Antigen Presentation to T cells: Major Histocompatibility Complex (MHC)

Antigen recognition strategies of B versus T cells

Discovery of MHC:

- Mouse genetics (inbred strains, congenic strains)
- T cell functional assays
- human leukocyte antigens (HLA)

Organization of MHC genes

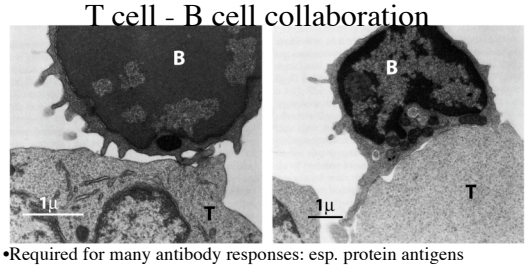
Structure of MHC proteins (class I and II)

MHC nomenclature (polymorphism, alleles, and haplotypes)

(teaching evaluations)

1

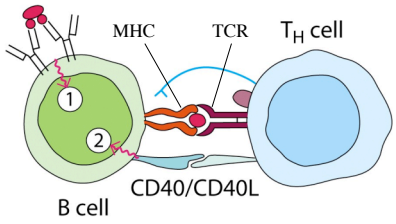
T cell - B cell collaboration



- Required for many antibody responses: esp. protein antigens
- Requires direct, physical B-T interaction
- Involves multiple cell surface receptors on T and B cells
- Both B and T cell must recognize antigen (but usually not the same epitope).
- Both B and T cells need signal 1 (through antigen receptor) and signal 2 (co-stimulation)

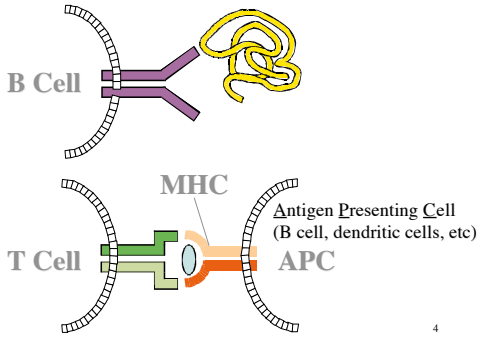
2

During T-B collaboration antigen is bound both by BCR on the B cell, and the TCR on the T cells



The BCR binds intact antigen.
The TCR binds a fragment of antigen bound to MHC proteins on the surface of the B cell.

Antigen Recognition by B and T lymphocytes



4

Antigen recognition by B cells vs. T cells

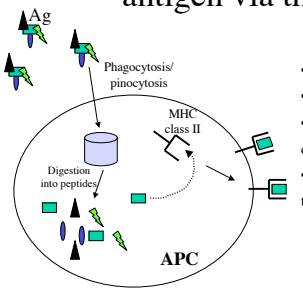
Both form their antigen receptors by V(D)J recombination.
Ig (alias: antibody, BCR) for B cells, TCR for T cells

B cells can bind intact protein antigen in solution.
(Receptor can be cell surface or secreted.)

T cells bind peptides displayed on the surface of another cell : an "antigen presenting cell" (dendritic cell, macrophage, or B cell).
(T cell antigen receptor exists only in cell surface form.)

5

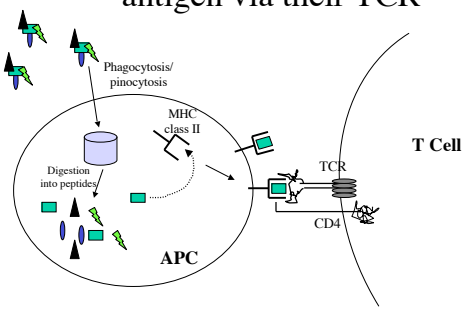
T cells recognize "processed" antigen via their TCR



- Antigen presenting cell ingests Ag
- Ag is degraded into peptides
- Peptides form complex with MHC class II molecules
- Peptide-MHC complexes transported to cell surface

6

T cells recognize "processed" antigen via their TCR



7

Humoral immune response:
Immunoglobulins produced by B-cell interact with pathogens and their toxic products in the extracellular spaces of the body.

