Immunology of Liver Transplantation

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Abstract

In comparison with other solid-organ transplants, liver allografts are immunologically privileged. Allografts are rejected by immune reactions of the host, and clinical therapy for liver allografts includes immunosuppression to prevent rejection. Orthotopic liver transplant causes systemic donor-specific T-cell tolerance. In addition, antigens introduced into hepatocytes or the portal vein cause tolerance. The basic mechanism in liver tolerance may include continuous exposure of diverse liver cell types to endotoxin derived from intestinal bacteria. This exposure promotes the expression of cytokines, antigen-presenting molecules, and costimulatory signals that inactivate T cells, partly by effects on liver antigen-presenting cells. A simple, reliable, noninvasive assay to evaluate antidonor alloreactivity may be important in implementing these approaches in the laboratory and clinic.

Key words: Antigen-presenting cells, Endotoxin, Hepatocyte, Rejection, T cell

Introduction

During the past 4 decades, liver transplant has evolved from a procedure with high mortality and morbidity to a successful therapy for end-stage liver disease. Current survival for elective liver transplant may be > 85% to 88% at 1 year and 70% to 75% at 5 years, and patients may have an excellent quality of life.\(^1\)

In comparison with other solid-organ transplants, liver allografts are immunologically privileged. Liver transplants have no hyperacute rejection despite a positive T-cell crossmatch, a low incidence of graft loss caused by chronic rejection, and the potential for hepatocyte regeneration after tissue injury. Nevertheless, destructive immunologic processes may occur, and acute liver allograft rejection may occur in 50% to 75% liver transplant recipients. Immunosuppressive drugs may cause major toxic effects that increase morbidity and mortality. In addition, current immunosuppressive regimens do not prevent chronic rejection, which is a major cause of graft loss.\(^2\)

Furthermore, various idiopathic autoimmune diseases target the liver, such as primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis.\(^3\) Therefore, liver transplant is complex, and the transplanted liver may have a paradoxical interaction with the host immune system. The immunologic reactions after liver transplant are important, may explain the clinical features of rejection, and may facilitate early diagnosis and appropriate treatment.

Allograft Rejection and Immunology

Liver transplant grafts originate from people who have varied immunologic characteristics. The genetically encoded, immunologically mediated barrier to transplant was recognized and defined during the previous century. Immunologic research has been important in the development of clinical transplant. Graft rejection is very complicated and may be caused by transplant antigens including major and minor histocompatibility antigens.

Allografts and cell-mediated rejection

Antibody-mediated, hyperacute vasculitic rejection after liver transplant can occur in people who have preformed antibodies against the donor major histocompatibility complex class I antigens. Acute
Allograft rejection usually is initiated by the many recipient T cells that recognize donor alloantigens. 6 In the T-cell–dependent pathway to rejection, the graft alloantigens are processed by specialized antigen-presenting cells. The molecules of the major histocompatibility complex of the graft are internalized by donor and recipient antigen-presenting cells. After intracellular processing, the major histocompatibility complex peptide fragments are presented to the recipient T cells. 7

Acute cellular rejection is the best characterized graft-specific type of immune rejection, and is defined by sudden deterioration in allograft function. Biopsy of the transplanted tissue shows infiltration by host T cells and other mononuclear leukocytes, and there are signs of damage to the graft by these infiltrating cells. Both CD4 and CD8 T cells participate in acute rejection, but the rejection response is mediated primarily by CD4 T cells that are activated by direct and indirect pathways. 8 The cells of the innate immune system, such as natural killer (NK) cells, also are present in allografts during rejection. The NK cells can recognize alloantigens because they constitutively express inhibitory receptors that are specific for self-antigens of the major histocompatibility complex class I. In addition, cytokines secreted by activated CD4 or CD8 T cells can activate NK cells that may initiate and promote rejection. 9

The killer immunoglobulinlike receptor 2D subtype (KIR2D) NK cells may be underrepresented in recipients before liver transplant and may recover after liver transplant. 10 In patients who have human leukocyte antigen (HLA) C allotypes C2/C2 and who have early acute rejection, the late recovery of KIR2D+ NK cells may be associated with acute rejection. 10 However, the early increase in KIR2D+CD8+ cells may be associated with successful graft outcome. 10 Therefore, the monitoring of KIR2D+ cells and determination of HLA-C genotype may be useful in liver transplant follow-up and may help determine which patients may have a lower risk of acute rejection.

