MHC

Learning Objectives:

- Definition of MHC
- Classification of MHC families (classes)
- Structures of MHC classes I and II
- Functions of MHC molecules (classes I, II & III)
- Clinical relevance of HLA

Immunity = State of protection from infectious disease

INNATE IMMUNITY **ACQUIRED IMMUNITY**

Innate Immunity = Non-specific Immunity

Acquired Immunity = Specific Immunity
= Adaptive Immunity

ACQUIRED IMMUNITY

Characteristic Features

1. Specificity – ***Ability to distinguish pathogens***

2. Diversity – ***Recognize millions of molecules***

3. Memory – ***Increased & faster second response***

4. Self/Non-self Discrimination – ***Respond to non-self***

Immune system responds to bacteria, viruses, toxins.

But not to the *whole* bacterium, virus or toxin !

Immune system responds to "ANTIGENS"

Antigens = Molecules that bind to an antibody or to a T cell receptor

Immunogens = Molecules that induce immune responses

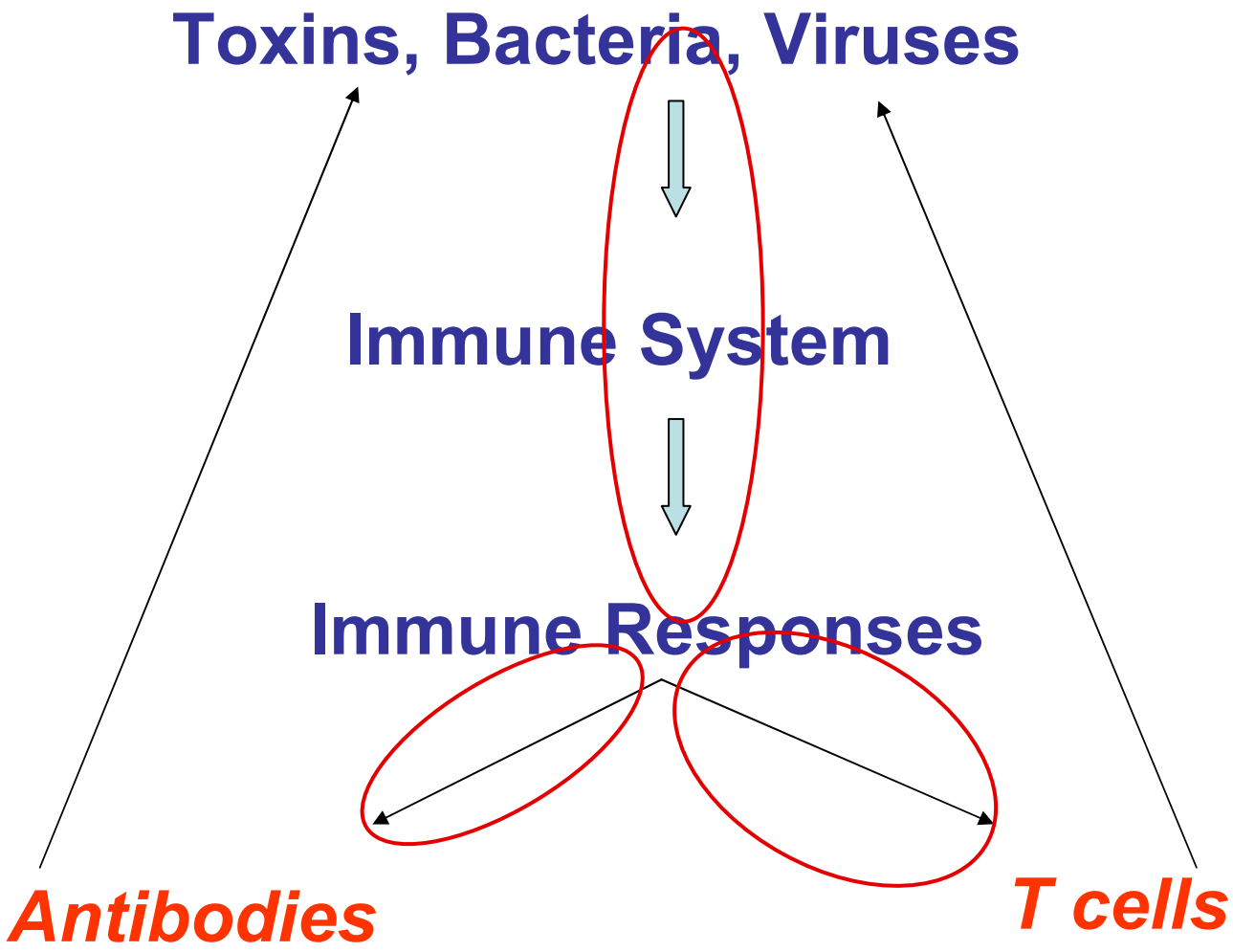
But the immune system does not respond to the *whole* antigen……just to small segments or regions of Ag

Epitope = Small immunogenic segment or region in an Ag

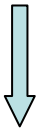
So, the immune system responds to *epitopes* on antigens of bacteria, viruses, toxins etc

Exogenous Ag = extracellular bacteria, proteins etc

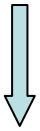
Endogenous Ag = intracellular bacteria, viruses etc


Toxins, Bacteria, Viruses
Immune System
Immune Responses
Antibodies
T cells

Antigens are INTERNALIZED by cells



Antigens are PROCESSED within cells



Epitopes are PRESENTED on cells by MHC molecules

What are MHC molecules?

MHC = Major Histocompatibility Complex

HLA = Human Leukocyte Antigens

Defination of MHC

- A collection of genes arrayed within a stretch of DNA on chromosome number 6 in human and chromosome 17 in mice.
- Determines whether transplanted tissue is accepted as self (***histocompatible***) or rejected as foreign (***histoincompatible***)

Referred to:

– HLA in human

– H-2 complex in mice

Major Histocompatibility Complex (MHC – HLA)

Histocompatibility = Ability to accept grafts between individuals

MHC = Region of multiple loci that are

(1) responsible for rejection of grafts and

(2) function in signalling between lymphocytes and cells that present antigens.

MHC (HLA) molecules recognize antigens, so MHC molecules are antigen-recognition molecules (like antibody molecules).

HLA molecules PRESENT antigens to T cells.

MHC.

- The MHC contains a set of genes located together on one chromosome as a ‘complex’.
- MHC genes code for several series or families of polymorphic glycoproteins, including two families of molecules that are expressed at the cell surface, the class I and class II molecules.
- These specialized membrane proteins act as guidance systems that allow T cells to recognize antigen.

Historical perspective.

- The term MHC derives from studies designed to investigate the fate of tissues (grafts) transplanted between individuals.

- As a result of these experiments, the MHC was recognized as an important ('major') set of genes ('complex') responsible for controlling whether grafts are accepted between individuals whose tissues are genetically similar ('histocompatible') or rejected by individuals who are not ('incompatible').

Note.

- MHC is not the only influence on tissue compatibility.
- A large number of genetic loci have been identified on different chromosomes that also play a role in graft rejection.
- These are called ‘minor histocompatibility genes’.

General features of the MHC.

- The MHC codes for 3 families of glycoproteins known as class I, class II, and class III MHC molecules.
- The members of two of these families, class I and class II molecules, are also sometimes referred to as MHC antigens or alloantigens because they can be recognized by the immune system during the rejection of tissue transplanted between MHC incompatible individuals.

