Cardiac transplantation today is an established and effective treatment for cardiac failure of many different causes with dilated cardiomyopathy and ischemic heart disease constituting by far the most frequent indications (about 40% each). Worldwide, there have been more than 31,000 heart transplants performed to date and several thousand combined heart and lung transplants. The introduction of new immunosuppressive agents since the 1970s, beginning with cyclosporine, has helped to increase the success rate of clinical heart transplantation to current 1- and 5-year survival rates of 90% and 60%, respectively. Nevertheless, rejection of the heart allograft, a potentially devastating response of the host immune system to transplanted tissue, remains a challenge in the quest for optimal management of transplant recipients. In the year 2000, acute transplant rejection still constitutes the leading cause of graft failure and recipient death during the first postoperative year. Chronic immunologic responses appear to be the cause of the occlusive long-term vascular changes in the cardiac transplant, variously referred to as graft arteriosclerosis, chronic rejection, or transplant vasculopathy, and now pose the most serious limitation to long-term graft and patient survival. Both acute and chronic transplant rejection represent highly complex immunologic processes, involving many components of the human immune system. In this review we will describe the various mechanisms of rejection mediated by the adaptive (antigen-specific) immune system, emphasizing human data over findings in experimental animals.

DEFINITIONS

In immunologic terms, routine clinical cardiac transplantation represents the situation of allotransplantation.

Allografts are tissues or organs transferred between genetically different members of the same species (ie, from one human individual to another), unless they are identical twins. Cells of allogeneic grafts express allelic, non-self variants of proteins encoded by various genes. Human proteins that are recognized as foreign by the recipient immune system are called alloantigens. Structural differences among allelic forms of these genes or among the proteins that they encode are referred to as polymorphisms. The following terms denote other forms of transplants.

Autograft: Tissue or organ transferred from one body site to another in the same individual as in skin or muscle grafts for burns or reconstructive surgery. No immune reaction (rejection) is elicited by autografts.

Isograft: Tissue or organ transferred between genetically identical individuals (ie, between human identical twins involving living related [partial] organ donations or bone marrow stem cells). Isografts (also known as syngrafts) are also not subject to rejection.

Xenograft: Tissue or organ transferred between members of different species (eg, pig to human), constituting maximal genetic disparity. Xenografts are usually rejected very rapidly (hours) by preformed natural antibodies against certain blood group determinants. Recent progress in protecting pig organs against this antibody-mediated destruction by genetic engineering has fueled the increasing research that is aimed at making pig-human xenotransplantation of kidneys and hearts a clinical reality. However, because of its experimental status and limited clinical experience, xenotransplantation will not be discussed in detail here.

COMPONENTS OF THE ALLOIMMUNE RESPONSE

Here we provide a brief overview of cells and molecules involved in graft rejection. The interplay among these components during allograft rejection will be described in more detail in a later section.

Transplantation Antigens

The alloantigens that are primarily responsible for the rejection of allogeneic tissues are also referred to as
histocompatibility (or tissue compatibility) antigens and are encoded by histocompatibility genes. Overall, more than 30 histocompatibility gene loci have been identified to date. Depending on the strength and rate with which these antigens elicit graft rejection, they are separated into major and minor histocompatibility genes/antigens. In human beings, the major histocompatibility antigens are known as human leukocyte antigens (HLAs), which are encoded in a large highly polymorphic genetic region on chromosome 6 termed the major histocompatibility complex (MHC). By molecular structure and genetic organization, human HLA antigens can broadly be subdivided into 2 classes: Class I molecules include the 3 classical polymorphic transplantation antigens HLA-A, HLA-B, and HLA-C as well as MHC-encoded class I-like molecules HLA-F, G, H, and J. Each class I molecule contains a 44 kd α transmembrane or heavy chain, a non-MHC encoded 12 kd β or light chain (also known as β2-microglobulin), and a short (9-11 amino acids) peptide derived from the intracellular protein pool, which is bound in a specific binding groove formed by folding of the α chain. The α chains are highly polymorphic, and these polymorphisms are clustered in the regions of the molecule that form the peptide binding groove and determine which peptides can bind to a particular allele of the α chain. In addition, α chain polymorphic amino acid residues, along with the bound peptide, also contribute to specific recognition of class I molecules by the antigen receptor on T lymphocytes as will be described below. Class I molecules are expressed on almost all nucleated cells, hematopoietic, or parenchymal, however, at varying expression levels.

