Chapter 5:

Antigen Recognition by T Lymphocytes

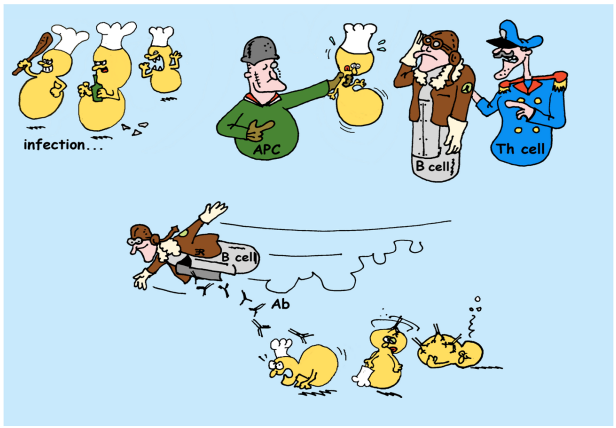
1

Recap of chapter 3

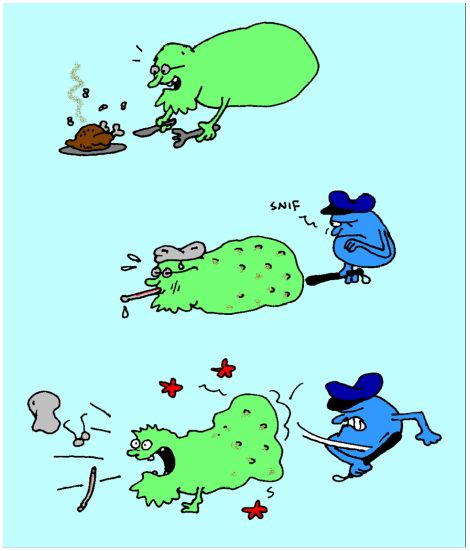
- What's the difference between the innate and adaptive immune system?
- In which way are the epitopes of B and T cells different?
- What does that imply for their role in the immune response?

2

Antigen recognition by B cells



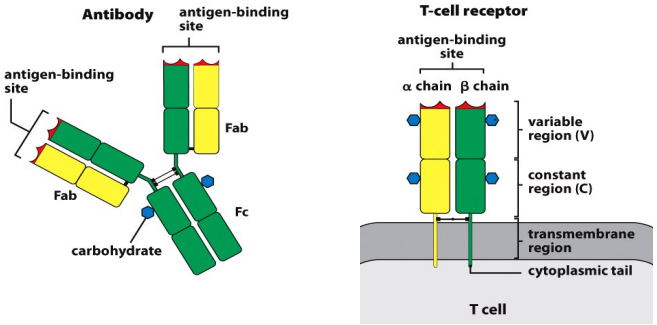
3



And by T cells…

4

Antibodies and T-cell receptors have a similar structure



The T-cell receptor resembles a membrane-associated Fab fragment of immunoglobulin.

Germline organization of TCR α and β

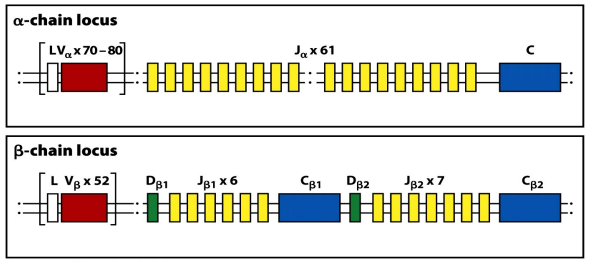


Figure 4-9 Immunobiology, 7ed. (© Garland Science 2008)

Rearrangement of the segments necessary to produce a functional receptor.