- The class I and class II MHC molecules are expressed mainly as membrane glycoproteins at the cell surface, whereas the products of class III genes are usually soluble molecules.
- Class III molecules include some of the components of the complement system, one of the major effector mechanisms of the humoral immune response; soluble effector molecules such as TNFβ; the enzyme 21-hydroxylase; and the HSP70

Large number of histocompatibility GENES in MHC

Complex	Complex Major Histocompatibility		
Class	I		
Region	B	C	A
Molecule	HLA-B	HLA-C	HLA-A

Large number of histocompatibility GENES in MHC

Complex	Complex Major Histocompatibility					
Class	II			I		
Region	DP	DQ	DR	B	C	A
Molecule	DP-HLA-	HLA-DQ	HLA-DR	HLA-B	HLA-C	HLA-A

Large number of histocompatibility GENES in MHC

Complex	Complex Major Histocompatibility							
Class	II			III		I		
Region	DP	DQ	DR			B	C	A
Molecule	DP-HLA-	HLA-DQ	HLA-DR	`C	TNF	HLA-B	HLA-C	HLA-A

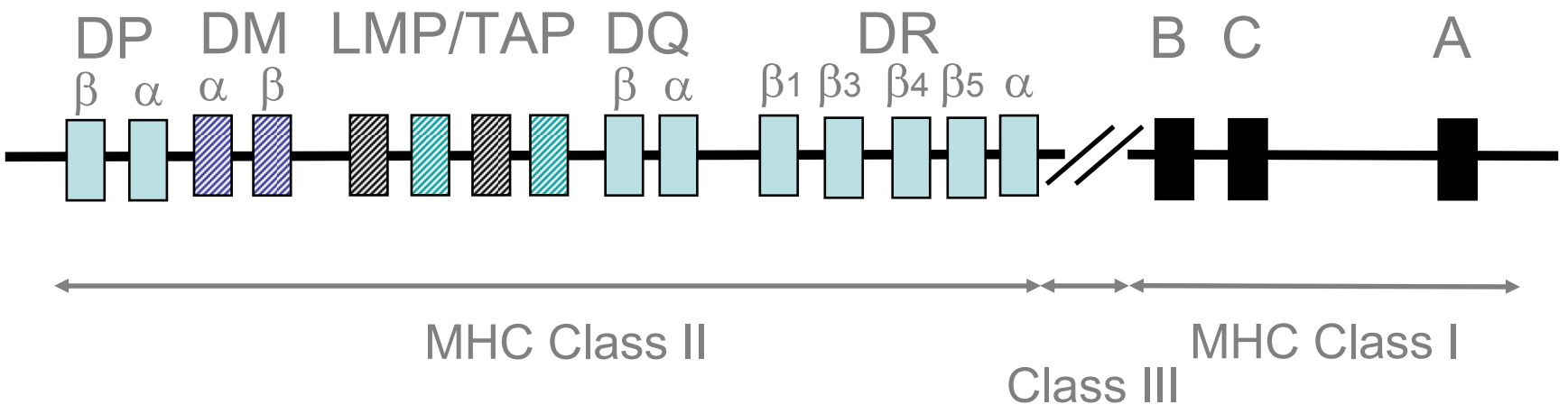
Where **are MHC molecules expressed ?**

Class 1 = On almost all nucleated cells

Class 2 = On Antigen Presenting Cells (APC)

Macrophages, B cells, Dendritic Cells

Simplified map of the HLA region



Polygeny

CLASS I: 3 types HLA-A, HLA-B, HLA-C (sometimes called class Ia genes)

CLASS II: 3 types HLA-DP HLA-DQ HLA-DR.

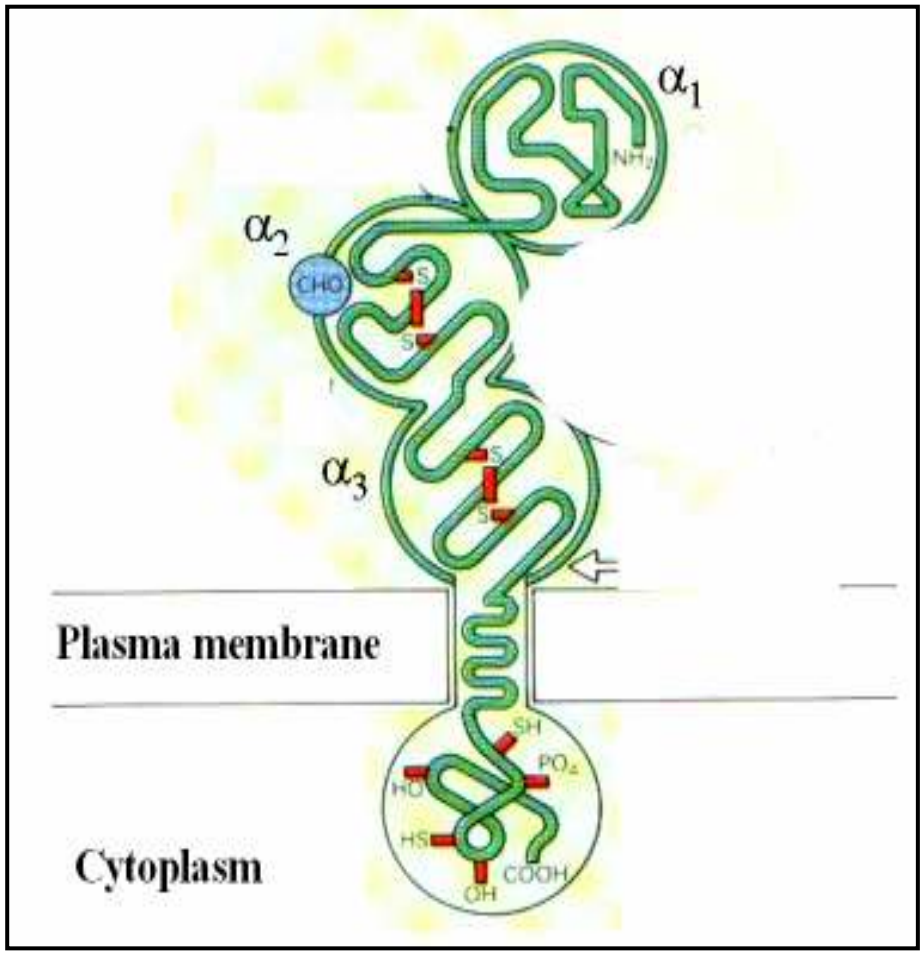
3 extra DRβ genes in some individuals can allow 3 extra HLA-DR molecules

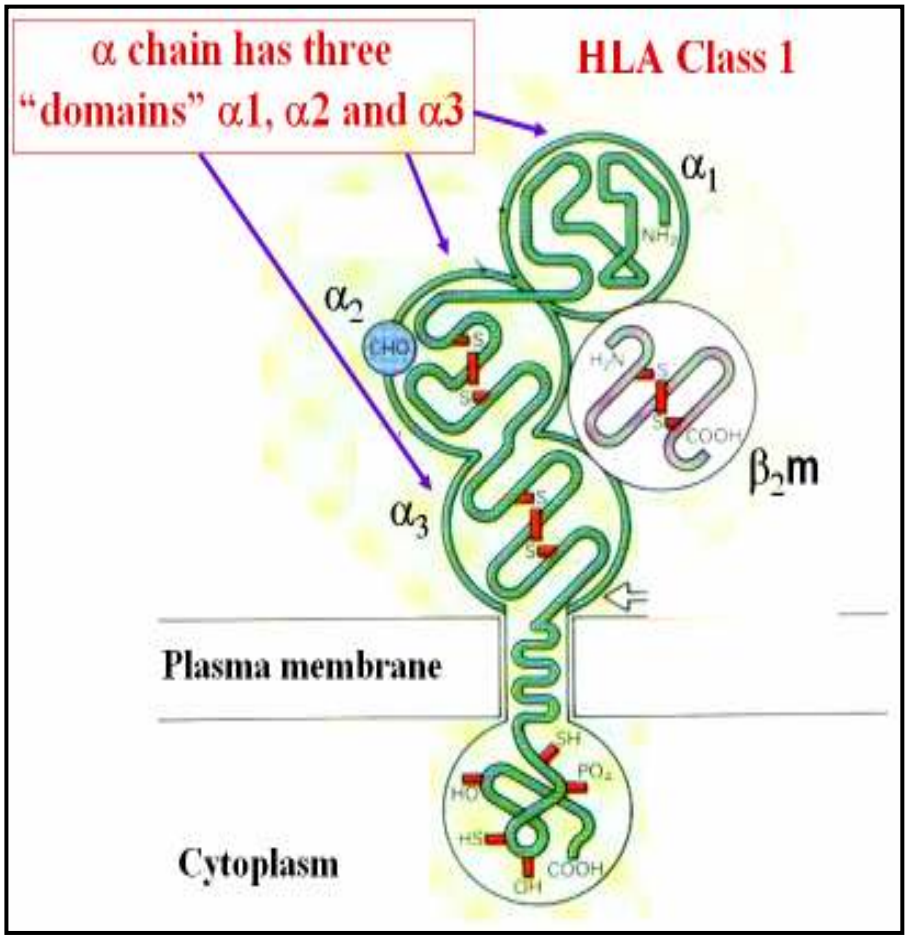
Maximum of 9 types of antigen presenting molecule allow interaction with a wide range of peptides.