HLA-DR is the most relevant antigen of HLA class II molecules, other surface-expressed antigens being HLA-DP and DQ. Class II molecules are composed of 2 MHC-encoded noncovalently associated transmembrane polypeptide chains (α/β), each about 30 to 35 kd. These chains fold to form a specific binding cleft for short peptides, which in this case are derived from ingested exogenous proteins. The overall structure of class II molecules resembles that of class I molecules but the peptide binding groove of class II molecules is open at its ends and can accommodate somewhat longer peptides. In HLA-DR molecules, only the β chain is polymorphic, whereas in DQ and DP molecules, both chains are polymorphic. As with class I molecules, class II polymorphisms determine which peptides may bind and, along with the bound peptide, contribute to T-cell recognition. Cellular expression of class II molecules is far more restricted than that of class I molecules, being largely confined to cells of hematopoietic lineage, vascular endothelial cells, or cells after activation with inflammatory stimuli.

As we have noted, the genes encoding HLA class I and II antigens display enormous polymorphism (more than any other human genetic loci); the different alleles have been given numerical designations (e.g., HLA-A2, B27, DR4), which in case of class I antigens reach well beyond 50 identified alleles per gene. The complete set of HLA alleles on each chromosome is also called an MHC haplotype. Because of the close genetic proximity and nonrandom coherence during meiosis (linkage disequilibrium), these haplotypes are usually inherited unaltered and codominantly expressed in the offspring. As a consequence, all individuals express HLA alleles of 2 haplotypes (1 maternal, 1 paternal). For the purposes of clinical organ transplantation, the 3 major class I antigens HLA-A, B, and C and the class II antigen HLA-DR are the most relevant; the allelic make-up of an individual can be determined by various methods of tissue typing and is eventually expressed by the formal numeric designation required for tissue matching and entry into organ distribution databases (e.g., HLA-A2/A7, B3/B27, C7/C12, and DR1/DR2).

The original form of MHC typing was based on serologic methods and has recently become increasingly superseded by modern molecular genetic techniques, especially polymerase chain reaction (PCR) approaches to gene sequencing. Here, specific DNA oligonucleotides are first bound to class I or class II MHC genes by DNA hybridization. In a next step, these DNA oligonucleotides are used as primers to amplify the genetic sequences, encoding the polymorphic regions of the MHC molecules that define the individual MHC specificity. Sequencing of these PCR amplification products then allows very specific genetic MHC typing to the level of the exact amino acid sequence, which is then expressed in a much more detailed notation (e.g., HLA-B*0703, HLA-DR1*0402). Side-by-side comparison of traditional serologic typing with the much more accurate genetic typing methods has revealed that, in the case of HLA-DR typing, up to 25% of serologic typing classifications had been inaccurate. Molecular typing has also replaced cell-based typing that had been performed with use of lines of alloresponsive T lymphocytes. The determinants recognized by these cell lines, originally called HLA-D, are largely comprised of HLA-DR alleles.

Tissue typing at the 4 major MHC loci (HLA-A, B, C, and DR) is generally performed before cardiac transplantation, and matches at class I or especially class II loci have been shown in retrospective studies to have a beneficial effect on graft survival, albeit smaller than in kidney transplantation. For reasons of limited ischemic preservation time, heart grafts are currently not routinely allocated on the basis of prospective tissue antigen typing and matching.

Minor histocompatibility antigens are polymorphic normal cellular constituents, not necessarily involved in