α-chain consists of **V and J**, β of **V, D, and J**

T-cell receptor diversity is generated by gene rearrangement

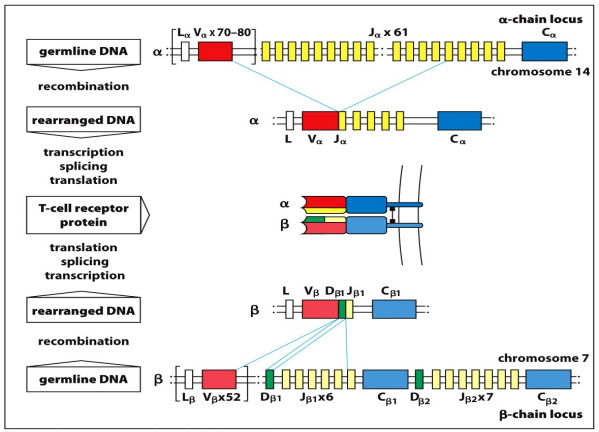


Figure 5.3 The Immune System, 3ed. (© Garland Science 2009)

Gene rearrangement similar for generation of T cell receptors and immunoglobulins

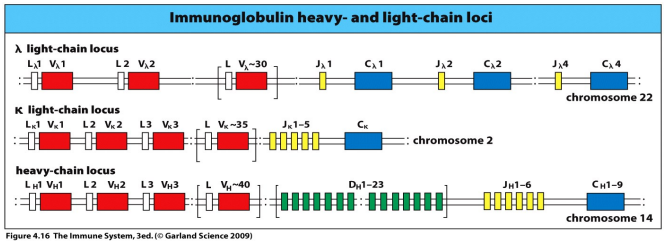


Figure 4.16 The Immune System, 3ed. (© Garland Science 2009)

Main difference:

T cell receptor C region simpler: only one Cα gene

Rearrangement of immunoglobulin genes occurs in the bone marrow, rearrangement of T cell receptor genes in the thymus.

The *RAG* genes were key elements in the origin of adaptive immunity

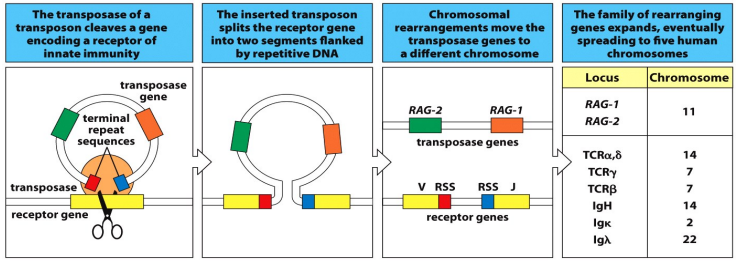
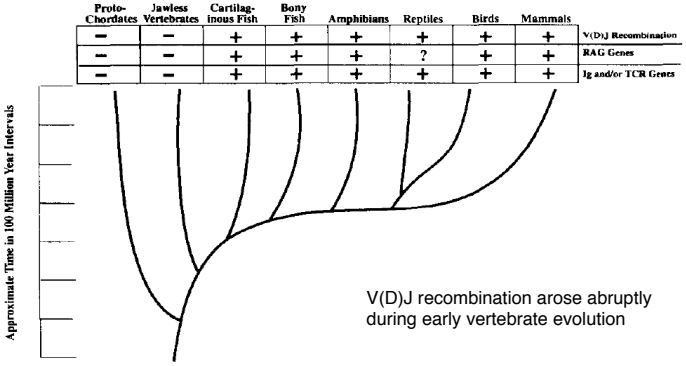


Figure 5.5 The Immune System, 3ed. (© Garland Science 2009)

RAG genes lack introns and resemble the transposase gene of transposons. Important for function: Recombination process results in an excision circle rather than a linear (and potentially harmful) element.

Evolution of RAG reflects the evolution of adaptive immunity



Thompson et al. (1995), Immunity 3:531-539

The magnitude of potential B and T cell receptor diversity

Element	Immunoglobulin		α:β T-cell receptors	
	H	κ+λ	β	α
Variable segments (V)	40	70	52	~70
Diversity segments (D)	25	0	2	0
D segments read in three frames	rarely	–	often	–
Joining segments (J)	6	5(κ) 4(λ)	13	61
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	1.9×10^6		5.8×10^6	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

Figure 5.9 The Immune System, 3ed. (© Garland Science 2009)