Structure of Class I MHC Molecules

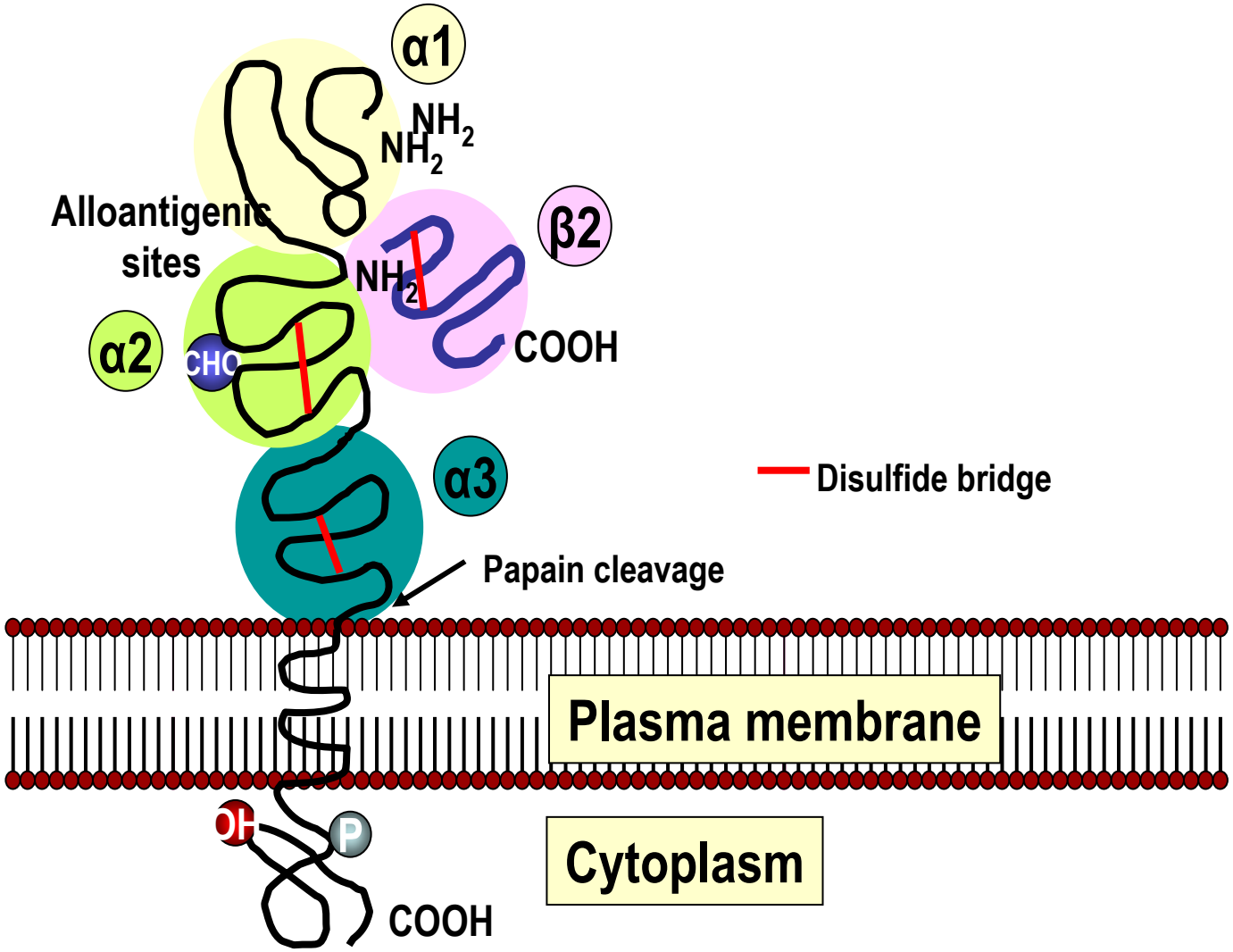
HLA-A, B, C molecules have a heavy chain (α) linked to a smaller β2-microglobulin molecule

HLA Class 1


α1
α2
CHO
α3
Plasma membrane
Cytoplasm


α chain has three
"domains" α1, α2 and α3
HLA Class 1
α1
α2
CHO
α3
β2m
Plasma membrane
Cytoplasm

Structure of Class I MHC



Structure of Class I MHC

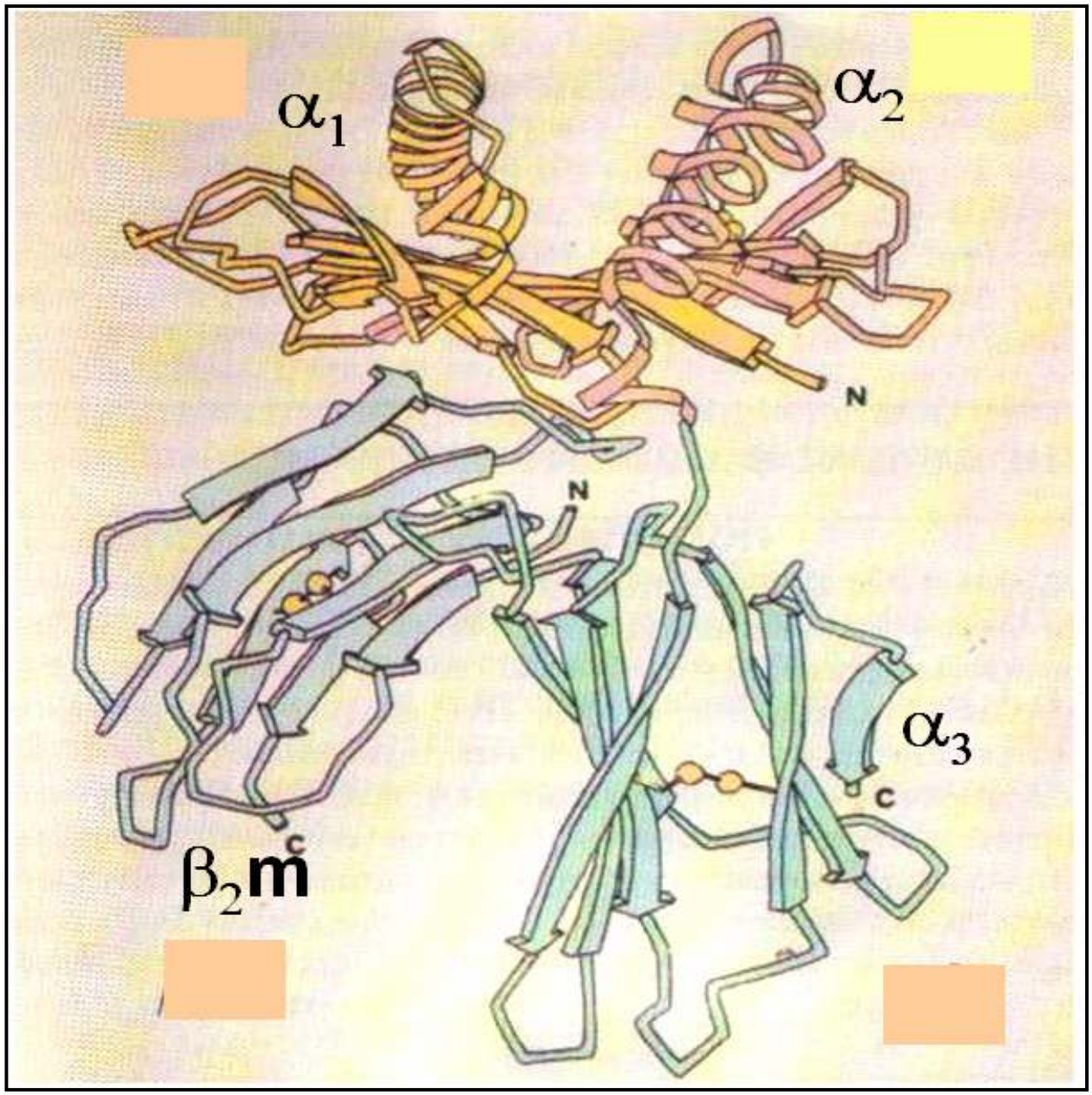
- Two polypeptide chains, a long α chain and a short β chain, called β2 microglobulin
- Four regions:
- Peptide-binding region - a groove formed from α1 and α2 domains of the α chain
- Immunoglobulin-like region – highly conserved α3 domain - site to which CD8 on T cell binds