T-cell mediated immunity:
T cells only recognize antigen as a small peptide fragment bound to an MHC molecule and displayed at the cell surface.

8

Major Histocompatibility Complex (MHC)

Review: antigen recognition strategies of B versus T cells

Discovery of MHC:

- **Mouse genetics (inbred strains, congenic strains)**
- **T cell functional assays**
- **human leukocyte antigens (HLA)**

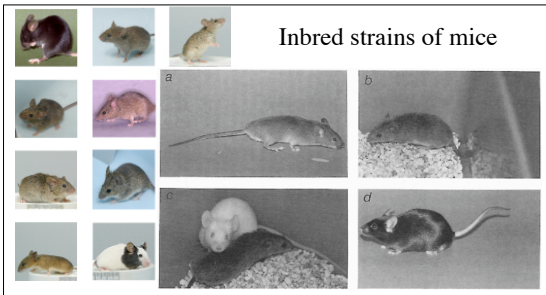
Organization of MHC genes

Structure of MHC proteins (class I and II)

MHC nomenclature (polymorphism, alleles, and haplotypes)

9

Inbred strains of mice



Originally bred as pets and selected for docility and coat color: "fancy mice"

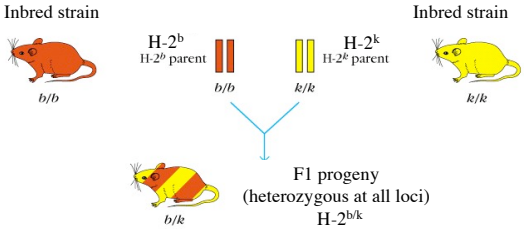
Starting around 1910 inbred strains were developed for research

Generated by repeated brother-sister matings

Genetically identical (homozygous) at all loci

10

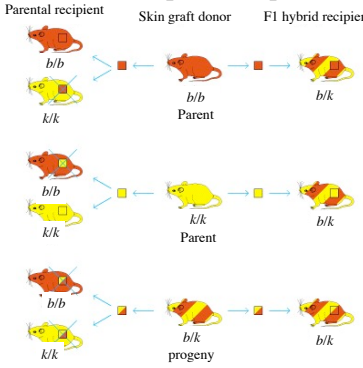
Progeny of 2 different inbred strains (F1 generation) are heterozygous at all genetic loci



The MHC locus is called "H-2" in mouse. Different inbred strains of mice differ at their MHC locus (different allelic form of the locus). This is designated by lower case superscripts: H-2^b and H-2^k for inbred parents, and H-$2^{b/k}$ for F1 progeny.

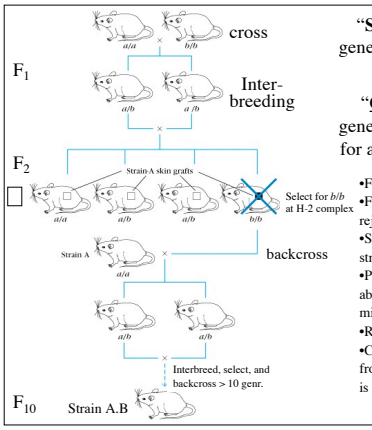
11

Skin transplants require MHC identity



McDevitt's and Gorer & Snell's experiments mapping the genetics of transplantation led to the discovery of the MHC

12



"**Syngenic**" mice are genetically identical at all loci (inbred).

"**Congenic**" mice are genetically identical except for a small genomic region

- F1 hybrid between inbred strains
- F2 progeny tested for ability to reject skin graft from A mice
- Selected progeny backcrossed to strain A mouse
- Progeny of backcross tested for ability to reject skin graft from A mice
- Repeat cycle >10 times
- Congenic strain containing all loci from strain A except MHC which is from strain B

13

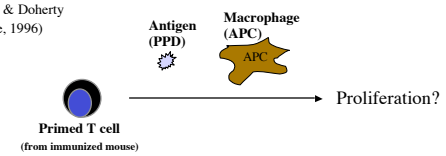
In vitro assay for T cell function

- Immunize mice with PPD (extract from heat-killed tuberculosis bacteria).
- Harvest splenic T cells from immunized mice and re-stimulate in vitro (recall response) with antigen (PPD) and antigen presenting cell (APC).
- Measure T cell response (proliferation: incorporation of radioactive thymidine).