The magnitude of potential B and T cell receptor diversity

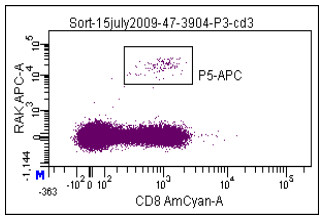
Element	Immunoglobulin		α:β T-cell receptors	
	H	κ+λ	β	α
Variable segments (V)	40	70	52	~70
Diversity segments (D)	25	0	2	0
D segm				
Joining				
Joints with N- and P-nucleotides	2	50% of joints	2	1
Number of V gene pairs	1.9×10^6		5.8×10^6	
Junctional diversity	$\sim 3 \times 10^7$		$\sim 2 \times 10^{11}$	
Total diversity	$\sim 5 \times 10^{13}$		$\sim 10^{18}$	

Somatic recombination results in combinatorial & junctional diversity

Figure 5.9 The Immune System, 3ed. (© Garland Science 2009)

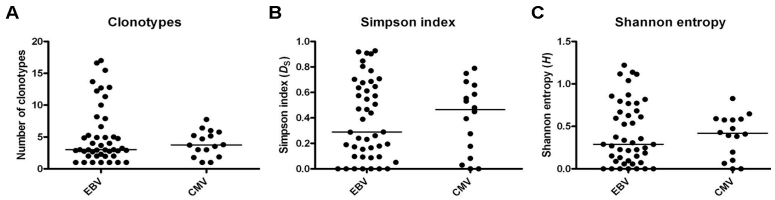
CDR3 analysis of specific T-cells

Vβ	CDR3 (AA)	Jβ	%
7.2	CASSLVLSSPTYYEQYF	2.7	51.8
3.1	CASSQTTSVNTEAFF	1.1	15.3
27	CASSSLNTEAFF	1.1	5.9
11.2	CASSHVINQFF	2.1	4.7
7.9	CASSLPRGRDNEQFF	2.1	4.7
11.2	CASSLGTGHNEQFF	2.1	3.5
5.6	CASSSNRDRNTIYF	1.3	2.4
7.9	CASSLGLGVNNEQFF	2.1	2.4
7.9	CASSSTGPGNSPLHF	1.6	2.4
29.1	CSVSAGEEDTQYF	2.3	1.2
4.2	CASSQVQGTSGGEQYF	2.7	1.2
12.3	CASSSMVAGEYEQFF	2.1	1.2
7.2	CASSLVVIQETQYF	2.5	1.2
7.9	CASSPSKPGDNEQFF	2.1	1.2
7.2	CASSPSKPGDNEQFF	2.1	1.2



13

T cell responses against different viruses



14

What do you think happens to an individual who lacks RAG?

15

A defect in V(D)J recombination results in severe immunodefiency

SCID = Severe combined immunodeficiency syndrome

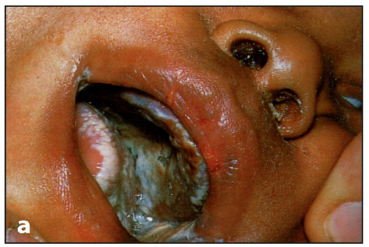


Figure 5.4 The Immune System, 3ed. (© Garland Science 2009)

- absence of adaptive immunity
- May be caused by mutations in at least 13 different genes, e.g. the RAG genes.
- fatal in the first 2 years of life because of opportunistic infections
- Therapy only possible if diagnosis is made at birth or shortly thereafter.
- Therapy in the form of bone marrow stem-cell transplantation

Buckley (2010) Immunol Res. 49(1-3):25-43

16

The composition of the T cell receptor complex

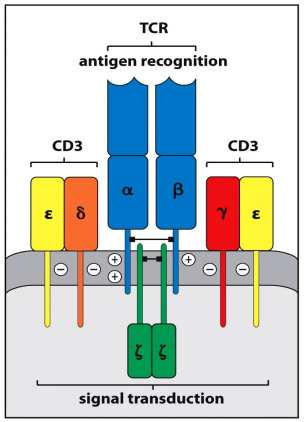


Figure 5.6 The Immune System, 3ed. (© Garland Science 2009)

Expression of the T cell receptor on the cell surface requires association with additional proteins

A distinct population of T cells expresses a second class of T-cell receptor with γ and δ chains

