Chapter 3
What Is Transplant Immunology and Why Are Allografts Rejected?

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Chapter Overview

This chapter focuses on how a transplanted organ is recognized by the recipient's immune system and how an allograft is rejected. It is important to understand fundamentals of immunology in order to better apply immunosuppressive strategies. Understanding how the recipient immune system recognizes the donor organ will also make it apparent to the reader that there are "holes" in our current immunosuppressive therapy. Many basic science laboratories are working to fill the "holes" and new immunosuppressive approaches are likely to be available in the future. While the focus of this chapter is on kidney transplant rejection, basic immunologic mechanisms of rejection are similar between all transplanted organs. Chapter 9 describes the optimal prescription of immunosuppressive medications.

The immunologic events relevant to solid organ transplantation are described in a temporal manner sequentially following the processes of donor harvest, anastomosis of the donor and recipient vessels, and the recipient immune response to the transplanted organ. Long-term immunologic responses that correlate with chronic rejection are also described, as is the concept of immunologic tolerance. Illustrations are provided that correlate with the processes described in the text.

Donor Harvest

The Donor Kidney Is Comprised of Immune Cells That Are Activated by Ischemia

The process of donor harvest involves a highly skilled team of professionals assembled to optimally remove organs from either a deceased or a living donor and pass on

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D.B. McKay, S.M. Steinberg (eds.), *Kidney Transplantation: A Guide to the Care of Kidney Transplant Recipients*, DOI 10.1007/978-1-4419-1690-7_3,

the “gift of life.” The harvest team works with vigorous attention to surgical detail (as described in Chapter 2 and 7), a key to subsequent organ function. Another key for excellent graft function involves attention to the immunologic events that initiate during the process of donor kidney harvest and transplantation.

The donor kidney is comprised not only of glomeruli, tubular cells, mesangium, and endothelium but also of resident immune cells such as dendritic cells,[1] as seen in the schematic in Fig. 3.1. Dendritic cells are specialized phagocytes found in the interstitial spaces of most tissues of the body that are easily activated to engulf fragments of damaged tissue and pathogens. Resident dendritic cells are usually dormant, but they acquire phagocytic ability and mobility upon the slightest injury to the kidney, even before the donor organ is transplanted into the recipient.[2,3]

One of the major ways resident dendritic cells become activated is through low blood flow to the kidney. In the case of a deceased donor, brain death plays a major role because it is characterized by rapid swings in blood pressure; an early hypertensive phase is followed by a hypotensive phase.[4] The rapid swings in blood