- Transmembrane region – stretch of hydrophobic amino acids spanning membrane

- Cytoplasmic region – contains sites for phosphorylation and binding to cytoskeletal elements

Structure of Class I MHC Peptide-binding Region

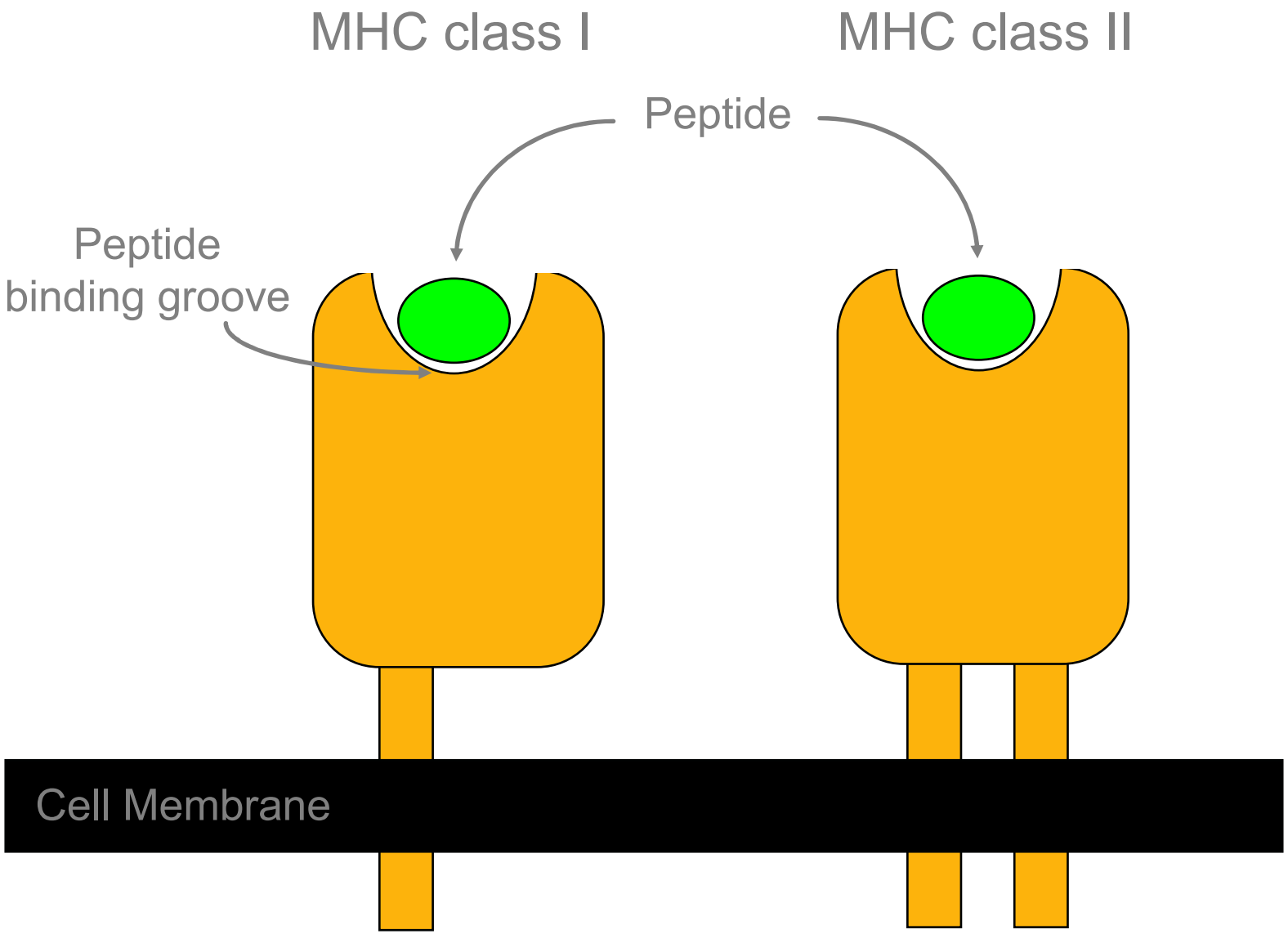
- a “groove” composed of an α-helix on two opposite walls and eight β-pleated sheets forming the floor
- residues lining groove most polymorphic
- peptide in groove 8-10 amino acids long
- specific amino acid on peptide required for “anchor site” in groove


α1
α2
N
N
α3
C
β2m
C

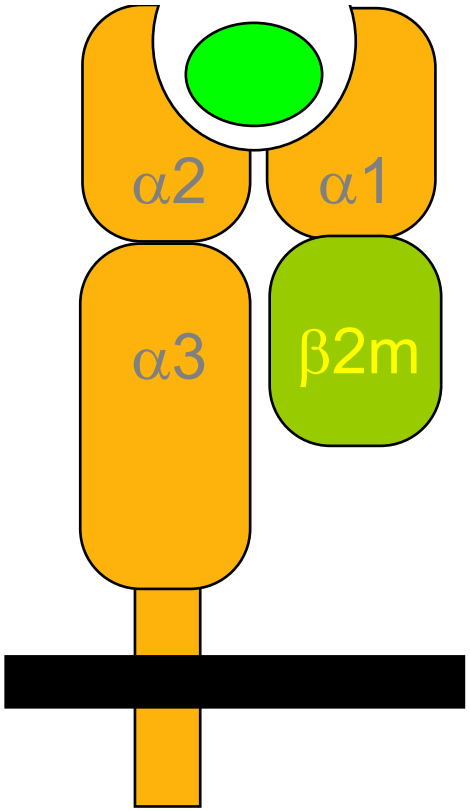
The α chain is highly polymorphic (exists in different forms in population = different alleles)

The α1 and α2 domains are most polymorphic, while α3 and β2m are not polymorphic

MHC molecules



Overall structure of MHC class I molecules



MHC-encoded α-chain of 43kDa

α-chain anchored to the cell membrane

Peptide antigen in a groove formed from a pair of α-helicies on a floor of anti-parallel β strands

β2-microglobulin, 12kDa, non-MHC encoded, non-transmembrane, non covalently bound to α-chain

α3 domain & β2m have structural & amino acid sequence homology with Ig C domains Ig GENE SUPERFAMILY