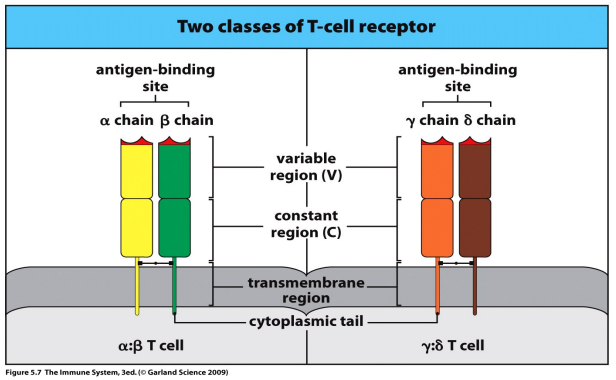


Figure 5.7 The Immune System, 3ed. (© Garland Science 2009)

T cells either express αβ receptors or γδ receptors! Never both!

T cells function by interacting with other cells

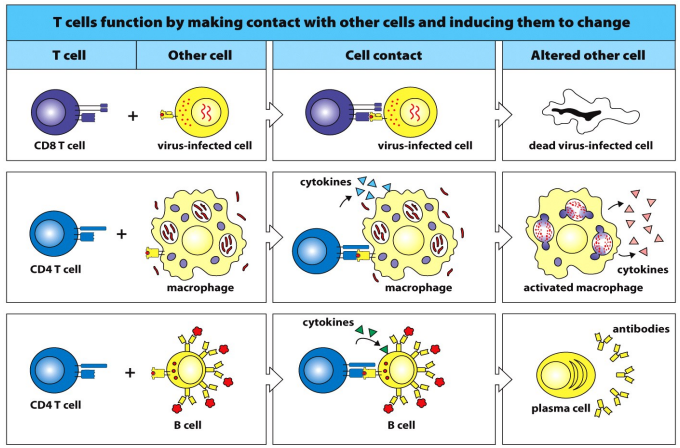


Figure 5.12 The Immune System, 3ed. (© Garland Science 2009)

MHC class I presents peptide antigens to CD8 T cells
MHC class II presents peptide antigens to CD4 T cells

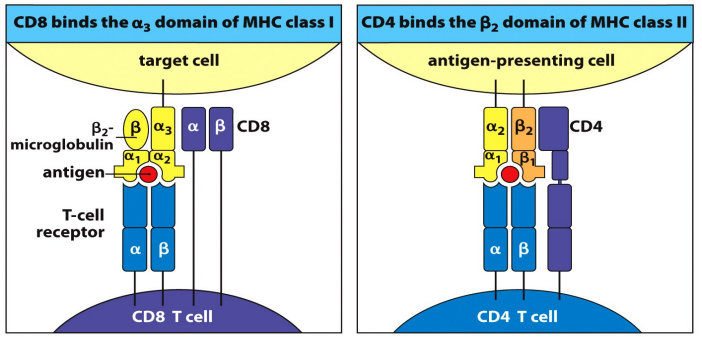


Figure 5.14 The Immune System, 3ed. (© Garland Science 2009)

MHC = major histocompatibility complex

The two classes of MHC molecules have very similar structures

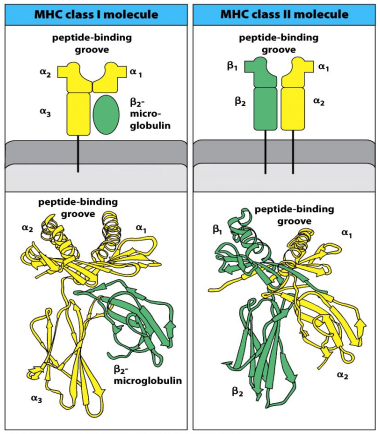


Figure 5.13 The Immune System, 3ed. (© Garland Science 2009)