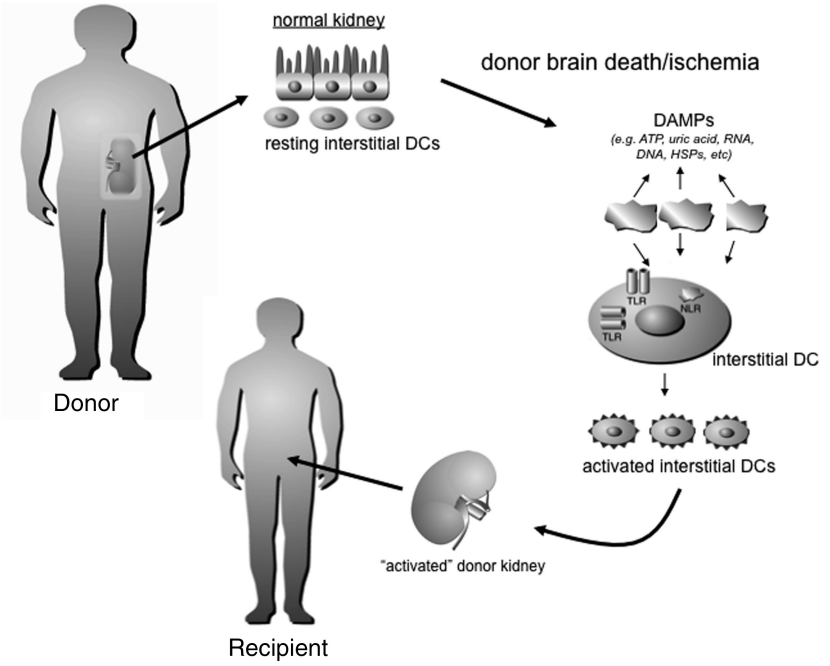

Fig. 3.1 Immunologic events within the donor kidney at the time of donor harvest. In response to ischemia/anoxia, cells within the donor kidney die and spill their intracellular contents into the tissue milieu. Included in the spilled contents are danger-activated molecules (DAMPs). DAMPs activate interstitial resident dendritic cells by binding to innate immune receptors on their cell surface (toll-like receptors, TLRs) or within the cytoplasm (TLRs and non-toll-like receptors, NLRs). By the time the donor kidney is transplanted into the recipient it is highly activated

pressure result from a catecholamine-induced autonomic storm. In animal models, brain death is accompanied by a massive cytokine storm that activates not only immune cells in the kidney but also parenchymal cells such as endothelium and tubular epithelial cells.[5] The donor kidney is thus highly "activated" even before removal of the deceased donor graft. Making the situation worse, the process of removing the kidney, from either a live or a deceased donor, unavoidably involves interruption of the organ's blood supply and frank anoxia of the organ, heightening the "activated" state of the donor organ.

Ischemia/Anoxia-Induced Death of Kidney Cells Results in the Release of Intracellular Contents and Activation of Donor Innate Immune Cells

The immune events associated with transplantation begin with ischemia/anoxia-induced death of donor kidney cells (Fig. 3.1). Ischemic cells spill their intracellular contents into the tissue milieu. The intracellular contents that are released from dead and dying cells contain immunologically active molecules called damage-activated molecular patterns (DAMPs).[6] The name "molecular patterns" refers to the fact that the molecules have structural similarity; it is the common molecular structure that defines the DAMPs. Examples of DAMPs are heat-shock proteins, ATP, uric acid, RNA, DNA, as well as proteins derived from the extracellular matrix including hyaluronan fragments and heparin sulfate proteoglycans.

Epithelial, mesenchymal, and endothelial cells within the donor kidney contain receptors for DAMPs. The DAMP receptors are located either on cell surfaces or within the cytoplasm of most cell types and provide a means for cells to rapidly respond to "danger" in their environment. Several families of these receptors have been identified including toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs).[7–9]

It is important to mention TLRs and NLRs because they are thought to trigger the immune events that cause acute rejection. Ligation of the TLRs or NLRs sets off a biochemical signaling pathway that induces inflammatory signals (cytokines/chemokines), cell death pathways, upregulation of costimulatory molecules, and upregulation of other cellular molecules that trigger cell activation.[10] The inflammatory cytokines and chemokines that are produced from the DAMP/TLR/NLR interactions are very strong attractants for recipient inflammatory cells. Thus, the greater the ischemic damage to the donor organ, the more the DAMP/TLR/NLR signaling, the more inflammatory signals are presented to the recipient at the time of transplantation, and the greater the activation of the recipient's immune system. Precise identification of putative DAMPs and understanding how they are regulated under conditions of ischemia is a major focus of investigation in basic science laboratories and within the pharmaceutical industry. It is likely that blockade of DAMP molecules or their receptors (TLRs and/or NLRs) will provide a significant new direction for preemptive immune suppression.

Over the past few years it has become clear that rejection of a transplanted organ involves not only T cells and B cells but also an entire system of immunologic defense that is rapidly activated and distinguished from cellular acute rejection. This newly identified *Innate Immune System* plays an essential role in the earliest events associated with rejection. Cells of the mammalian innate immune system are exquisitely sensitive to molecules released from injured tissue and microbial products. In the case of a transplanted organ, the innate immune system triggers the adaptive immune system leading to cellular rejection.[11] Our current immunosuppressive medications are targeted to cells of the adaptive immune system. As yet, we have no therapies that specifically target the innate immune system. Table 3.1 shows basic differences between the innate and the adaptive immune systems.