14

APC must be from same inbred mouse strain as primed T cell

Zinkernagel & Doherty
(Nobel Prize, 1996)



Macrophage	Primed T cell	Antigen	T cell prdif.
none	strain 1	no	100 cpm
none	strain 1	yes	300 cpm
strain 1	strain 1	no	800 cpm
strain 1	strain 1	yes	119,000 cpm
strain 5	strain 1	no	2000 cpm
strain 5	strain 1	yes	2200 cpm

15

T cells responses depend on both the antigen and something expressed by the APC.

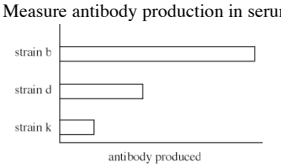
The strain difference that controls T cell - APC co-operation maps to the MHC locus: the same locus that controls skin graft rejection.

T cell responses show "MHC restriction"

16

Inbred strains of mice differ in their ability to respond to simple antigens:

Immunize different inbred mouse strains with polypeptides consisting of repeats of the same amino acids (ie poly-alanine). Measure antibody production in serum.



This differences also map to MHC locus!

17

MHC= Major Histocompatibility Locus

- Maps to small region on chromosome 17.
- Controls skin graft and tumor rejection.
- Controls transplant survival.
- Controls T-B collaboration.
- Controls immune responses to simple antigens.

18

Human Leukocyte Antigens (HLA)

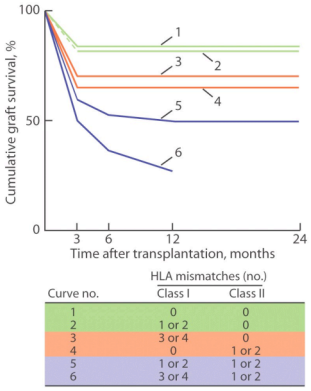
Patients that receive ABO-matched blood transfusions generate antibodies against the donor white blood cells (leukocytes). The antigens recognized by these anti-leukocyte antibodies are called human leukocyte antigens or HLA.

You can determine a person's "HLA" type by testing their white blood cells for reactivity to a panel of anti-leukocyte antibodies.

HLA are encoded by the human MHC locus!!

Anti-HLA antibodies provide a useful tool for determining whether individuals have same or different MHC genes.

19



Curve no.	HLA mismatches (no.) Class I	Class II
1	0	0
2	1 or 2	0
3	3 or 4	0
4	0	1 or 2
5	1 or 2	1 or 2
6	3 or 4	1 or 2

MHC locus also controls transplant survival in humans

20

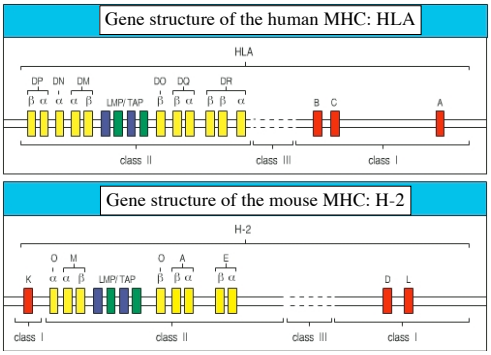
Major Histocompatibility Complex (MHC)

Review: antigen recognition strategies of B versus T cells
Discovery of MHC:
- Mouse genetics (inbred strains, congenic strains)
- T cell functional assays
- human leukocyte antigens (HLA)

Organization of MHC genes
Structure of MHC proteins (class I and II)
MHC nomenclature (polymorphism, alleles, and haplotypes)

21

MHC: a complex loci encoding several genes related to antigen presentation.



