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HLA: Basic Terminology and Nomenclature

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Definition: Human Leukocyte Antigen (HLA)?

A gene complex that encodes the major histocompatibility complex (MHC) proteins in humans.

- Cell surface glycoproteins are expressed in almost all cells in the body.
- This gene complex is located on chromosome 6p21.
- Aka. MHC

What are the characteristic features of HLA?

Highly *polygenic* (composed of many genes)

- Class I, Class II and Class III

Highly *polymorphic* (contains multiple variations of antigens or alleles)

- HLA B*27:05 vs B*27:08 are distinct

Pleiotropic (has many functions)

- Distinction of self from non-self
- Major player in antigen presentation and initiation and coordination of immune response

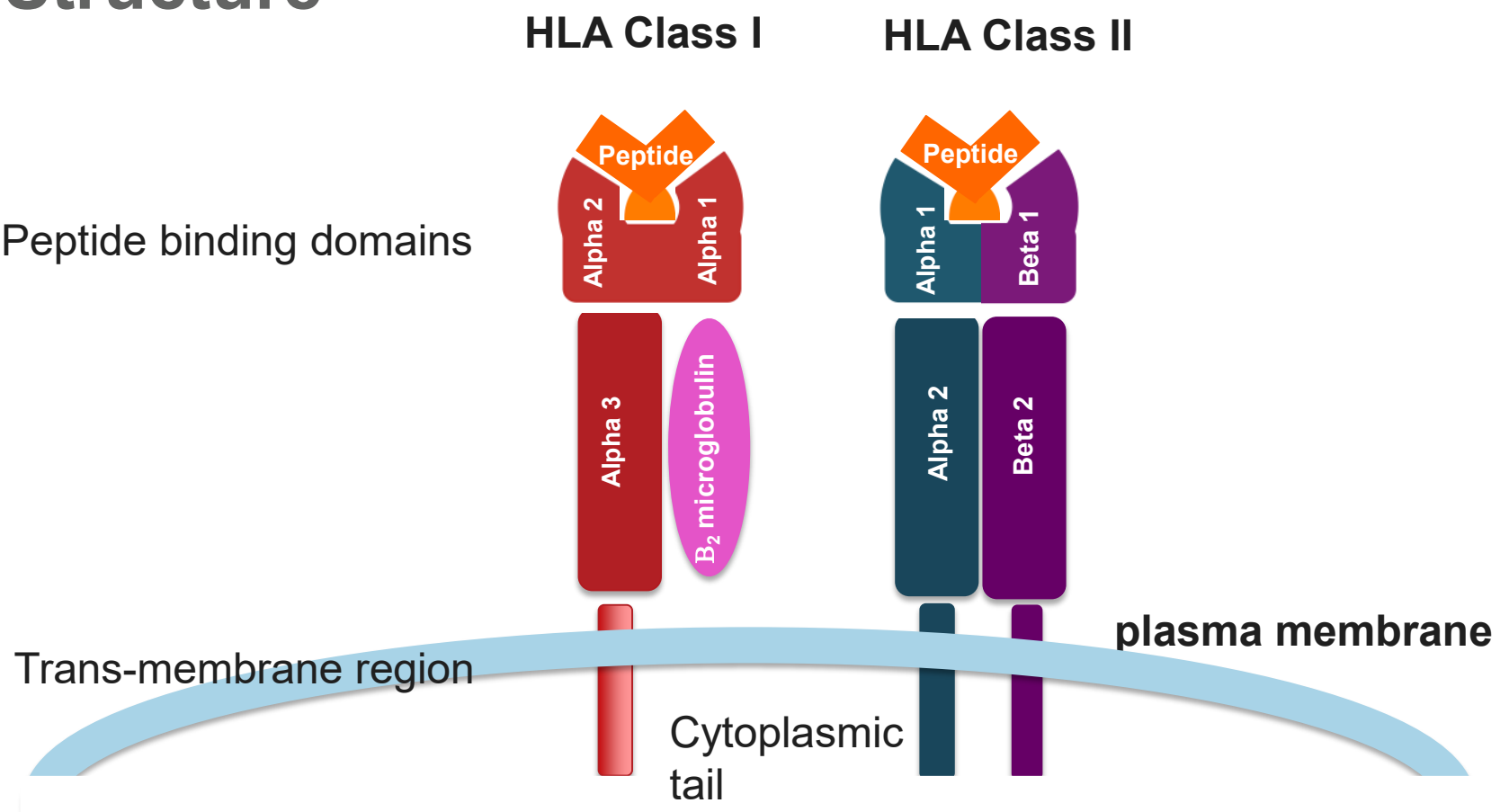
Comparison of Histocompatibility Genes

	CLASS I	CLASS II
Classical Genes	A, B, C	DR, DQ, DP
Distribution	Most somatic cells	Antigen presenting cell
Polypeptide chains	A single α chain (45-47 kD), non-covalently linked to β2 microglobulin chain (12 kD)	A single α chain (32-34kD) non-covalently linked to a single β chain (29-32kD)
Composition of antigen binding clefts	α1and α2 domains	α1 and β1 domains
Binding site for T cell co-receptor	CD8 binds to α3 region	CD4 binds to β2 region
Size of peptide binding cleft	Accommodates 8-11 amino acid residues	Accommodates 10-30 amino acid residues

Cellular and molecular immunology updated 6th Ed page 102.