Table 3.1 Innate vs. adaptive immune systems

Components	Innate	Adaptive
Physical components	Skin, mucosa, epithelium (e.g., urinary tract epithelium, respiratory epithelium)	None
Cellular components	Dendritic cells, macrophages, neutrophils, mast cells, natural killer cells	T cells B cells
Activation stimulus	"Nonspecific stimuli" molecules (e.g., DAMPs, PAMPs)	"Specific stimuli" (e.g., alloantigen)
Response Time	**Hours** →	**Days**

Anastomosis of Donor and Recipient Vessels

Activation of the Recipient's Adaptive Immune Response Begins with Anastomosis of the Donor and Recipient Vessels

As soon as the donor and recipient blood vessels are connected, several important things occur. First, the recipient is exposed to a torrent of DAMPs/cytokines/chemokines derived from the ischemic donor organ. In response, the recipient's innate immune cells (such as neutrophils, natural killer cells, and macrophages) vigorously infiltrate the donor tissue and add to the ischemia-induced tissue injury.[12,13] Another thing that happens, almost simultaneously, is that activated donor dendritic cells migrate out of the graft to T-cell-rich regions of recipient lymph nodes where they encounter naive recipient T cells.[14,15] Dendritic cells and T cells are highly motile and, within lymph nodes, interact with each other in a dynamic, hectic, panoply.[16,17] The lymph node is comprised of multiple filaments that provide scaffolding for dendritic cells and T cells and structural stability for their interactions. The encounter between donor dendritic cells and recipient T cells is the key initiating event of cellular rejection. A schematic of these events is shown in Fig. 3.2.

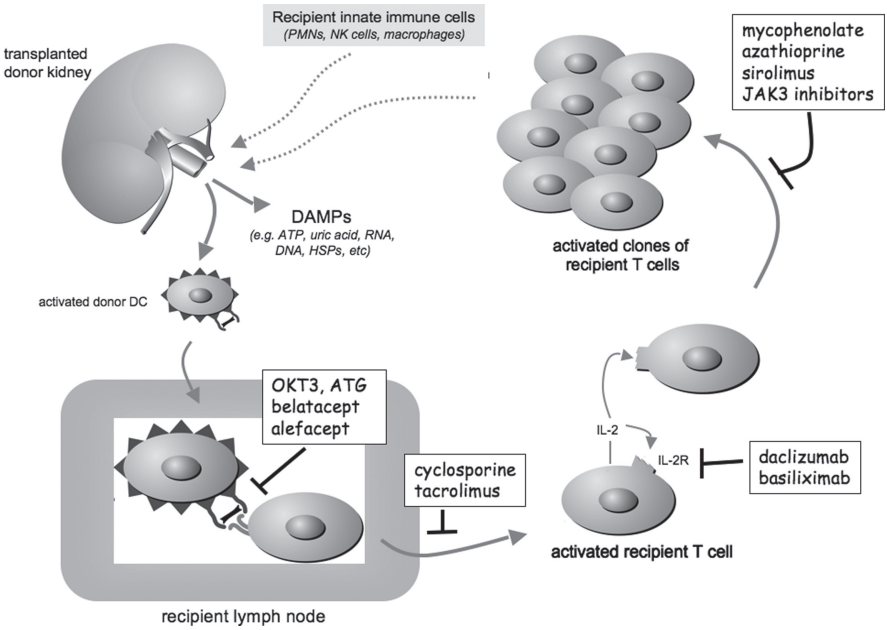

Fig. 3.2 Activation of the recipient adaptive immune system following transplantation. The recipient's immune system is activated rapidly following anastomosis of donor and recipient vessels. As soon as the vessels are connected, DAMPs/cytokines/chemokines as well as activated dendritic cells from the donor organ infuse into the recipient circulation. In response recipient innate immune cells are attracted to the donor organ and vigorously infiltrate the graft, worsening the damage induced by ischemia/anoxia. Donor dendritic cells migrate from the allograft to recipient lymph nodes, where they encounter recipient T cells. Engagement of donor dendritic cells with recipient T cells results in activation of the T cells, leading to their maturation. The activated T cells express IL-2 receptors on their surface and secrete IL-2. IL-2 then acts on the IL-2Rs to cause the T cells to undergo division and produce clones of T cells that participate in the rejection response. The process is blocked at several stages by immunosuppressive medications, as indicated. Corticosteroids act at multiple sites in the cascade as well as on innate immune responses

