Transplantation immunology: Solid organ and bone marrow

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Development of the field of organ and tissue transplantation has accelerated remarkably since the human MHC was discovered in 1967. Matching of donor and recipient for MHC antigens has been shown to have a significant positive effect on graft acceptance. The roles of the different components of the immune system involved in the tolerance or rejection of grafts and in graft-versus-host disease have been clarified. These components include antibodies, antigen-presenting cells, helper and cytotoxic T-cell subsets, immune cell-surface molecules, signaling mechanisms, and cytokines. The development of pharmacologic and biological agents that interfere with the alloimmune response has had a crucial role in the success of organ transplantation. Combinations of these agents work synergistically, leading to lower doses of immunosuppressive drugs and reduced toxicity. Reports of significant numbers of successful solid-organ transplantations include those of the kidneys, liver, heart, and lung. The use of bone marrow transplantation for hematologic diseases, particularly hematologic malignancies and primary immunodeficiencies, has become the treatment of choice in many of these conditions. Other sources of hematopoietic stem cells are also being used, and diverse immunosuppressive drug regimens of reduced intensity are being proposed to circumvent the mortality associated with the toxicity of these drugs. Gene therapy to correct inherited diseases by means of infusion of gene-modified autologous hematopoietic stem cells has shown efficacy in 2 forms of severe combined immunodeficiency, providing an alternative to allogeneic tissue transplantation. (J Allergy Clin Immunol 2010;125:S324-35.)

Key words: *Bone marrow transplantation, solid-organ transplantation, graft rejection, graft-versus-host disease*

Abbreviations used
ADA: Adenosine deaminase
ALG: Antilymphocyte globulin
APC: Antigen-presenting cell
ATG: Antithymocyte globulin
CGD: Chronic granulomatous disease
GVHD: Graft-versus-host disease
IL-2R: IL-2 receptor
SCID: Severe combined immunodeficiency

Efforts to transplant organs or tissues from one human subject to another had been unsuccessful for many decades until the discovery of the human MHC in 1967.[1] Identification of this genetic region launched the field of clinical organ and tissue transplantation. In 1968, the World Health Organization Nomenclature Committee designated that the leukocyte antigens controlled by the closely linked genes of the human MHC be named HLA (for human leukocyte antigen). This chapter reviews general immunologic concepts that have supported the success of human organ and tissue transplantation and summarizes current medical progress in the field of transplantation medicine.

TRANSPLANTATION ANTIGENS

MHC

Histocompatibility antigens are tissue cell-surface antigens capable of inducing an immune response in a genetically dissimilar (allogeneic) recipient, resulting in the rejection of the tissues or cells bearing those antigens. The genes that encode these antigens reside in the MHC region on the short arm of human chromosome 6 (Fig 1). The HLA complex contains more than 200 genes, more than 40 of which encode leukocyte antigens.[2,3] These genes and their encoded cell-surface and soluble protein products are divided into 3 classes (I, II, and III) on the basis of their tissue distribution, structure, and function.[3-5] MHC class I and II genes encode codominantly expressed HLA cell-surface antigens, and class III genes encode several components of the complement system, all of which share important roles in immune function.

Class I MHC antigens are present on all nucleated cells and are each composed of a 45-kd α heavy chain encoded by genes of the HLA-A, HLA-B, or HLA-C loci on chromosome 6 and associated noncovalently with a 12-kd protein, β_2-microglobulin, encoded by a gene on chromosome 15 (Fig 2).[3] MHC class II antigens have a more limited tissue distribution and are expressed only on B lymphocytes, activated T lymphocytes, monocytes, macrophages, Langerhans cells, dendritic cells, endothelium, and epithelial cells.[5] Each is a heterodimer composed of noncovalently associated α and β chains of approximately 230 amino acids encoded by genes of the HLA-D region (Fig 2). On cells expressing both class I and class II HLA antigens, there are 3 class I antigens and 3 or more (usually 4) class II heterodimers.

Class III genes are located between the HLA-B and HLA-D loci and determine the structure of 3 components of the complement system: C2, C4, and factor B.[3,4] HLA antigens are inherited in a Mendelian dominant manner. Because of the closeness of the different loci of the MHC and the resultant low crossover frequency, however, HLA genes are almost always inherited

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together. To date, 3756 different class I and II HLA gene alleles have been identified.[2] The fixed combination of these genetic determinants present in 1 chromosome of a subject is referred to as a haplotype. Chromosome 6 is an autosome, and therefore all subjects have 2 HLA haplotypes (1 for each chromosome), and there are only 4 possible combinations of haplotypes among the offspring of any 2 parents. Thus there is a 25% probability that biological siblings will have identical HLA alleles.