MHC molecules bind a variety of peptides

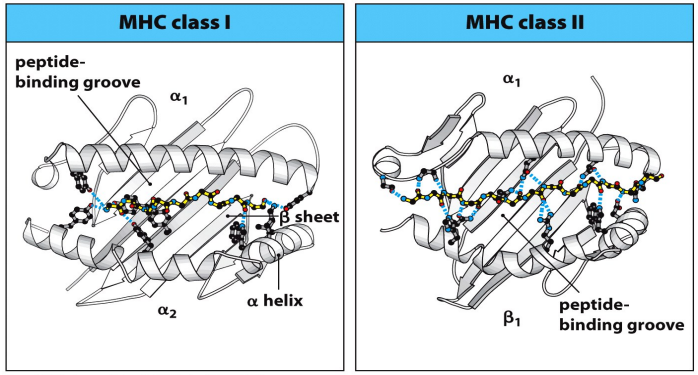
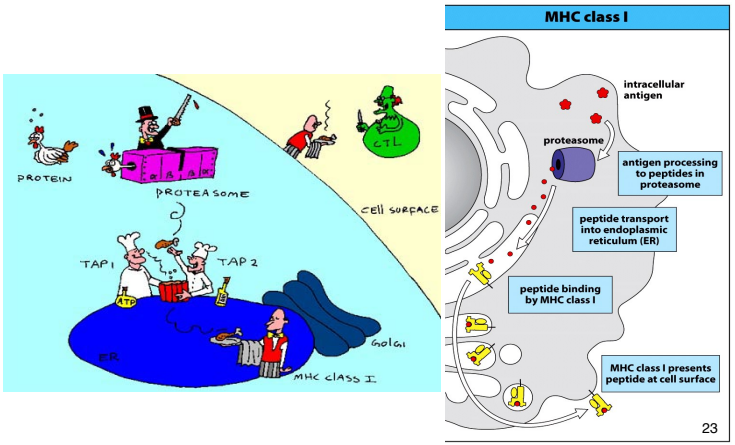


Figure 5.15 The Immune System, 3ed. (© Garland Science 2009)

Processing of antigens which bind to MHC class I or II occurs in different cellular compartments



Processing of antigens which bind to MHC class I or II occurs in different cellular compartments

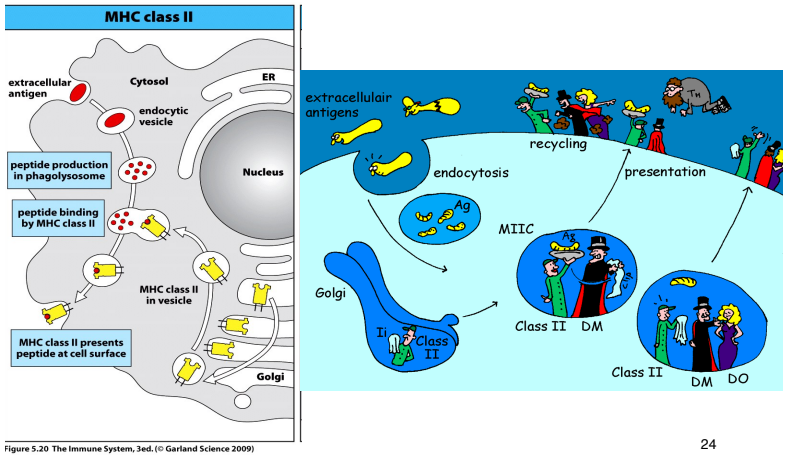
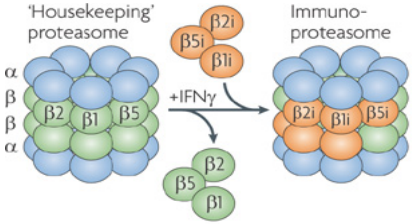


Figure 5.20 The Immune System, 3ed. (© Garland Science 2009)

In infected tissue, cells switch to immunoproteasome for protein degradation



Prefential cleavage after hydrophobic or basic residues produces peptides that fit the C-terminal binding motif of TAP and many HLA allotypes.