Allografts and humoral rejection

The production of antidonor major histocompatibility complex antibodies is associated with acute and chronic graft damage from graft vasculopathy. Donor-specific antibodies may damage the graft by activating complement and mononuclear cells with Fc receptors that recognize the heavy chain of antibodies. Antidonor antibodies also may inhibit signaling cascades directly within endothelial cells. 11 Humoral rejection of allografts may be observed after kidney, heart, and lung transplant, but liver allografts usually recover. Most transplanted organs have insidious and progressive dysfunction. This process previously had been termed chronic rejection, but donor-specific immune rejection may not be the only or primary cause. 12

In 1000 liver transplant patients in 1 center during 20 years, most (95%) of the 39 patients who had rejection had antibodies before rejection, but 41% concurrently transplanted control liver transplant patients had antibodies and survived. 13 Therefore, liver transplants were not exceptional. 14 The liver allograft may be partially resistant to antibody-mediated damage, but high levels of antibodies against donor-specific antigens may be associated with worse outcomes and may be a risk factor for graft dysfunction. 15

Allografts and memory T-cell–mediated rejection

Memory T cells may be divided into central memory and effector memory subsets, based on their circulation pattern and functional responsiveness. After repeat exposure to donor antigens, donor-reactive memory T cells may be more sensitive to antigens, function more rapidly, produce effector cytokines, survive longer than unexposed T cells, and directly or indirectly produce cytolytic effects on the transplanted tissue. 16,17 After continuous exposure to foreign antigens, memory T cells accumulate and comprise 50% total T cells in adults. 18 In addition, donor-reactive memory T cells may be generated in the absence of alloantigen exposure by heterologous immunity; memory T cells may be primed by antigenic peptides from pathogens that may cross-react with allogeneic peptides of the donor major histocompatibility complex. Therefore, alloreactive T cells that have no previous graft exposure may acquire a memory phenotype and may include donor-reactive memory T cells after transplant, even when the recipient is receiving immunosuppressive therapy. Memory T cells may be efficient at mediating allograft rejection because they may
generate effector immune responses rapidly upon repeat challenge.19,20

**Costimulatory pathways**

Optimal activation of T cells occurs after the cells receive 2 distinct and coordinated signals. The first signal is provided by the T-cell receptor, which may recognize peptides of the major histocompatibility complex I or II on antigen-presenting cells. The second signal is provided by the interaction of costimulatory molecules on the T cells and ligands on antigen-presenting cells. The importance of costimulation was demonstrated in experimental models. Inhibition may occur when 1 signal, in the absence of the second signal, causes T-cell anergy; the T cells may recognize cognate antigens with the T-cell receptor but may fail to mount a functional response upon repeat encounter with the antigen.

The 2 costimulatory pathways that are important in the generation of a complete T-cell response include CD28/B7 and CD40/CD154. The CD28 pathway has been intensively investigated. The CD28 antigen is a prototypical costimulatory molecule. In humans, CD28 is expressed on 90% CD4 T cells and 50% CD8 T cells. In addition, ligands for CD28, including B7-1 (CD80) and B7-2 (CD86), are present on various antigen-presenting cells including dendritic cells, B cells, and macrophages.21 The CD80 antigen is expressed only sporadically on normal liver cells but may be present on 25% Kupffer cells in 45% transplanted livers. The CD86 antigen is observed on most Kupffer cells in all transplanted liver and normal liver tissue. The effects of ligation of CD28 by CD80 or CD86 may include increased cytokine synthesis, cell proliferation, and intracellular signaling. Immunohistochemical analysis of the expression of CD86 in biopsies of liver transplant recipients has shown increased expression of CD86 in the graft during severe acute cellular rejection.22

The CD40/CD154 costimulatory pathway also is important in the immune response of allotransplant. The CD40 antigen is expressed primarily on antigen-presenting cells, but it also may be expressed on nonimmune cells including endothelial cells, mast cells, platelets, and epithelial cells. However, CD154 is expressed primarily on CD4 T cells after activation, NK cells, B cells, and CD8 T cells. The CD154 antigen combines with CD40, which is important for the activation of dendritic cells, B cells, and macrophages. The CD40 antigen up-regulates the production of interleukin 12 in dendritic cells and causes the production of various proinflammatory cytokines in macrophages. The CD154 antigen also is detected on Kupffer cells and sinusoidal macrophages in the liver during chronic rejection but not in stable liver allografts or the normal liver.23

The CD28/B7 interactions frequently are measured with cytotoxic T-lymphocyte antigen (CTLA) immunoglobulin (Ig). In an orthotopic rat liver transplant model, repeated administration of CTLA-Ig and donor splenocytes causes extended graft survival > 100 days, but the delayed administration of CTLA4-Ig (alone or with donor splenocytes) does not cause graft survival.24 Cross-linking B7 on antigen-presenting cells with CTLA4-Ig may induce indoleamine 2,3-dioxygenase, which may inhibit local T-cell activation.25,26

The CD154/CD40 interaction may promote dendritic cell maturation in the absence of CD4+CD25+ regulatory lymphocytes because dendritic cells promote the maintenance of immaturity.27,28 This interaction may explain the importance of the activation of dendritic cells by innate immune mechanisms and activated T cells. Therefore, CTLA4-Ig and anti-CD154 may be beneficial in preclinical models of transplant, but clinical application in liver transplant is not established.

**Mechanisms of Allograft Rejection**

Liver allograft rejection is the rejection of the liver transplant by the recipient (host-versus-graft reaction).29 Graft rejection may be hyperacute, acute, or chronic (Table 1).