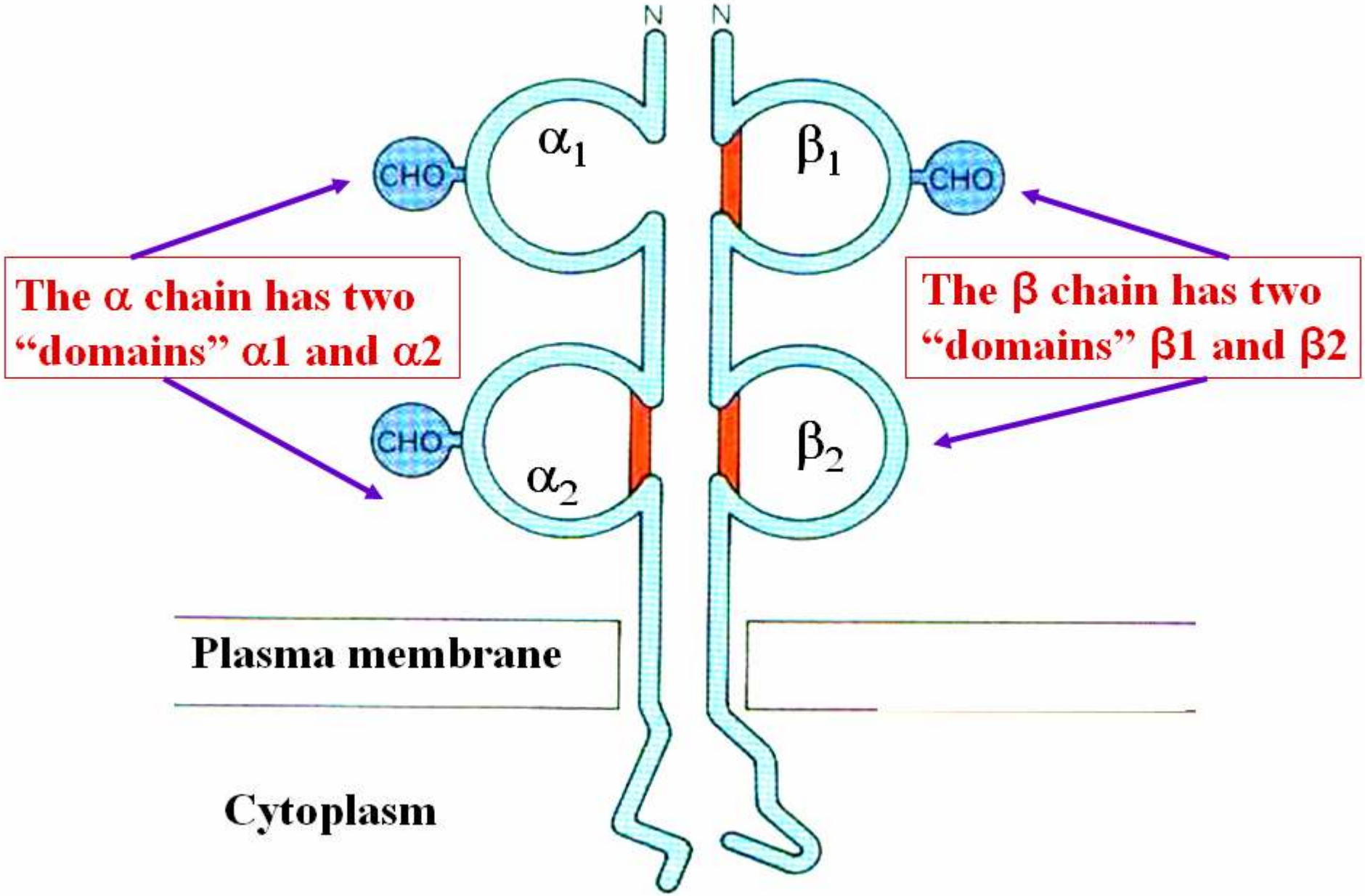
Structure of Class II MHC Molecules

HLA-DP, DQ and DR molecules are made up of one heavy chain (α) and one light chain (β) each

The α chain has two "domains" α1 and α2

The β chain has two domains β1 and β2

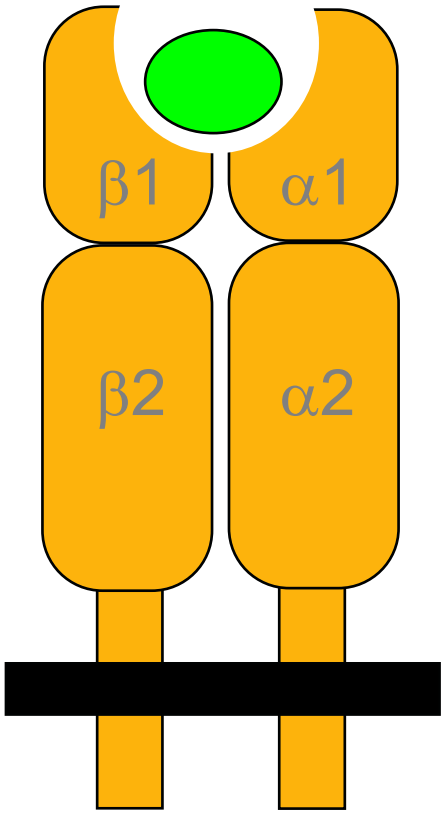
HLA Class 2


N
N
CHO
CHO
CHO
α_1
β_1
α_2
β_2
The α chain has two "domains" α1 and α2
The β chain has two "domains" β1 and β2
Plasma membrane
Cytoplasm

The α1 and β1 domains are highly polymorphic

The α2 and β2 domains are not polymorphic

Overall structure of MHC class II molecules



MHC-encoded, α-chain of 34kDa
and a β-chain of 29kDa

α and β chains anchored to the cell membrane

No β-2 microglobulin

Peptide antigen in a groove formed from a pair of α-helicies on a floor of anti-parallel β strands

α2 & β2 domains have structural & amino acid sequence homology with Ig C domains Ig GENE SUPERFAMILY

Structure of Class II MHC

- Two polypeptide chains, α and β, of roughly equal length.
- Four regions:
- Peptide-binding region – a groove formed from the α1 and β1 domains of the α and β chains – site of polymorphism
- Immunoglobulin-like region – conserved α2 and β2 domains – β2 is site to which CD4 on T cell binds

- Transmembrane region – stretch of hydrophobic amino acids spanning membrane

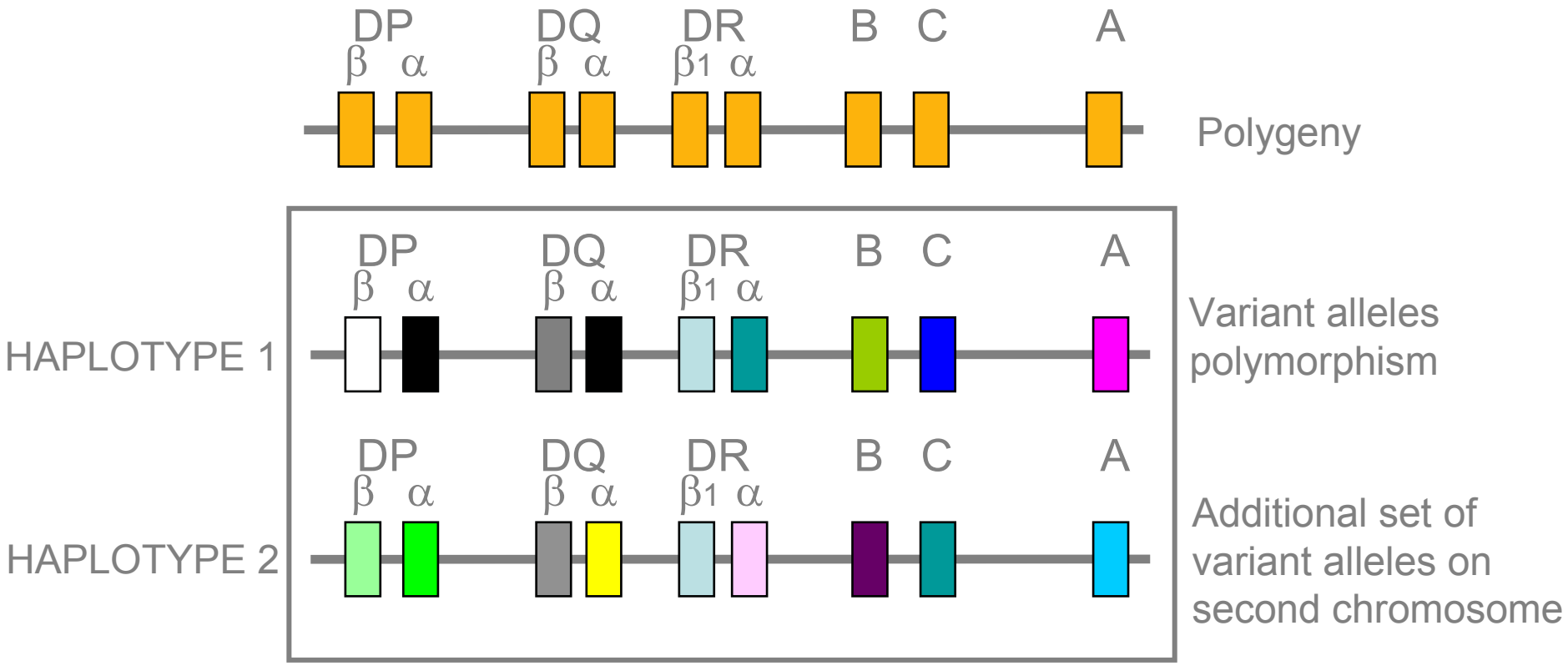
- Cytoplasmic region – contains sites for phosphorylation and binding to cytoskeletal elements