Klein *et al.* (2009), Nat Rev Immunol 9(12):833-44

25

MHC class I binds peptides as part of a peptide-loading complex

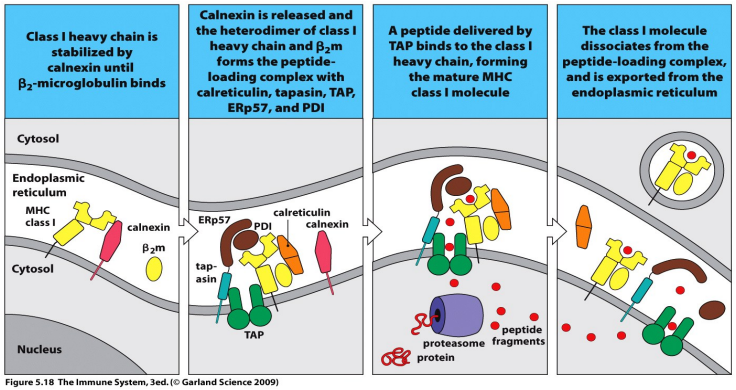


Figure 5.18 The Immune System, 3ed. (© Garland Science 2009)

26

In the ER, peptides may be further trimmed from the N-terminal end by an amino peptidase

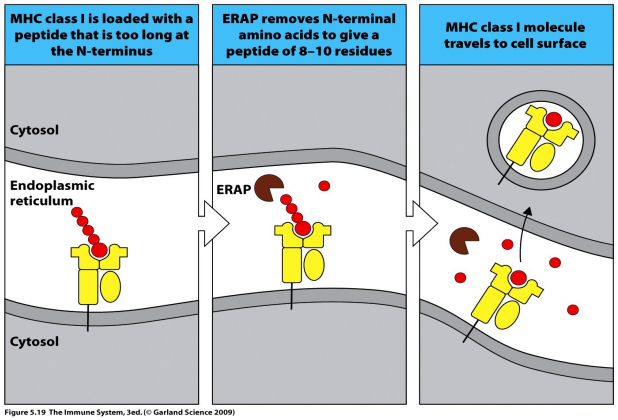


Figure 5.19 The Immune System, 3ed. (© Garland Science 2009)

27

The MHC class II antigen processing pathway

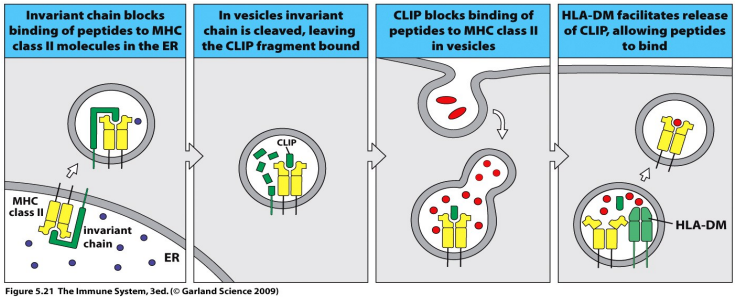


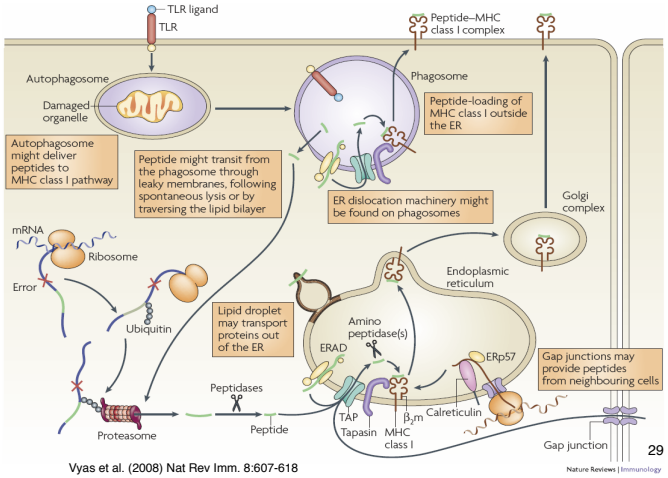
Figure 5.21 The Immune System, 3ed. (© Garland Science 2009)

MHC class II molecules are prevented from binding peptides in the endoplasmic reticulum by the invariant chain

CLIP = class II-associated invariant-chain peptide

28

Cross-presentation by dendritic cells



Vyas et al. (2008) Nat Rev Imm. 8:607-618

29

Differential expression of MHC class I and II molecules

professional antigen-presenting cells

Tissue/cell	MHC class I	MHC class II
Hematopoietic		
T cells	+++	+*
B cells	+++	+++
Macrophages	+++	++
Dendritic cells	+++	+++
Neutrophils	+++	–
Erythrocytes	–	–
Non-hematopoietic		
Thymic epithelium	+	+++
Liver hepatocytes	+	–
Kidney epithelium	+	–
Brain	+	– †