Interaction of Donor Dendritic Cells with T Cells – How the Recipient Becomes Aware of the Foreign Donor Kidney

Donor dendritic cells and recipient T cells contact each other within lymph nodes. The two cell types engage each other using cell surface receptors – the human leukocyte antigen (HLA) molecule on the dendritic cell and T-cell receptor (TCR) of the T cell. Each of these receptors is a sophisticated molecular complex.

The T-cell receptor (TCR) is comprised of two chains (an alpha chain and a beta chain) and several associated molecules called the CD3 chains.[18] The CD3 chains are the target for OKT3, an antibody that has been used in the past to prevent rejection and to treat severe episodes of rejection.

The HLA molecules are highly polymorphic, allowing presentation of a diverse number of "foreign" peptides. The foreign peptides are derived from the allograft. Each cell simultaneously expresses many different HLA molecule/foreign peptide complexes, which provide great complexity to the system. As described in Chapter 4, two kinds of HLA molecules are important in transplantation, HLA class I and class II molecules. HLA class I molecules can be found on all nucleated cells in the body, whereas HLA class II molecules are found on antigen-presenting cells (such as dendritic cells, macrophages, B cells, endothelial cells, and even some epithelial cells).

Foreign proteins can be presented by HLA molecules to either CD4 T cells or CD8 T cells. If the foreign protein is adjoined to HLA class II molecules it will be presented to CD4 T cells. On the other hand, if adjoined to HLA class I molecules, it will be presented to CD8 T cells. Both CD4 and CD8 T cells participate in the rejection process. The T cells discriminate between "self" (antigens of the recipient) and "nonself" (antigens of the donor) based on the "foreignness" of the HLA/peptide complex that is presented to them.[19]

Recipient Immune Response to Transplanted Organ

Formation of the Immunologic Synapse – Target of Costimulatory and Adhesion Molecule Blockers (Belatacept and Alefacept)

As soon as the dendritic cell HLA/peptide complex engages the T-cell receptor, several cell surface molecules coalesce at the junction between the two cell types and form what is called an "immunologic synapse"[20] (shown schematically in Fig. 3.3). Included in the synapse are the juxtaposed T cell (TCR and associated CD3 molecules) and dendritic cell (HLA/peptide complex). Additional molecules coalesce in the synapse, including costimulatory and adhesion molecules. These molecules bind with their complementary ligand (one on the T cell and one on the dendritic cell) and provide important "go" signals to the T cell. The immunologic synapse needs to be formed in order for the T cell to receive the proper combination of activation signals.

Within minutes of immunologic synapse assembly, profound biochemical signaling events are initiated within the T cell.[21] The biochemical events are "tuned" by the length of time the T cell stays in contact with the HLA/peptide complex. If a greater disparity exists between the HLA molecules of the donor and the HLA molecules of the recipient (e.g., a complete HLA mismatch between the donor and the recipient) then the cells stay in contact for a longer period of time. This longer contact time results in more robust signaling within the T cell. Two new immunosuppressive agents in clinical trials in transplant recipients are aimed at disrupting the normal signaling events that occur with this contact – belatacept ($CTLA_4Ig$ fusion protein)[22,23] and alefacept (anti-CD2 antibody).[24]