MHC= Major Histocompatibility Locus

- Also called HLA (human leukocyte antigen) locus in humans
- Also called H-2 in mice
- Complex loci containing three classes of genes-- I, II, III

23

MHC molecules

- Class I: associates with β2-microglobulin, expressed on all tissues except brain and RBCs. Present antigen to CD8 "killer: T cells.
- Class II: heterodimers of α and β chains, expressed only on "professional" antigen presenting cells (APCs: B cells, macrophage, dendritic cells). Present antigen to CD4 "helper" T cells.
- Class III: Generally encode various secreted proteins that have immune functions, including components of the complement system and molecules involved in inflammation.

24

Tissue distribution of MHC molecules

Tissue	MHC class I	MHC class II
Lymphoid tissues		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Other antigen-presenting cells (eg Langerhans' cells)	+++	+++
Epithelial cells of the thymus	+	+++
Other nucleated cells		
Neutrophils	+++	–
Hepatocytes	+	–
Kidney	+	–
Brain	+	– †
Non-nucleated cells		
Red blood cells	–	–

25

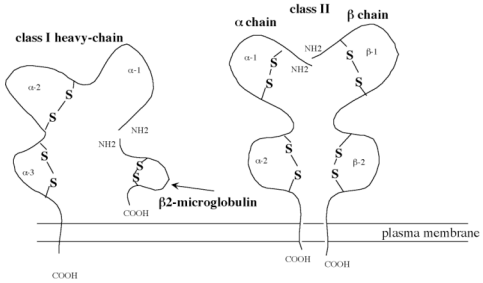
Major Histocompatibility Complex (MHC)

Review: antigen recognition strategies of B versus T cells
Discovery of MHC:
- Mouse genetics (inbred strains, congenic strains)
- human leukocyte antigens (HLA)
- T cell functional assays

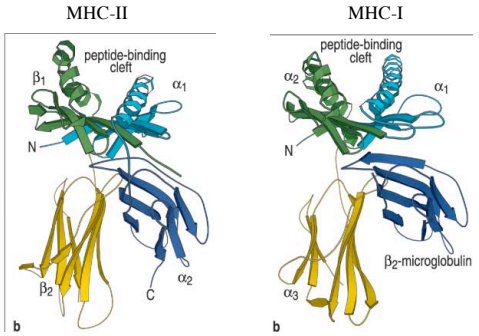
Organization of MHC genes
Structure of MHC proteins (class I and II)
MHC nomenclature (polymorphism, alleles, and haplotypes)

26

Structure of Class I and Class II MHC molecules



MHC class II molecules resemble MHC class I molecules in overall 3D structure



Major Histocompatibility Complex (MHC)

Review: antigen recognition strategies of B versus T cells
Discovery of MHC:
- Mouse genetics (inbred strains, congenic strains)
- human leukocyte antigens (HLA)
- T cell functional assays

Organization of MHC genes
Structure of MHC proteins (class I and II)
MHC nomenclature (polymorphism, alleles, and haplotypes)

29

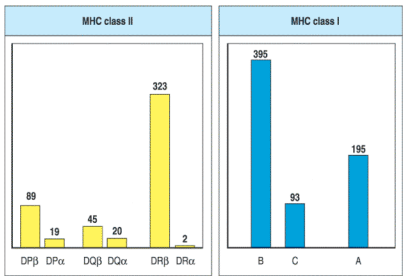
Genetic polymorphism: many alternative forms of the same gene, or alleles are present in a population-- "normal" variants

Mutation: an alteration in the sequence of a gene as compared to the sequence of the predominant allele in a population (e.g., β-globin mutation in sickle-cell anemia)

The genetic loci encoding **MHC genes are extremely polymorphic**: many different alleles of each locus are present in the population

30

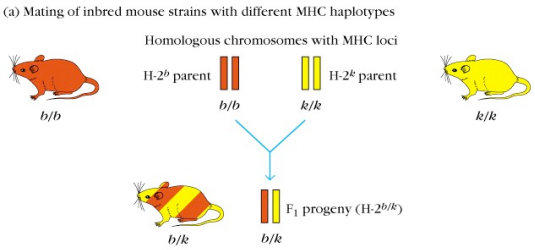
MHC Alleles Show Extensive Polymorphism



# of distinct alleles in population

haplotype

- The set of genes within a complex locus which are inherited as a group because they are linked on a chromosome



Mouse MHC nomenclature

The MHC locus in mouse (H-2) encodes 3 MHC-class I proteins (K, D, L) and 2 MHC-class II proteins (I-A and I-E). (Note that individual mouse MHC genes are designated by upper case letters.)