Figure 5.23 The Immune System, 3ed. (© Garland Science 2009)

30

The major histocompatibility complex

- Cluster of closely linked genes on chromosome 6
- Numerous genetic variants of MHC class I and II present in the human population

  => diversity due to multigene families and genetic polymorphism

The human MHC: human leukocyte antigen (HLA) complex

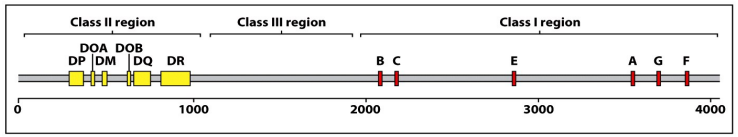


Figure 5.26 The Immune System, 3ed. (© Garland Science 2009)

31

Most of the genes in the HLA class II region are involved in the processing and presentation of antigens to T cells

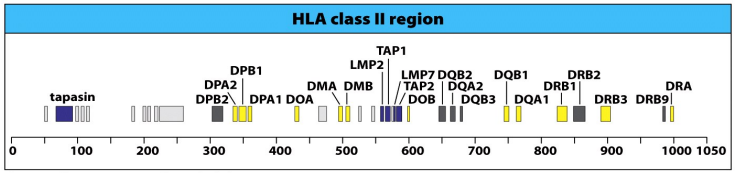


Figure 5.28 The Immune System, 3ed. (© Garland Science 2009)

32

Human MHC regions differ in their number of DR genes

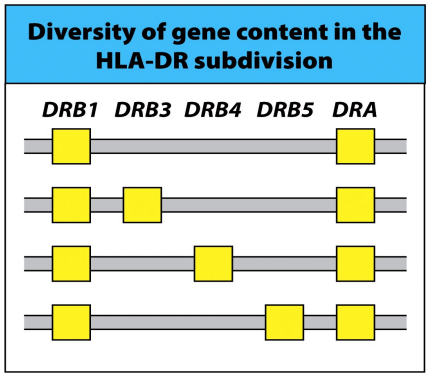


Figure 5.27 The Immune System, 3ed. (© Garland Science 2009)

33

Diversity of HLA molecules in human population is caused by copy number variation in concert with polymorphism

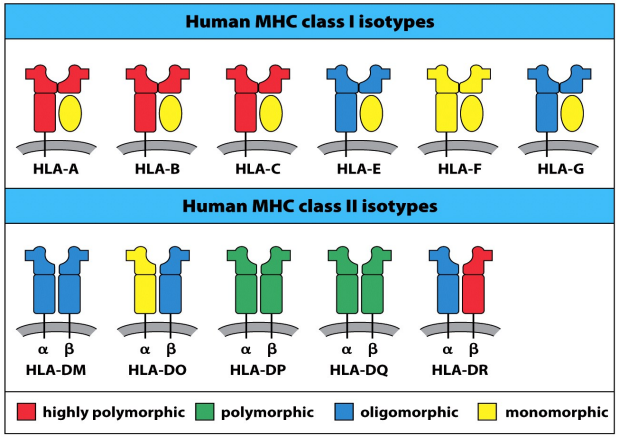


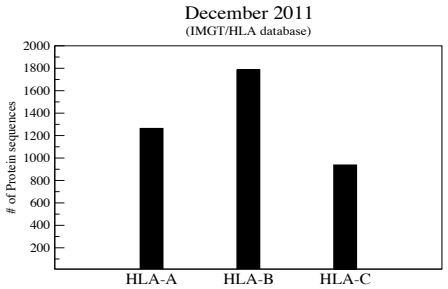
Figure 5.24 The Immune System, 3ed. (© Garland Science 2009)

34

HLA polymorphism

MHC class	HLA locus	Number of allotypes
MHC class I	A	506
	B	872
	C	274
	E	3
	F	4
	G	10
MHC class II	DMA	4
	DMB	7
	DOA	3
	DOB	4
	DPA1	15
	DPB1	114
	DQA1	25
	DQB1	66
	DRA	2
	DRB1	466
	DRB3	37
	DRB4	7
	DRB5	15