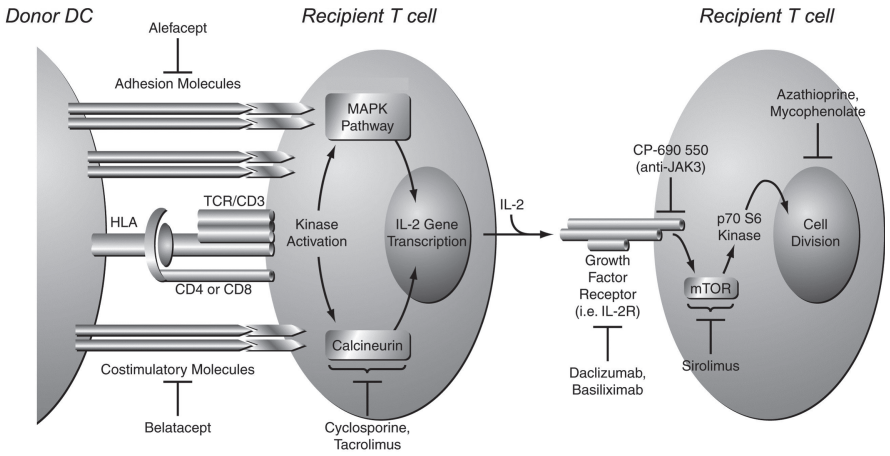

Fig. 3.3 T-cell signaling events that occur upon engagement of the donor dendritic cells. Upon donor dendritic cell/recipient T-cell engagement the immunologic synapse is formed, which consists of donor HLA molecules, recipient TCR and CD4 or CD8 molecules, costimulatory molecules, and adhesion molecules. Following immunologic synapse formation, the T cell is activated through two intracellular signaling pathways. One pathway leads to activation of calcineurin and the other to activation of mitogen-activated protein kinases (MAPKs). The end result is IL-2 gene transcription. Cyclosporine and tacrolimus block one limb of the activation, the calcineurin pathway. The MAPK pathway is not completely blocked by either cyclosporine or tacrolimus and therefore T-cell signaling still occurs. IL-2 acts on IL-2R on T cells causing the activation of mTOR, allowing the cell to progress through the cell cycle, ultimately promoting cell division. Sirolimus blocks mTOR, thereby interfering with cell division

T-Cell Receptor-Mediated Signaling Events – Target of Calcineurin Inhibitors (Cyclosporine and Tacrolimus)

Within seconds of immunological synapse assembly, several molecules are brought into close proximity on the surface of the T cell. This "closeness" results in the activation of cytoplasmic enzymes called kinases that transfer phosphate groups between adjacent molecules. The transfer of phosphate groups sets off a chain reaction that results in the sequential activation of molecules within the cytoplasm of the T cell.[25] The activated cytoplasmic molecules comprise defined molecular cascades that lead to transmission of the signal from the cell surface to the nucleus. Once the signal reaches the nucleus, genes are transcribed that lead to the secretion of cytokines, such as interleukin 2, and trigger entry of the T cell into cell cycle, causing it to divide. The T cell that divides in response to the donor DC is highly specific to the donor HLA/peptide complex, and so when the T cell divides it produces clones of T cells with specificity to the donor DC peptide. Current immunosuppressive strategies are designed to block the biochemical events in T cells before this stage. Failure to block this stage is akin to allowing the formation of massive numbers of ballistic missiles directed to a unified target. Once the button is pushed, it is very hard to stop the destructive salvo.

Several immunosuppressive medications have been developed that target early stages of T-cell activation (Fig. 3.2). Most potent are the calcineurin inhibitors, cyclosporine and tacrolimus.[26] These molecules bind to a carrier protein that is present in many tissues and therefore calcineurin inhibitors affect not only T cells but also many other cells in the body. Cyclosporine binds to cytoplasmic carrier proteins called cyclophilins and tacrolimus binds to cytoplasmic FK-binding proteins (FKBPs). There are several isoforms of both cyclophilins and FKBPs; their relative amounts vary between tissues and account for the tissue-specific toxicities. The relative toxicities and efficacy of these two types of calcineurin inhibitors are discussed in Chapter 9. A new strategy is to target protein kinase C isoforms with small molecule inhibitors. AEB071 or sotrastaurin is one such PKC inhibitor in clinical trials in renal transplant recipients.

