

1 Basic concepts

1.1 The human leukocyte antigen (HLA) system

1.1.1 Introduction

Discovery of the *major histocompatibility complex (MHC)* originated in investigations of tissue transplantation. If tissue is transplanted from one individual to another, genetically unrelated individual of the same species, the transplant will be recognized as foreign and subsequently destroyed. The strength of this immunological reaction intrinsically depends on the disparity between donor and recipient regarding what are referred to as transplantation antigens. Both weak transplantation antigens, the so-called *minor histocompatibility antigens (mHag)*, and strong transplantation antigens contribute to transplant rejection. Strong antigens are denoted as major histocompatibility antigens and are encoded in the MHC. Historically, these molecules have also been referred to as *immune response (Ir) genes* because of their ability to profoundly influence immune-mediated tissue rejection. Structurally, MHC gene products are highly polymorphic molecules that are expressed on the cell surface. However, their significance extends well beyond transplantation. Thus, MHC molecules play a pivotal role in the recognition of self and non-self in addition to signaling danger to the organism, as hypothesized in the “danger model.” Moreover, they imprint and orchestrate the immune response. These latter functions comprise the developmentally new part of the immune system, referred to as *adaptive immunity*, which is characterized by the hallmarks of antigen specificity and memory of an immune response. However, adaptive immunity is strongly linked to *innate immunity*. A prerequisite of the antigen-specific cellular immune response is the necessity to process and present antigen; this function is carried out by the *major histocompatibility antigens*, which also act as *antigen-presenting molecules*.

To distinguish between the dual function of major histocompatibility antigens, i.e., as antigen-presenting molecules and as antigens in the immunological sense, the term “molecules” is used for MHC gene products to avoid confusion with the presented peptide antigen. In addi-

tion, since the MHC is found only but in all vertebrates, within each species the generic term MHC is supplemented by a species-specific designation. Thus, in humans, the MHC is denoted as the *human leukocyte antigen (HLA)* system.

The pivotal importance of the HLA system for the transplantation of cells, tissues, or organs builds on the antigen-presenting function of HLA molecules and their ability to prime the immune response while also discriminating between self and non-self. In the context of transplantation, exposure to non-self HLA molecules leads to alloreactivity via two pathways. In the direct pathway, HLA molecules act as antigen-presenting molecules, while in the indirect pathway they are presented as antigens/peptide fragments.

The clinical relevance of the HLA system is evidenced by the relationship between the degree of HLA matching and transplant survival (solid organ transplantation) as well as by transplant rejection and acute and chronic graft-versus-host-reactions (hematopoietic stem cell transplantation). An alloantibody response against HLA molecules may ensue after transplantation or transfusion. The aim of clinical immunogenetics and histocompatibility testing is therefore the detection of genetic (e.g., HLA polymorphism) and serological (e.g., anti-HLA antibodies) markers of histocompatibility in order to identify and assess potential incompatibilities between donor and recipient, optimize donor selection, and minimize the risk to the transplant recipient.

Furthermore, a number of diseases, including those of autoimmune and infectious origin, are characterized by an association with and/or linkage to genes and alleles of the HLA gene complex. Possibly, antigen presentation by HLA molecules contributes to the immunopathogenesis of these diseases. Also, tumor-antigen-directed therapies often require identification of the restricting HLA antigen or allele for patient selection.

1.1.2 Genetics, polymorphism, and nomenclature of the HLA system

► Genetic make-up

HLA complex. The genes of the HLA system are located within a complex on the short arm of human chromosome 6 (6p21.1–6p21.3), en-

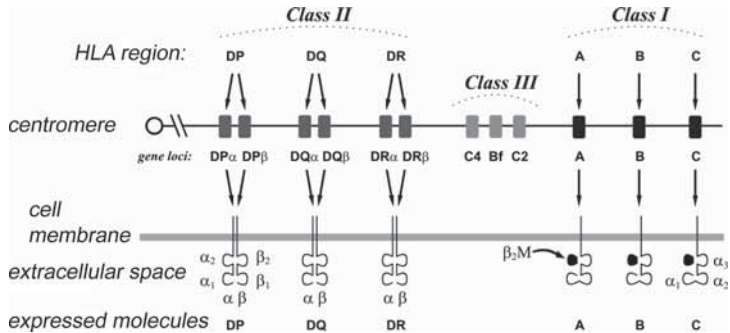


Fig. 1: The chromosomal organization of expressed HLA class I and class II genes is shown, along with the composition of the corresponding surface-expressed molecules. β_2 -M denotes β_2 -microglobulin. For orientation, the positioning of selected genes of the class III region are also shown.

comprising approximately 3,600 kilobase pairs (kbp). Within this complex, three regions, called the class I, class II, and class III regions, are distinguished. The class I region is located on the telomeric end of the HLA complex (Fig. 1). The class III region harbors genes encoding proteins with different functions, albeit often immune-system-related, such as complement factors C2, factor B, and C4A and C4B. Genes for tumor necrosis factor (TNF α , β), heat shock protein (HSP 70), and steroid-21-hydroxylases can be found in this region as well. The loci of HLA class II genes are positioned centromeric to those of class I and class III (Fig. 1).

HLA class I genes. The class I genes include both those that are functionally expressed and those that are not expressed (Table 1). HLA-A, -B, and -C encode the classical serologically defined specificities. HLA-E, -F, and -G are also functionally active. HLA-E is expressed on nearly all cell types but is structurally distinct from HLA-A, -B, and -C. It is the least polymorphic of all HLA class I molecules and acts as a ligand for receptors of the innate and the adaptive immune systems. The pre-

Table 1: Synopsis of the known HLA class I genes.

Name	Previous designation	Expression	Function
HLA-A	–	Expression	Antigen presentation to T lymphocytes
HLA-B	–	Expression	Antigen presentation to T lymphocytes
HLA-C	–	Expression	Antigen presentation to T lymphocytes
HLA-E	E, ‘6.2’	Expression	Regulation of NK cell function
HLA-F	F, ‘5.4’	Expression	???
HLA-G	G, ‘6.0’	Expression	Regulation of NK cell function
HLA-H	H, AR, ‘12.4’	Pseudogene	
HLA-J	cda 12	Pseudogene	
HLA-K	HLA-70	Pseudogene	
HLA-L	HLA-92	Pseudogene	
HLA-N	HLA-30	Gene fragment	
HLA-P	HLA-90	Gene fragment	
HLA-S	HLA-17	Gene fragment	
HLA-T	HLA-16	Gene fragment	
HLA-U	HLA-21	Gene fragment	
HLA-V	HLA-75	Gene fragment	
HLA-W	HLA-80	Gene fragment	
HLA-X	HLA-X	Gene fragment	
HLA-Y	HLA-BEL/COQ/DEL	Gene fragment	
HLA-Z	HLA-Z1	Gene fragment	