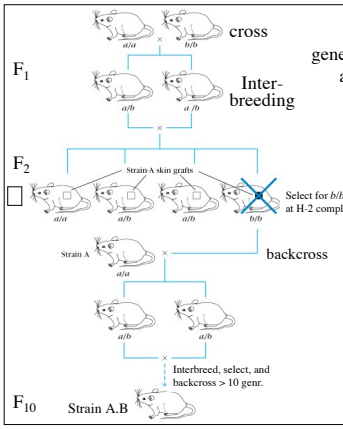
The MHC locus is polymorphic: each inbred strain has distinct versions (allelic forms) of the MHC genes. These are designated by lower case superscripts. (For example, K^b would indicate the "b" allelic version of the "K" MHC gene).

The entire locus containing all the MHC genes is usually inherited as a group. The version of the MHC locus in a particular inbred strain of mice (its MHC haplotype) is also designated by lower case superscripts. (For example, H-2^b).

TABLE 8-1 H-2 haplotypes of some mouse strains

Prototype strain	Other strains with the same haplotype	Haplotype	H-2 ALLELES K	IA	IE	S	D
CBA	AKR, C3H, B10.BR, C57BR	*k*	*k*	*k*	*k*	*k*	*k*
DBA/2	BALB/c, NZB, SEA, YBR	*d*	*d*	*d*	*d*	*d*	*d*
C57BL/10 (B10)	C57BL/6, C57L, C3H.SW, LP, 129	*b*	*b*	*b*	*b*	*b*	*b*
A	A/He, A/Sn, A/Wy, B10.A	*a*	*k*	*k*	*k*	*d*	*d*
B10.A (2R)*		*b2*	*k*	*k*	*k*	*d*	*b*
B10.A (3R)		*i3*	*b*	*b*	*k*	*d*	*d*
B10A. (4R)		*b4*	*k*	*k*	*b*	*b*	*b*
A.SW	B10.S, SJL	*s*	*s*	*s*	*s*	*s*	*s*
A.TL		*t1*	*s*	*k*	*k*	*k*	*d*
DBA/1	STOLI, B10.Q, BDP	*q*	*q*	*q*	*q*	*q*	*q*

The MHC haplotype of CBA mice is H-2^k, and one of its class II MHC genes is IA^k.
The MHC haplotype of C57BL/10 mice is H-2^b, and one of its class I MHC genes is D^b.
While the MHC locus is usually inherited as a group, recombination within the MHC locus can occur when two different strains are crossed.

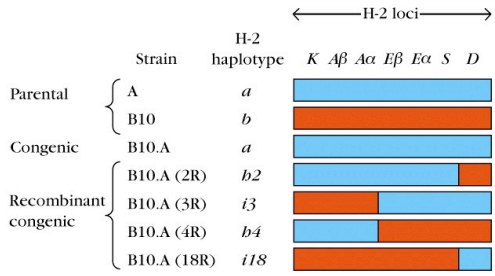


"**Congenic**" mice are genetically identical except for a small genomic region

- F1 hybrid between inbred strains
- F2 progeny tested for ability to reject skin graft from A mice
- Selected progeny backcrossed to strain A mouse
- Progeny of backcross tested for ability to reject skin graft from A mice
- Repeat cycle >10 times
- Congenic strain containing all loci from strain A except MHC which is from strain B
- Recombinant congenic strains have part of MHC locus from one parental strain and part from another.

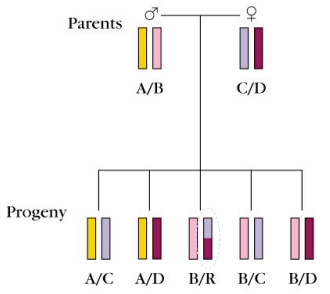
35

"**Congenic**" mice are genetically identical except for a small genomic region.
Meiotic recombination within the MHC locus can generate congenic mice with portions of the MHC locus derived from each parent.