T-Cell Activation: Cytokine Production – Target of Anti-IL-2 Receptor Blockers [Daclizumab (Zenapax®) and Basiliximab (Simulect®)] and the JAK3 Inhibitor CP-690 550

Once the T cell is activated through the T-cell receptor it manufacturers and secretes cytokines, such as interleukin 2 (IL-2) (Fig. 3.3). Once secreted, the cytokines act on receptors that are present on their own T cells (autocrine stimulation) as well as other T cells (paracrine stimulation). Interleukin-2 is a prototype for the cytokine-induced signaling of T cells. After secretion, IL-2 binds to a receptor (called the IL-2R) on the surface of T cells and activates three different cytoplasmic signaling cascades: the mitogen-activated protein (MAP) kinase pathway, the phosphoinositide 3-kinase (PI3K) pathway, and the Janus kinase/signal transducers and activators of transcription protein pathway (JAK/STAT).[27] These three pathways regulate various functions of the cells, such as gene transcription, cell division, cell survival, and cell death. A pharmacologic approach to inhibiting one limb of this pathway (the JAK/STAT pathway) is currently in clinical trials in transplantation using the JAK3 inhibitor CP-690 550.[24] Another strategy to block the cytokine signaling pathway has been to prevent the cytokine (IL-2) from interacting with its receptor. Two monoclonal antibodies have been widely used for this purpose – daclizumab and basiliximab.[28]

T-Cell Division: Target of Azathioprine, Mycophenolate, and Sirolimus

Once the T cell receives a "go" signal, through cytokine receptor-mediated signaling, it begins to make the proteins needed to undergo DNA replication. The biochemical signaling events that culminate in cell cycle progression are complex and are induced by many different signals besides IL-2. One of the steps common to many of the stimuli that induce the T cell to divide is a molecule called

mTOR (mammalian target of rapamycin). This molecule is blocked by sirolimus, which is a potent immunosuppressive medication now commonly used for maintenance immunosuppression.[29] Sirolimus binds to a cytoplasmic carrier protein called FKBP12 that is similar to the carrier protein for FK506 (tacrolimus) and is also present in many cell types. Since blockade of cell cycling is so potent, several other mTOR inhibitors have been developed and are either approved for therapeutic use or are currently in clinical studies, including Everolimus, Temsirolimus, and Zotarolimus. Temsirolimus is used for treatment of renal cell carcinoma,[30] while the others are approved for organ transplant rejection and coronary artery restenosis. Since cell division is so dependent on mTOR, the use of mTOR inhibitors in pregnant women is probably contraindicated due to concerns regarding their effect on the developing fetus.[31]

Azathioprine and mycophenolate mofetil also target the cell cycle, but at a later stage than sirolimus.[32] Azathioprine is a purine synthesis inhibitor. Purines are biochemically significant components of RNA, DNA, ATP, GTP, AMP, NADH, and coenzyme A. Mycophenolic acid is available as the prodrug mycophenolate mofetil (CellCept) or mycophenolate sodium (Myfortic). The way that mycophenolate works is that it inhibits inosine monophosphate dehydrogenase, the enzyme that controls the rate of synthesis of guanine monophosphate, a nucleotide important to synthesis of RNA. Since azathioprine and mycophenolate mofetil effectively block cell division, they have been a mainstay of maintenance immunosuppressive regimens for many years.

Corticosteroids also have several anti-inflammatory effects and therefore it is difficult to attribute a single effect to their efficacy. Steroids affect both innate and adaptive immune responses by altering the trafficking of neutrophils, decreasing phagocytosis by macrophages and dendritic cells, and directly affecting T-cell proliferation, activation, and differentiation.[33] Therefore, withdrawal of steroids might be risky because steroids play such an important role in suppressing multiple limbs of the immune response.

Effectors of Rejection – The Adaptive Immune System

The traditional cells that we associate with acute rejection (T cells and B cells) are part of the *Adaptive Immune System*, and to clarify nomenclature they will be described below.

T cells

T cells are white blood cells produced in the thymus (thus the designation "T") that divide rapidly and play a primary role in the cellular immune response seen in acute cellular rejection. T cells have a specialized cell surface receptor that is a highly sophisticated molecular complex called the T-cell receptor (TCR).