MHC molecules are highly polymorphic

i.e., exist as many alleles in the population

i.e., are different in different individuals

Diversity of MHC molecules in the individual



MHC molecules are CODOMINANTLY expressed
Two of each of the six types of MHC molecule are expressed

Genes in the MHC are tightly LINKED and usually inherited in a group

The combination of alleles on a chromosome is an MHC HAPLOTYPE

Other genes in the MHC

MHC Class 1b genes

Encoding MHC class I-like proteins that associate with β-2 microglobulin:
HLA-G interacts CD94 (NK-cell receptor). Inhibits NK cell attack of foetus/ tumours
HLA-E binds conserved leader peptides from HLA-A, B, C. Interacts with CD94
HLA-F function unknown

MHC Class II genes

Encoding several antigen processing genes:
HLA-DMα and β, proteasome components (LMP-2 & 7), peptide transporters (TAP-1 & 2), HLA-DOα and DOβ
Many pseudogenes

MHC Class III genes

Encoding complement proteins C4A and C4B, C2 and FACTOR B
TUMOUR NECROSIS FACTORS α AND β

Immunologically irrelevant genes

Genes encoding 21-hydroxylase, RNA Helicase, Caesin kinase
Heat shock protein 70, Sialidase

How many types of HLA molecules do you have?

Three Class I molecules – HLA-A, HLA-B and HLA-C

Three Class II molecules – HLA-DP, HLA-DQ, HLA-DR

But, we get one set of HLA genes from our mothers and another set from our fathers

These two sets are frequently different

So, we may have as many as 12 types of HLA molecules

MHC molecules are highly polymorphic

i.e., many HLA alleles in the population

more than 100 types of -A, -B, -C

as many as 400 types of HLA-B !

i.e., HLA are different in different individuals

…..and that is why tissue grafts are rejected !

But, what is the *FUNCTION* of the MHC?

FUNCTIONS of MHC (HLA) MOLECULES

MHC molecules PRESENT antigens to cells

Class I HLA molecules present epitopes to cytotoxic T cells

Class II HLA molecules present epitopes to helper T cells

MHC = Cell-surface molecules that PRESENT antigen to T cells

MHC molecules are essential for immune recognition

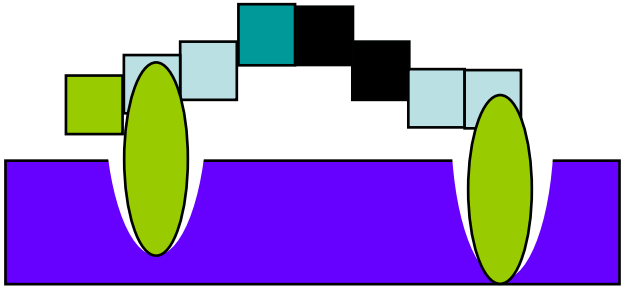
Differential distribution of MHC molecules

Tissue	MHC class I	MHC class II
T cells	+++	+/-
B cells	+++	+++
Macrophages	+++	++
Other APC	+++	+++
Epithelial cells of thymus	+	+++
Neutrophils	+++	-
Hepatocytes	+	-
Kidney	+	-
Brain	+	-
Erythrocytes	-	-

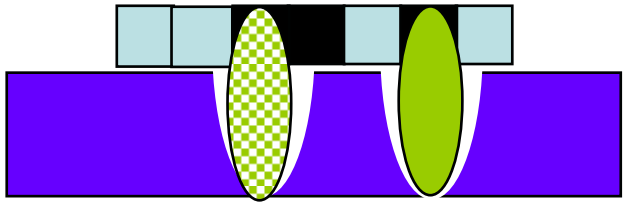
Cell activation affects the level of MHC expression
The pattern of expression reflects the function of MHC molecules:
Class I is involved in anti-viral immune responses
Class II involved in activation of other cells of the immune system

Role of MHC in diseases.

Polymorphism in the MHC affects peptide antigen binding



MHC allele A



MHC allele B

Changes in the pockets, walls and floor of the peptide binding cleft alter peptide MHC interactions and determine which peptides bind.