The ABO system

ABO incompatibility does not cause stimulation in mixed leukocyte cultures, indicating that ABO compatibility is of much less importance than HLA compatibility in graft survival. However, ABO incompatibility can result in hyperacute rejection of primarily vascularized grafts, such as those of the kidney and heart.[6] This is thought to occur because (1) ABO blood group antigens are highly expressed on kidney and cardiac grafts, particularly those from patients who are blood group A or B antigen secretors, and (2) preformed naturally occurring antibodies to blood group substances are present in mismatched recipients. Advances in immunosuppressive therapies to prevent immune rejection of the graft have more recently allowed performance of organ transplantations across the ABO barrier.[7]

Donor-recipient HLA matching

Two laboratory methods are used to pair donors and recipients for transplantation. The first matching method involves the determination of HLA antigens on donor and recipient leukocytes by using either serologic or DNA-typing methods. The second method is functional and involves the measurement of the response of immunocompetent cells from the recipient to antigens present on donor cells (and *vice versa* for bone marrow transplantation). Results of both methods are generally consistent with each other. Disparities that are serologically detected are referred to as antigen mismatches, whereas differences that can be identified only by DNA-based typing are called allele mismatches. Because these methods take considerable time to perform, results are not known in time for some solid-organ transplantations, such as lung transplantations, which are performed based on immediate organ availability. Since 2000, the National Donor Matching Program performs HLA typing of donor volunteers exclusively using a DNA-based method, the PCR single-strand oligonucleotide probe. Currently, approximately 60% of volunteer donors on the National Donor Matching Program Registry had their HLA types determined by using this method. Efforts continue to improve the efficiency of HLA typing and to reduce the costs of the assays.[8]

Donor-recipient serologic cross-matching

Serologic cross-matching is of particular importance to the success of primarily vascularized grafts, such as those of the kidney and heart. Serum from the prospective recipient is tested against cells from the potential donor for the presence of antibodies to red blood cell or HLA antigens. The presence of such antibodies correlates with hyperacute renal graft rejection.[6] For this reason, a positive serologic cross-match result has been considered a contraindication to renal transplantation, although therapeutic strategies, such as the use of plasmapheresis, are proposed when the mismatch cannot be avoided.[7]

Usefulness of HLA typing in clinical organ and tissue transplantation

Although typing for intrafamilial transplants of all types is clearly of great value, the usefulness of HLA typing in cadaveric kidney grafting has been a point of controversy since cyclosporine became available.[9] Although short-term survival rates did not appear to be that different for closely or poorly matched cadaveric kidneys, the degree of HLA matching does correlate with long-term survival.[10] Until 1980, only HLA-identical siblings could be used as bone marrow donors because both graft rejection and lethal graft-versus-host disease (GVHD) were common complications if this was not the case.[11] Fortunately, the development during the past 3 decades of techniques to rigorously deplete post-thymic T cells from donor marrow has permitted numerous successful half-HLA-matched marrow transplantations with no or minimal GVHD.[12,13]

MECHANISMS OF GRAFT REJECTION

Role of alloimmune antibodies

The strongest evidence for a role for antibodies in graft rejection is the hyperacute rejection of primarily vascularized organs, such as the kidney and heart. High titers of antidonor antibodies can be demonstrated in recipients presenting with these reactions.[6] These antibodies combine with HLA antigens on endothelial cells, with subsequent complement fixation and accumulation of polymorphonuclear cells. Endothelial damage then occurs, probably as a result of enzymes released from polymorphonuclear leukocytes; platelets then accumulate, thrombi develop, and the result is renal cortical necrosis or myocardial infarction.[14]

Leukocytes and cytokines in graft rejection

Allograft rejection results from the coordinated activation of alloreactive T cells and antigen-presenting cells (APCs). Although acute rejection is a T cell–dependent process, the destruction of the allograft results from a broad array of effector immune mechanisms. Cell-cell interactions and the release by primed T_H cells of multiple types of cytokines (IL-2, IL-4, IL-5, IL-7, IL-10, IL-15, TNF-α, and IFN-γ) recruit not only immunocompetent donor-specific $CD4^+$ T cells, $CD8^+$ cytotoxic T cells, and antibody-forming B cells but also nonspecific inflammatory cells, which constitute the majority of cells infiltrating an allograft.[15] Other cells specific to the transplanted organ might play a role in the balance of tolerance and rejection, such as the Kupffer cells and the sinusoidal epithelial cells in the liver.[16]

Stimulation of $CD4^+$ T cells through their antigen receptors is not sufficient to initiate T-cell activation unless costimulation is provided by interaction of other ligand-receptor pairs present on the surfaces of T cells and APCs during the encounter. Some of these interactive pairs include the T-cell surface molecule CD2 and its ligand CD58 on APCs, CD11a/CD18-CD54, CD5-CD72, CD40 ligand–CD40, and CD28–CD80 or CD86. $CD4^+$ T-cell anergy or tolerance induction occurs when the T-cell receptor interacts with the APC unless signals are provided through 1 or more of these receptor-ligand interactions (particularly through CD40 ligand–CD40 and CD28–CD80 or CD86) or by cytokines (eg, IL-1 and IL-6 from the APC). Thus T-cell accessory proteins and their ligands on APCs are target molecules for antirejection therapy.[17,18] If costimulation does occur, the $CD4^+$ T cell becomes activated, which leads to stable