<table>
<thead>
<tr>
<th>Type of Rejection</th>
<th>Time After Transplant</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Minutes to hours</td>
<td>Pre-existing antidonor antibodies and complement</td>
</tr>
<tr>
<td>Acute</td>
<td>Days to weeks</td>
<td>Primary activation of T cells</td>
</tr>
<tr>
<td>Chronic</td>
<td>Months to years</td>
<td>Antibodies, Slow cellular reactions, Immune complexes, Recurrence of disease</td>
</tr>
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**Hyperacute rejection**

Hyperacute rejection is rare after liver transplant and occurs within minutes to hours after the anastomosis is made between host and graft blood vessels. Hyperacute rejection is mediated by pre-existing antibodies that are specific to the graft antigens,
including ABO blood type, HLA, and vascular endothelial cell antigens. These different antigens may activate complement in the host and cause damage to endothelial cells. The pathologic changes of hyperacute rejection include thrombotic occlusion of the graft vessels, ischemia, denaturation, and necrosis.

**Acute rejection**

Acute rejection after liver transplant is rare and occurs from several days to 3 months after transplant. The pathologic features of acute rejection include acute vasculitis, parenchymal cell necrosis, and infiltration of lymphocytes and macrophages. It has been difficult to determine the participation of, and relation between, specific effector pathways during acute liver transplant rejection. However, acute rejection is mediated by humoral and/or cellular mechanisms. Antibodies may injure the graft by activating complement and mononuclear cells, and Fc receptors may recognize alloantigens on the endothelial cell and cause vasculitis.

The CD8+ cells alone are sufficient to cause acute allograft rejection. In addition, CD4+ cells may secrete cytokines such as interleukin 2 and express cytotoxic molecules. The Fas ligand pathway may be important in various hepatic problems, and this pathway is active during liver allograft rejection. Delayed hypersensitivity also is important in acute rejection and is initiated by alloantigen-primed CD4+ cells that are specific to the donor class II antigens. Repeat exposure to specific alloantigens may cause CD4+ cells to release the proinflammatory cytokine interferon γ, that may activate macrophages and the release of various inflammatory mediators. These inflammatory mediators may augment the cellular antigraft response or cause direct tissue damage.

**Chronic rejection**

Chronic rejection is an indolent but progressive allograft injury that usually is irreversible and causes failure of most vascularized solid-organ allografts. It is the most important obstacle to morbidity-free long-term survival. Within 5 years after transplant, chronic rejection occurs in 30% to 50% heart, lung, pancreas, and kidney allograft recipients but only 4% to 8% liver transplant recipients.

Liver allografts differ from other solid-organ transplants because chronic rejection after liver transplant potentially is reversible. This feature of liver transplant has been attributed to the unique immunologic privilege and regenerative capacity of the liver. Liver transplants that have chronic rejection have a decreased number of bile ducts (vanishing duct syndrome). Chronic rejection also is characterized by vasculopathy, fibrosis, and progressive loss of organ function.

**Prevention of Allograft Rejection**

Allograft rejection is prevented by graft selection before transplant, including matching for ABO blood group and HLA type. Most liver transplant centers use blood group compatibility as the primary immunologic selection criterion. It is feasible to obtain a donor liver that has compatible ABO and Rh blood groups, even in urgent situations. Many transplant centers also perform liver transplant with ABO-incompatible grafts, and the outcomes of ABO-incompatible liver transplants are similar to outcomes with blood-type-matched transplants in some centers. However, infection is a major cause of morbidity and mortality after ABO-incompatible liver transplant. At present, liver transplant from ABO-compatible but not ABO-identical donors is common, especially for recipients that have less common blood groups. The results of ABO-identical grafts are slightly better than the ABO-compatible but ABO-nonidentical grafts. Allograft rejection is an occasional complication after ABO-compatible, ABO-nonidentical liver transplant because of the immunocompetent passenger lymphocytes within the transplanted liver that may produce antibodies against the recipient erythrocytes.

Kidney transplant in patients that have a positive crossmatch for donor-specific cytotoxic antibodies have rapid graft loss. However, this may not occur after liver transplant. In addition, the major histocompatibility complex antigens are important in kidney transplant, but the liver may be a privileged organ with minimal rejection. Some liver grafts may survive without immunosuppression. Therefore, some surgeons have not used HLA matching in patient selection for liver transplant, especially when there is a shortage of donors. Retrospective data have not shown any clear survival advantage associated with close HLA matching, and there may be a disadvantage with some aspects of HLA matching. In > 500 liver transplants, overall graft
survival was reduced in grafts matched for HLA. Development of rejection and allograft survival are not improved by close matching for HLA antigens, and poorer HLA matching may favor graft survival and may be associated with a decreased incidence of rejection, especially with HLA-A locus matching. The immunologic features of liver transplant are complex. Allograft tolerance has been established in experimental models, but further developments are needed to improve clinical tolerance in liver transplant.

References