MHC allele A

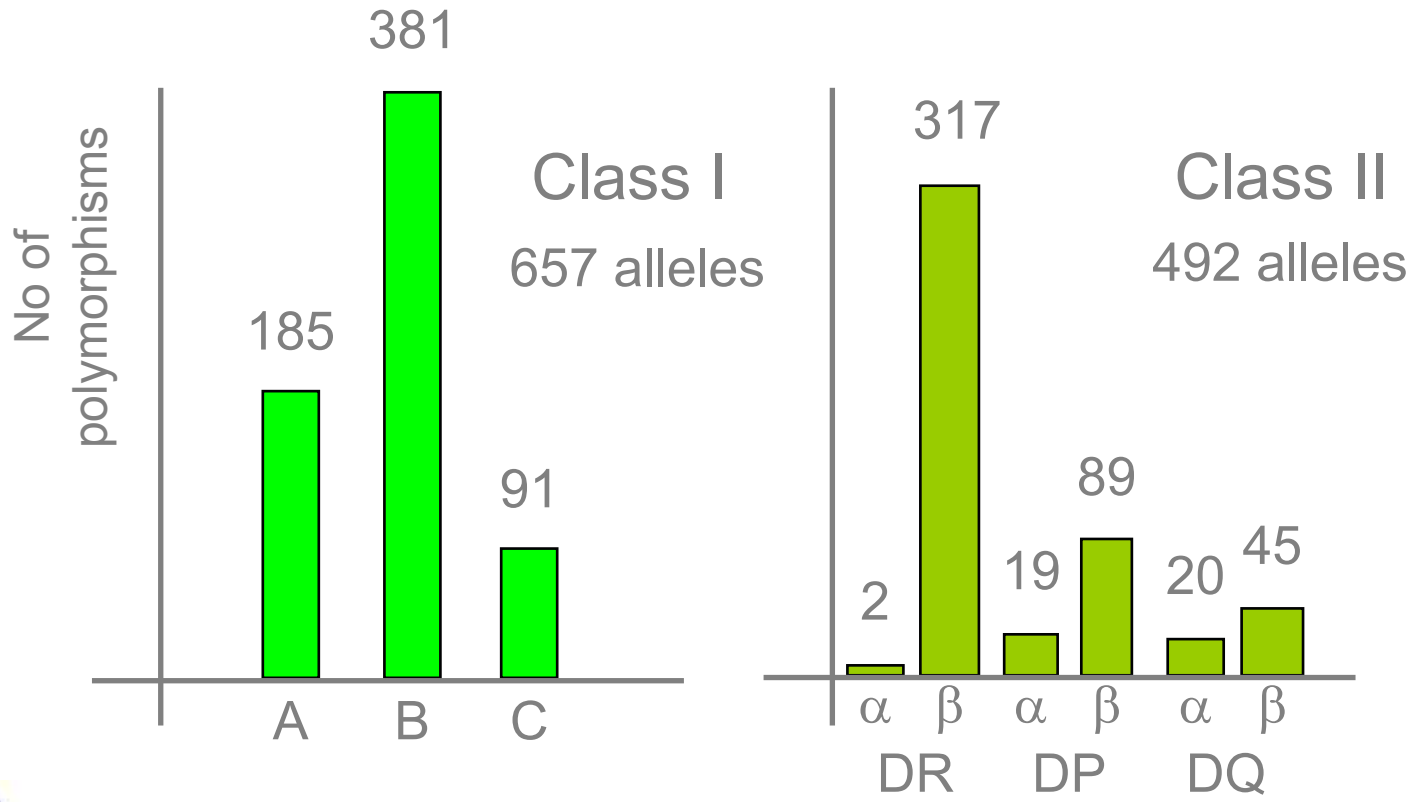
MHC allele B

Products of different MHC alleles bind a different repertoire of peptides

Polymorphism in the MHC

Variation >1% at a single genetic locus in a population of individuals
Each polymorphic variant is called an allele

In the human population, over 1,200 MHC alleles have been identified



Data from http://www.anthonynolan.org.uk/HIG/index.html July 2000

How diverse are MHC molecules in the population?

IF

- each individual had 6 types of MHC
- the alleles of each MHC type were randomly distributed in the population
- any of the 1,200 alleles could be present with any other allele

~6 x 10^{15} unique combinations

In reality MHC alleles are NOT randomly distributed in the population

Alleles segregate with lineage and race

	Frequency (%)		
Group of alleles	CAU	AFR	ASI
HLA-A1	15.18	5.72	4.48
HLA- A2	28.65	18.88	24.63
HLA- A3	13.38	8.44	2.64
HLA- A28	4.46	9.92	1.76
HLA- A36	0.02	1.88	0.01

How can 6 invariant molecules have the capacity to bind to 1,000,000,000,000,000 different peptides with high affinity?

MHC molecules

- Adopt a flexible “floppy” conformation until a peptide binds
- Fold around the peptide to increase stability of the complex
- Use a small number of anchor residues to tether the peptide
  this allows different sequences between anchors
  and different lengths of peptide

Replacement substitutions occur at a higher frequency than silent substitution

Suggests that selective pressures may operate on MHC polymorphism

Evolution of pathogens to evade MHC-mediated antigen presentation

In south east China & Papua New Guinea up to 60% of individuals express HLA-A11

HLA-A11 binds an important peptide of Epstein Barr Virus
Many EBV isolates from these areas have mutated this peptide so that it can not bind to HLA-A11 MHC molecules

Evolution of the MHC to eliminate pathogens

In west Africa where malaria is endemic HLA-B53 is commonly associated with recovery from a potentially lethal form of malaria

Association of HLA with Disease

Class I, HLA-B27 associated		
Ankylosing spondylitis	B27	87.4
Reiter's disease	B27	37.0
Post-salmonella arthritis	B27	29.7
Post-shigella arthritis	B27	20.7
Post-yersinia arthritis	B27	17.6
Post-gonococcal arthritis	B27	14.0
Uveitis	B27	14.6
Amyloidosis in rheumatoid arthritis	B27	8.2
Other class I associations		
Subacute thyroiditis	B35	13.7
Psoriasis vulgaris	Cw6	13.3
Idiopathic hemochromatosis	A3	8.2
Myasthenia gravis	B8	4.4

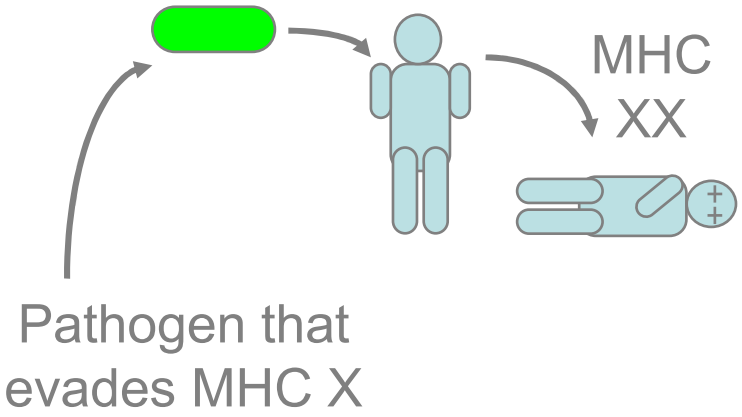
Association of HLA with Disease

Hashimoto's disease	DR11	3.2
Primary myxedema	DR17(*3)	5.7
Thyrotoxicosis (Graves')	DR17(*3)	3.7
Insulin-dependent diabetes	DQ8	14
	DQ2/8	20
	DQ6	0.2
Addison's disease (adrenal)	DR17(*3)	6.3
Goodpasture's syndrome	*DR2	13.1
Rheumatoid arthritis	DR4	5.8
Juvenile rheumatoid arthritis	DR8	8.1
Sjögren's syndrome	DR17(*3)	9.7
Chronic active hepatitis (autoimmune)	DR17(*3)	13.9
Multiple sclerosis	*DR2,*DQ6	12
Narcolepsy	DQ6	38
Dermatitis herpetiformis	DR17(*3)	56.4
Celiac disease	DQ2	250
Tuberculoid leprosy	*DR2	8.1

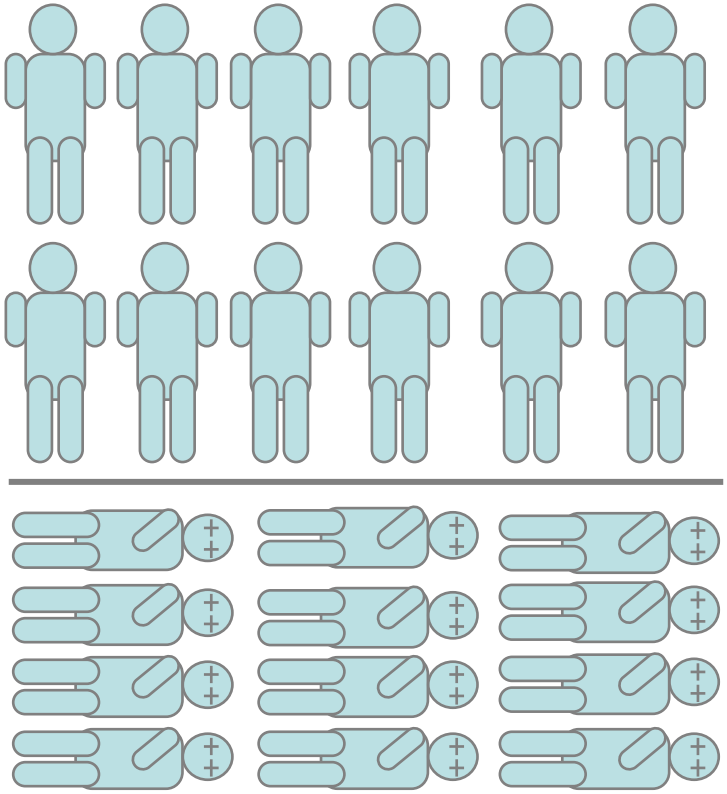
MHC molecules are targets for immune evasion by pathogens.