HLA haplotypes in a typical human family

(note that human and mouse have different nomenclature for MHC genes and haplotypes)

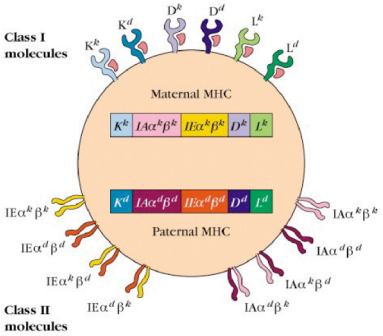


Meiotic recombination scrambles HLA haplotypes

Haplotypes	HLA Alleles					
	A	B	C	DR	DQ	DP
A	1	7	w3	2	1	1
B	2	8	w2	3	2	2
C	3	44	w4	4	1	3
D	11	35	w1	7	3	4
R	3	44	w4	7	3	4

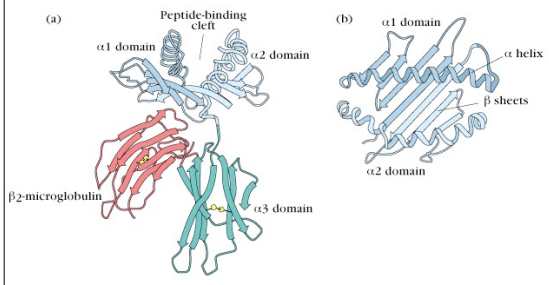
37

Co-dominant Expression of MHC Alleles



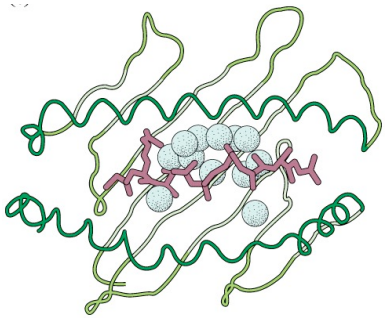
38

Ribbon diagram MHC class I

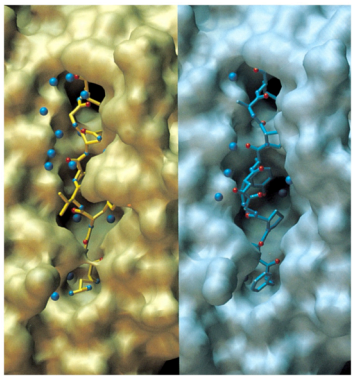


39

Peptide in the groove of a class I molecule

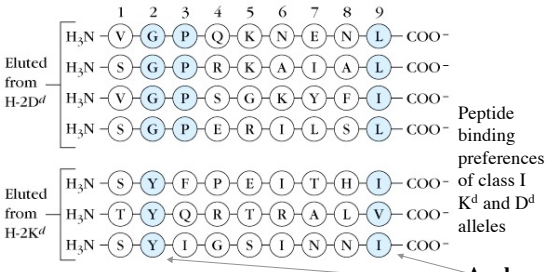


40



41

Peptide binding preferences of class I K^d and D^d alleles



A = alanine
E = glutamic acid
F = phenylalanine
G = glycine
H = histidine
I = isoleucine
K = lysine
L = leucine
N = asparagine
P = proline
Q = glutamine
R = arginine
S = serine
T = threonine
V = valine
Y = tyrosine

42

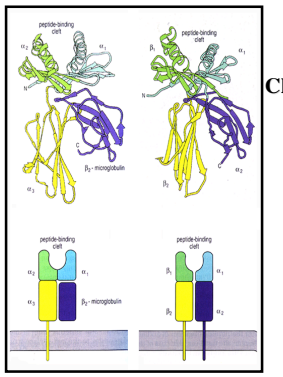
Naturally Processed Peptides

Class I - Associated	*Class II - Associated*
Conservation of length (9±1 AA) Allele specific motifs K^d – Y – – – – – – – L I K^b – – Y – F – – L – Y A2 – L – – – V – – V B27 – R – – – – – – F Source: - Cytosolic - Nuclear	Longer (12-22 AA) Core sequence and ragged ends VGSDWRFLRGYHQYAYDG VGSDWRFLRGYHQYA VGSDWRFLRGYHQY SDWRFLRGYHQYA Source: - Serum - Secretory - Membrane

