically ill patients with end-stage lung disease. Allocation of lungs is based on the lung allocation score (LAS), a scoring system introduced in 2005 [52]. Pulmonary diagnoses are categorized into to four groups for the calculation of LAS: group A, obstructive lung disease; group B, pulmonary

TABLE 2-4. Factors used in calculating the lung allocation score (LAS)

• Underlying cause of lung disease
• Age of recipient
• Body mass index
• Presence or absence of diabetes mellitus
• New York Heart Association functional status (I, II, III)
• Forced vital capacity (FEV) (percent predicted)
• Pulmonary arterial systolic pressure
• Supplemental oxygen required at rest (L/min)
• Pulmonary capillary wedge pressure
• Distance walked within 6 min
• Need for mechanical ventilation
• Serum creatinine concentration
• pCO ₂

vascular disease; group C, cystic fibrosis and immunodeficiency disorders; and group D, restrictive lung disease. The LAS system was designed to estimate waitlist mortality in a fashion that allows transplantation for compromised patients while avoiding candidates whose likelihood of survival is poor. Clinical variables used to calculate the LAS score are shown in Table 2-4. A raw allocation score is calculated based on these variables and then normalized to obtain the actual LAS, which has a range of 0–100. Higher scores indicate that the patient is more likely to benefit from a lung transplant.

In 2013, 1946 lung transplants were performed, including adult and pediatric recipients, the most ever in a single year. Bilateral lung transplantation remains the preferred procedure, accounting for approximately 70 % of lung transplants performed in 2013. In 2013, 28.7 % of all US lung recipients were aged 65 years or older, compared with 7.2 % in 2003.

Short-term survival (30-day and 1-year) and long-term survival (3-year and 5-year) have plateaued since implementation of the LAS. Overall, 5-year unadjusted patient survival was 53.6 %. Survival was consistently lowest among recipients aged 65 years or older, those with LAS greater than 60, and those in diagnosis group B. Fifty percent of lung transplants currently are performed without any induction antibody therapy. Tacrolimus and mycophenolate derivatives are the preferred agents for maintenance immunosuppression and are being used in more than 90 % of lung recipients. Almost all patients are on steroids at 1 year post transplant. About 20 % and 40 % of the patients experience first acute rejection by 12 and 24 months post transplant, respectively. About 2 % of patients develop PTLTD by 5 years of posttransplant with incidence up to 6 % for patients who are serologically negative for EBV at the time of transplantation.

2.5.6 Intestinal Transplantation [53]

Improvement in the medical and surgical treatment of patients with intestinal failure has resulted in a recent decrease in the

number of intestinal transplantations being performed in the USA. Short-gut syndrome remains to be the most common indication. More than half the transplants are actually combined intestine-liver transplants. The number of intestine transplants decreased from 91 in 2009 to 51 in 2013. The number of intestine-liver transplants steadily decreased from a peak of 135 in 2007 to a low of 44 in 2012, but increased slightly to 58 in 2013.

Graft survival for intestine transplants has improved over the past decade. Graft failure in the first 90 days posttransplant occurred in 14.1 % of intestine recipients and in 11.2 % of intestine-liver recipients in 2013. The graft failure rate was 24.5 % at 1 year for transplants performed between 2011 and 2012, 43.6 % at 3 years for transplants performed between 2009 and 2010, 48.5 % at 5 years for those performed between 2007 and 2008, and 68.4 % at 10 years for transplants performed between 2001 and 2002.

For induction therapy in 2013, 54 % of intestine transplant recipients received T cell-depleting agents, 11 % received IL-2 receptor antagonists, and 38 % received no induction. The initial immunosuppression agents used most commonly in 2013 were tacrolimus (95.0 %), steroids (73.0 %), mycophenolate (35.0 %), and mammalian TOR inhibitors (15.0 %). Steroids were used in 70.0 % of recipients at 1 year posttransplant. Acute rejection occurred in 35–40 % of patients at 12 months and in approximately 50 % at 24 months.

For patients who underwent intestine transplantation between 2001 and 2011, 9.9 % of intestine recipients and 6.8 % of intestine-liver recipients developed PTLTD within 5 years posttransplant. The incidence was highest among recipients who were negative for EBV: 12.5 % of EBV-negative intestine recipients and 8.2 % of EBV-negative intestine-liver recipients.

2.6 The Future of Solid Organ Transplantation: Strategies for Achieving Tolerance

A long-standing goal in the field of solid organ transplantation is to induce immunologic tolerance to the graft such that the host's immune system can respond normally to immune stimuli without immunosuppression and with the specific absence of a detrimental immune response directed at the transplanted organ. Studies in animal models suggest that tolerance to an allograft can be achieved under a variety of conditions including elimination of the donor-reactive immune cells (deletion), induction of immunologic ignorance (the immune system fails to recognize transplant antigens), induction of anergy, or active inhibition by regulatory T cells [54]. True immunologic tolerance has been achieved in human kidney transplant recipients when a bone marrow transplant has been performed between HLA identical donors, followed by a kidney transplant using the same

donor. Based on these experiments of nature several groups have attempted to use bone marrow ablation, either marrow or stem cell transplantation, and adjunctive combinations of early immunosuppression in an effort to achieve at least “operational” tolerance [55–57].

Tregs suppress immune responses, potentially via local cytokine production and through prevention of dendritic cell activation. The recent recognition of multiple Treg phenotypes, including those that are CD25+ CD4+ Foxp3+, as well as newly developed methods for inducing Treg expansion in vitro and in vivo, has excited the transplant community [58, 59]. While only limited success has thus far been achieved toward developing human allograft tolerance in humans, multiple groups are studying whether and how Tregs can be exploited to prolong graft survival and potentially induce robust allograft tolerance.

2.7 Summary

The field of solid organ transplantation has advanced considerably in the past half century, based largely on improved understanding of the mechanisms of allograft rejection and the parallel development of effective immunosuppressive drugs. Currently available immunosuppressive drugs are not completely effective in preventing or treating allograft rejection. Moreover, long-term treatment with these agents is associated with toxicities including infection and malignancy—topics that will be covered in detail elsewhere in this book. Thus, organ transplantation remains an imperfect modality. Effective strategies for creating true immune tolerance might allow organ transplantation without the use of immunosuppressive drugs. However, a breakthrough of that kind would only partially offset the most important limitation in the field: a continued shortage of organ donors.

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