- T cells can only be activated by interaction between the antigen receptor and peptide antigen in an MHC molecule
- There is strong selective pressure on pathogens to evade the immune response
- The MHC has evolved two strategies to prevent evasion by pathogens
- More than one type of MHC molecule in each individual

Example: If MHC X was the only type of MHC molecule

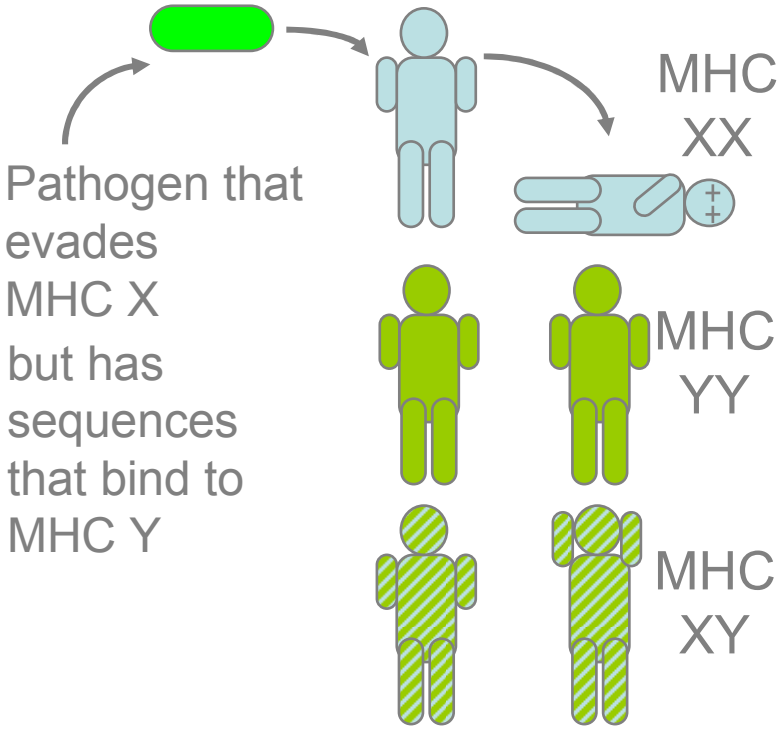


Survival of individual threatened

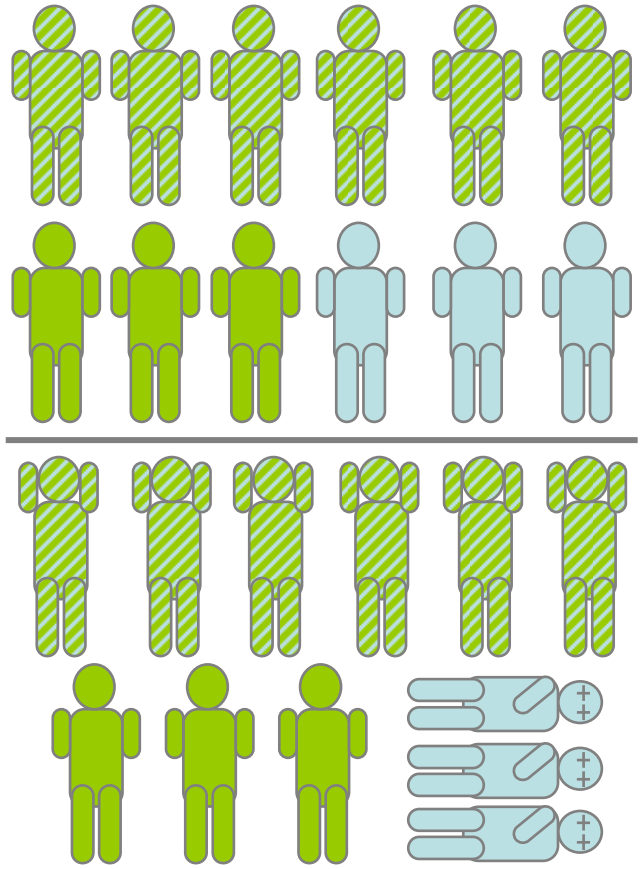


Population threatened with extinction

Example: If each individual could make two MHC molecules, MHC X and Y

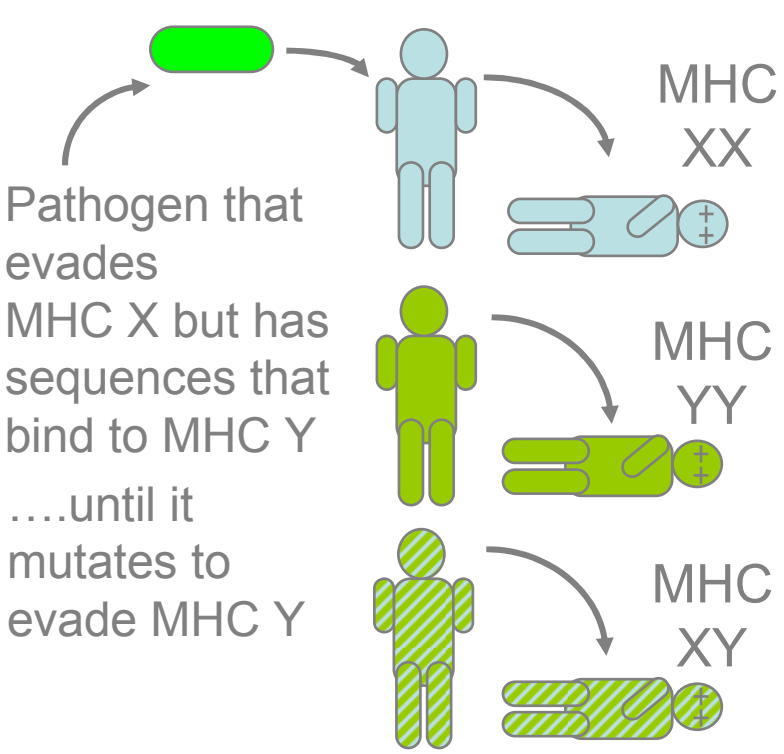


Impact on the individual depends upon genotype

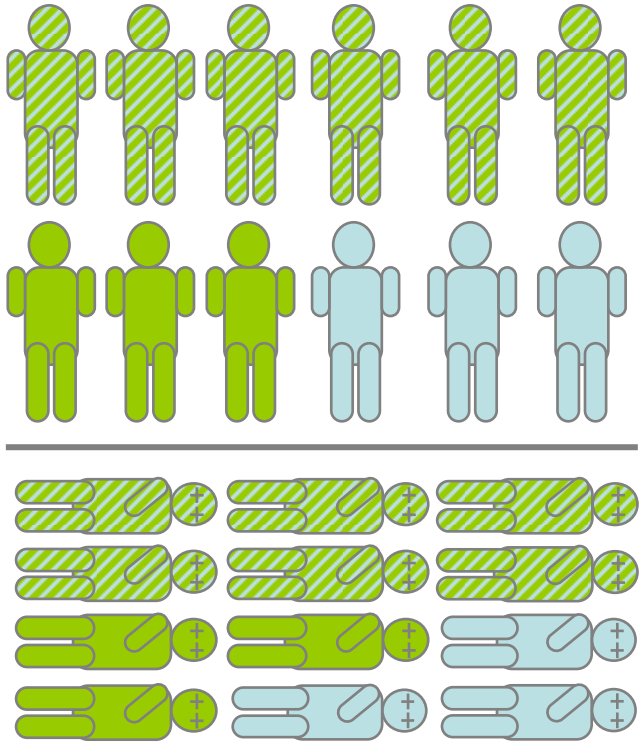


Population survives

Example: If each individual could make two MHC molecules, MHC X and Y……and the pathogen mutates



Survival of individual threatened



Population threatened with extinction

The number of types of MHC molecule can not be increased *ad infinitum*

Molecular basis of MHC types and variants

POLYGENISM

Several MHC class I and class II genes
encoding different types of MHC molecule
with a range of peptide-binding specificities.

POLYMORPHISM

Variation >1% at a single genetic locus in a
population of individuals
MHC genes are the most polymorphic known

The type and variant MHC molecules do not vary in the lifetime of the individual

The diversity in MHC molecules exists at the population level
This sharply contrast diversity in T and B cell antigen receptors which exists within the individual

Summary of Aspects of MHC

- MHC molecules are membrane-bound.
- Recognition by T cells requires cell-cell contact.
- Peptide from cytosol associates with class I MHC and is recognized by Tc cells.
- Peptide from vesicles associates with class II MHC and is recognized by Th cells.