There are different types of T cells, such as T helper cells (also called CD4 T cells), T cytotoxic cells (also called CD8 T cells), memory T cells, and gamma delta T cells. The CD4 or CD8 molecules are coreceptor molecules that strengthen the contact between CD4 T cells with HLA class II molecules or CD8 T cells with HLA class I molecules. HLA molecules are discussed briefly above and also in Chapter 4. The following is a brief description of the basic types of T cells:

T helper cells: T helper cells (CD4 T cells) rapidly divide upon exposure to foreign proteins into various subsets (Th1, Th2, Th3, Th17, ThF) that secrete different cytokines.[34] Cytokines are messengers of the immune response and, in the case of graft rejection, they function to recruit the army of recipient immune cells aimed at destruction of the foreign allograft.

Cytotoxic T cells: Cytotoxic T cells (CD8 T cells) also divide rapidly upon exposure to foreign proteins. When activated, cytotoxic T cells directly destroy target cells by releasing cytotoxins such as perforin and granzyme. Perforins form pores in the target cell membranes and granzymes enter the target cell and destroy the cell from within.[35] Cytotoxic T cells play a role in graft rejection as well as destruction of virally infected tissue.

Memory T cells: Memory T cells are either helper T cells or cytotoxic T cells and they respond rapidly to foreign antigens. Whether memory T cells differentiate linearly or in parallel with the helper and cytotoxic T cells is not yet known. Nevertheless, memory T cells survive in an inactive state in the host for long periods of time after the initial exposure to foreign antigen. If the host is reexposed to the same foreign proteins, memory T cells will quickly expand and mount an aggressive response. This phenomenon is the basis for immunologic memory and it is the reason that prior exposure to transplanted organs or multiple blood transfusions (which also exposes the recipient T cells to foreign antigen) results in an enhanced immune response that is difficult to control.[36]

Regulatory T cells: Regulatory T cells are also seen in the helper and cytotoxic T cell lineages and they play an important role in the immune response to a transplanted organ. Formerly known as suppressor T cells, these specialized T cells function to shut down cell-mediated immunity toward the end of an immune response.[37] Experimental strategies in rodents have shown that expanding regulatory T cells during the rejection response can control allograft rejection, although reliable clinical strategies in humans to expand regulatory T cells are not yet available.[38]

Gamma delta T cells: Gamma delta T cells are a specialized type of T cell, with a unique type of T-cell receptor that does not play a direct role in graft rejection. These cells are found in the gut mucosa and skin and are important for wound healing.[39] Their effective suppression by sirolimus might be a reason that there is a high incidence of wound healing defects with the use of sirolimus.[40]

B Cells

B cells are another type of leukocyte, which produces antibodies in response to foreign proteins. B cells are formed in the bone marrow and play a primary role in the humoral immune response. The primary role of B cells is to produce antibodies in response to antigens, to act as antigen-presenting cells, and to develop into memory B cells. Like T cells, B cells have a functional cell surface receptor (called the B-cell receptor, or BCR) that allows them to "recognize" foreign antigens.[41] Unlike T cells they do not have to have the antigen "presented" to them in a processed form, but rather they can recognize foreign antigens in a soluble form in the blood or lymph. To become fully functional B cells need signals from T helper cells that direct them to either become a plasma cell capable of producing antibodies or a memory cell capable of a vigorous response upon re-exposure to foreign antigens.[41]

Donor-Specific Antibodies (DSAs)