Structure

Peptide binding domains



Understanding Historical Nomenclature

- Initially, serologic methodology was used to describe the polymorphism of the class I and later the class II loci.
- New HLA antigens were defined at the international workshops with the extensive exchange of typing reagents between laboratories and HLA scientists exhaustively examining the reactivity of antisera which were submitted as defining a particular specificity.
- When an HLA antigen was established as reproducibly defined, it was given a formal designation to be used by all laboratories which consisted of a number preceded by a workshop ”w” designation.
- When sufficient antisera were available for a particular specificity and most laboratories in the world had gained experience in accurately defining the specificity, the “w “designation was removed from all loci.
- The “w” designation was also removed from the C locus alleles but will remain part of the antigen nomenclature to avoid confusion with the complement factors in the most current nomenclature.

The ever-expanding list of HLA alleles: changing HLA nomenclature and its relevance to clinical transplantation Brian D. Tait Transplantation Reviews 25 (2011) 1–8

Challenges of Converting Serologic Typing into Molecular Typing

- Improvements in serologic techniques and increased reproducibility allow some of the antigens defined as combinations of closely related antigens, which could be distinguished serologically.
  - Eg: HLA-B15 consists of 8 closely related specificities, HLA-B-62, HLAB-63, HLA-B70, HLA-B71, HLA-B72, HLA-B75, HLA-B76, and HLA-B77.

- Serologic supertypes are the broad specificities. Eg: B15
- "Splits" or Subtypes are the finer specificities that comprised the supertype. Eg: B62 or B63, etc.

- As the splits were discovered, they were given number designations that again give no indication as to the supertype to which they belong. Eg: Molecular B*15:12 is equivalent of HLA-B76.

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Caveats of HLA Nomenclature

- The assigned numbers reflect the chronological order of discovery rather than a systematic numbering system.

- "*To the uninitiated, the HLA numbering system is not something that can be deduced by studying the designated numbers of the supertypes and subtypes, and to those who work in the field, it is something that must be learnt*."

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Current Nomenclature

Species	Locus	Antigen Equivalent	Allele	Silent Mutation	Outside exon	Expression Modifier
HLA	A*	03:	01:	01:	02	N,L,S,Q

Examples

- A*03 is low resolution typing by molecular method. In most cases this is equivalent to the antigen.

http://hla.alleles.org/nomenclature/naming.html

Current Nomenclature

	1st Field	2nd Field	3rd Field	4th Field			
Species	**Locus**	**Antigen Equivalent**	**Allele**	**Silent Mutation**	**Outside exon**	**Expression Modifier**
HLA	A*	03:	01:	01:	02	N,L,S,Q

Examples

- A*03 is low resolution typing by molecular method. In most cases this is equivalent to the antigen.
- A*03:01 is the allele. It designates a unique protein sequence.
- A*03:01:01 vs A*03:01:02 difference is due a synonymous (silent) mutation

http://hla.alleles.org/nomenclature/naming.html

Current Nomenclature

	1st Field	2nd Field	3rd Field	4th Field		
Species	**Locus**	**Antigen Equivalent**	**Allele**	**Silent Mutation**	**Outside exon**	**Expression Modifier**
HLA	A*	03:	01:	01:	02	N,L,S,Q

Examples

- A*03 is low resolution typing by molecular method. In most cases this is equivalent to the antigen.
- A*03:01 is the allele
- A*03:01:01 vs A*03:01:02 difference is due a synonymous (silent) mutation
- A*03:01:01:02N is a null allele (exon or intron)

Other Expression Modifiers (L-Low expression, S-Secreted molecule ,Q- Questionable)

- HLA-A*24:02:01:02L
- HLA-B*44:02:01:02S
- HLA-A*32:11Q

http://hla.alleles.org/nomenclature/naming.html

Terminology

Epitope (Antigenic determinant): is the minimum structural unit composed of a few amino acids in the HLA antigen that can be recognized by a B or T cell receptors.

Private Epitopes: Epitopes that are present only on a single gene product such as HLA-A2.

Public Epitopes: Refers to epitopes that are shared by more than one HLA antigen. HLA antibodies will show reactivity with the antigens that contains the public epitope.

Cross-reactive groups (CREGs): is a group of antigens that share a public epitope, as demonstrated by the ability of a specific antibody to react with all of them. This group of HLA antigens all together show the described cross reactivity are a called CREGs.

HLA and Its Clinical Relevance

- HLA is an important barrier for hematopoietic stem cell (HPC) transplantation. Therefore HLA matching and compatibility between the donor and the recipient is required for successful HPC transplantation.
  - HLA antigens also have role in graft- versus-host disease (GVHD), a potentially serious complication of allogeneic stem cell transplantation.

- In solid organ transplantation HLA antibodies play an important role and HLA matching is not as important.
  - When patients are exposed to foreign HLA antigens due to pregnancy or blood transfusions or transplantation, they can make antibodies against epitopes of those HLA molecules. This is called HLA alloimmunization.

- Presence of HLA antibodies against graft can cause antibody mediated rejection and graft loss.

- HLA alloimmunization also causes platelet refractoriness. This condition creates difficulty in finding compatible platelet units especially in transfusion dependent HPC transplants patients.

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