43

MHC Molecule Structure

Class I **Class II**

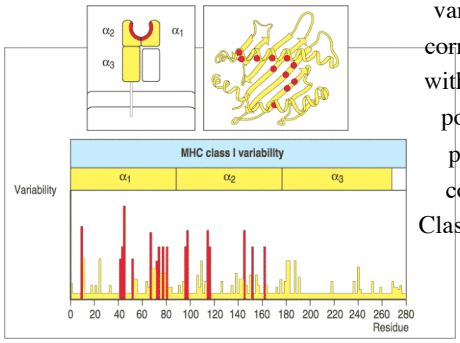


44

Peptide Binding Grooves of MHC Molecules

Class I **Class II**

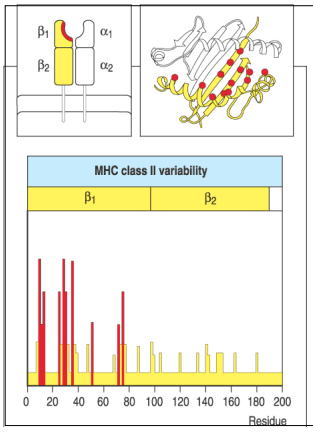
45



MHC variability corresponds with sites of potential peptide contact: Class I MHC

46

Fig 5.15 part 1 of 2 © 2001 Garland Science



MHC variability corresponds with sites of potential peptide contact: β chain of class II MHC

47

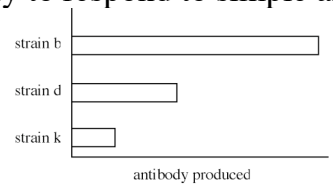
Variability of MHC vs. antigen receptors (BCR, TCR)

Polymorphism (hundreds of alleles) at the MHC locus creates diversity within a species but does not produce diversity within an individual. (All cells within an individual express a similar set of MHC genes.)

V(D)J rearrangement of generates an essentially limitless number of antigen receptors. Each B cell or T cell clone in an individual expresses a unique version of the antigen receptor (>10^8 variations / individual).

48

Inbred strains of mice differ in their ability to respond to simple antigens



Differences map to MHC locus

The mechanism: strain H-2^k lacks MHC alleles which can bind to peptides generated from specific antigen!

Should we be concerned that some humans might not be able to mount an immune response against some microbes?

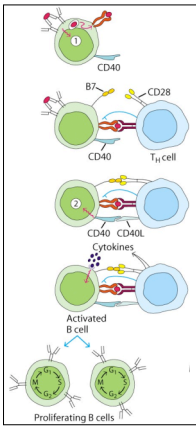
HLA Alleles

	A	B	C	DR	DQ	DP
A	1	7	w3	2	1	1
B	2	8	w2	3	2	2
C	3	44	w4	4	1	3
D	11	35	w1	7	3	4
R	3	44	w4	7	3	4

- Each human has six different class I alleles and six different class II alleles
- Each microbe contains at least thousands of potential peptide sequences
- Very likely that some foreign peptide can bind to self MHC and activate T cells

MHC and risk of disease

Disease	Allele	**Relative Risk**
Alkylosing Spondylitis	HLA B27	90
Narcolepsy	HLA DR2	130
IDDM (diabetes)	HLA DR4/DR3	20



T cell dependent B cell response

- Sequence of events:
- Antigen binding to BCR provides "Signal 1" to B cell.
- Antigen is internalized, processed and antigenic peptides are displayed on MHC for T cell recognition.
- T_H (helper T cell) recognizes antigen-MHC complex via the T cell antigen receptor (TCR): provides "Signal 1" to T cell.
- B7 on B cell binding to CD28 on T cell provides "Signal 2" to T cell.
- T cell activation leads to up-regulation of CD40L which bind to CD40 providing "Signal 2" to B cell.
- Cytokine production by activated T cell also help to activate B cell.
- B cell proliferates and differentiates into antibody secreting B cell (plasma cell).