Plasma cells can produce antibodies against HLA antigens and nonHLA antigens that may or may not be specific to the donor [endothelial antigens such as MHC class I polypeptide-related sequence A or B (MICA and MICB) antigens, smooth muscle cell antigens such as vimentin, and cell surface receptors such as the type 1 angiotensin II receptor (AT1R)].[42–45] It is difficult to detect these antibodies before transplantation as they often develop against antigens that are only expressed with tissue injury. DSAs are now measured in the clinic to detect reactivity of the recipient B cells against the donor antigens. If the titer of specific DSAs rises, it suggests inadequate immunosuppression and several therapeutic options, including plasmaphaersis, thymogoblulin, intravenous immune globulin (IVIG), and anti-CD20 antibody (rixtuximab), can be attempted.[46] Emerging therapies include proteosome inhibitors such as bortezomib.[47,48] It is important to address donor-specific antibodies because antibody deposition results in complement fixation, which triggers lysis of donor kidney cells through the membrane attack complex as well as by NK cells and macrophages. Several studies have suggested that antibodies to recipient HLA antigens and to endothelial antigens may be a driver of not only acute antibody-mediated rejection (AMR) but also chronic rejection.[49,50]

Acute Cellular vs. Humoral Rejection

Older concepts of acute rejection have considered T cells to be responsible for acute cellular rejection and B cells responsible for humoral rejection, but this is a simplistic view as both cell types as well as cells (e.g., neutrophils, NK cells, macrophages,

and dendritic cells) and molecules (e.g., DAMPs) of the innate immune system harmonize in a unified quest to reject the foreign tissue. The pathologic features of acute cellular and humoral rejection are discussed in Chapter 12.

After Transplantation: The Later Phase Months to Years Later

Chronic Allograft Dysfunction, Chronic Allograft Nephropathy

All allografts are eventually lost to a process that involves variable contributions from immunologic and nonimmunologic factors. Several theories have evolved to explain the immunology of chronic allograft dysfunction/nephropathy.[51] One theory is that there is an insidious recipient immune response to the antigens of the donor, manifest as a slow decline in allograft function over time. The immunologic response can come from recipient dendritic cells engulfing and processing donor peptides and presenting these to recipient T cells (indirect presentation), from chronic recipient B-cell activation (producing antidonor-specific antibodies), as well as by endothelial activation and vascular fibrosis. Additional contributions likely come from direct medication toxicities (e.g., calcineurin inhibitors) or chronic viral infections (e.g., BK virus). Clinical data have clearly shown that we have not yet solved the problem of chronic rejection. Whether chronic immune activation plays a major role is unknown at this time. Several pharmacologic strategies have been employed, including minimization of calcineurin inhibitors and use of alternative medications such as sirolimus, in lieu of calcineurin inhibitors.

The Concept of Immunological Tolerance

The goal of tolerance is the holy grail of transplantation. Tolerance is strictly defined as immunologic unresponsiveness to a particular antigen, while retaining the ability to respond to another antigen. Immunologic tolerance is demonstrated by immunologic unresponsiveness to a transplanted organ of one donor, followed by adequate immunologic responses to a second genetically unrelated donor. Usually the test of "true tolerance" involves transplantation of second graft from the original donor and a third-party graft onto the recipient to demonstrate that the second graft is not rejected, while the third-party graft is rejected. Tolerance is obviously difficult to test for in humans, but it has been achieved and validated in animal models. At this time there are no clinically acceptable methods to induce acceptance of the donor graft by the recipient without the continued use of immunosuppressive medications. Two clinical studies have suggested that the recipient's immune system can be taught to accept the transplanted organ as its own using extensive initial induction therapy and a bone marrow transplant.[52,53]

At this time, tolerance has not yet been reliably achieved clinically and therefore it is important to maintain adequate immunosuppression. Even a brief lapse in

immunosuppressive medication dosing allows the recipient's immune response to become active and to respond again to donor antigens. The donor antigens do not change, they are always there, and the recipient's immune response always needs to be suppressed to prevent a reaction to the antigens (see the discussion of nonadherence in Chapter 22). The recipients' immune response will never accept the allograft as its own and there will forever be a simmering battle that can easily expand when there is a lapse in immunosuppressive medications.

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Kidney Transplantation: A Guide to the Care of Kidney Transplant Recipients

McKay, D.B.; Steinberg, S.M. (Eds.)

2010, XIV, 407 p. 44 illus., 13 illus. in color., Softcover
ISBN: 978-1-4419-1689-1