Figure 5.25 The Immune System, 3ed. (© Garland Science 2009)



35

Genetic mechanisms that generate new MHC polymorphisms

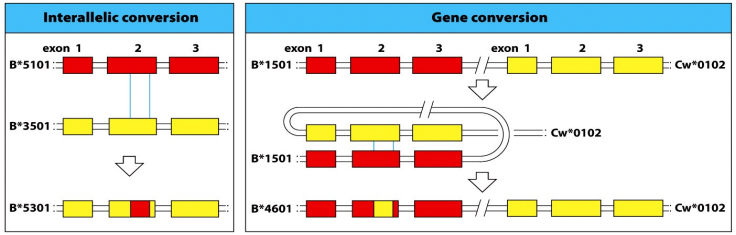


Figure 5.34 The Immune System, 3ed. (© Garland Science 2009)

36

MHC polymorphism affects the binding and presentation of peptide antigens to T cells

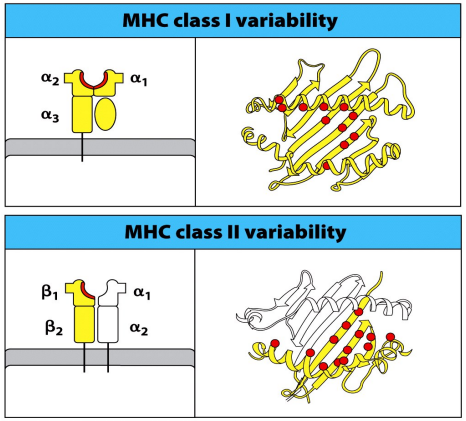


Figure 5.29 The Immune System, 3ed. (© Garland Science 2009)

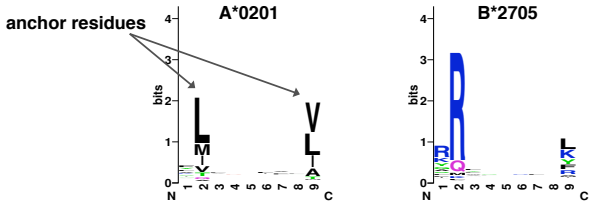
The most polymorphic amino acid residues map to the peptide binding site.

37

Peptide binding motifs of some HLA class I and II allotypes

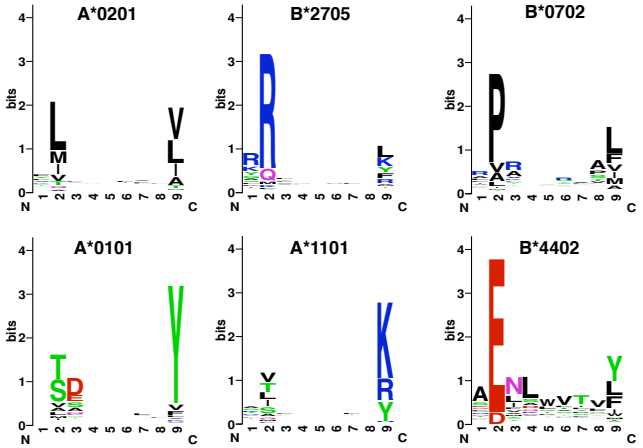
	MHC molecule	Amino acid sequence of peptide-binding motifs and bound peptides	Source of bound peptide
		Position in peptide sequence N 1 2 3 4 5 6 7 8 9 C	
Class I	HLA-A*0201	Peptide-binding motif [A/M] . . . . V . [V/L]	
		Bound peptide I L K E P V H G V	HIV reverse transcriptase
	HLA-B*2705	Peptide-binding motif . R . . . . . [R/K]	
		Bound peptide S R Y W A I R T R	Influenza A nucleoprotein
Class II	HLA-DRB1*0401	Self peptide G V Y F Y L Q W G R S T L V S V S	Igκ light chain
	HLA-DQA1*0501 HLA-DQB1*0301	Self peptide I P E L N K V A R A A A A	Transferrin receptor

Figure 5.30 The Immune System, 3ed. (© Garland Science 2009)



38

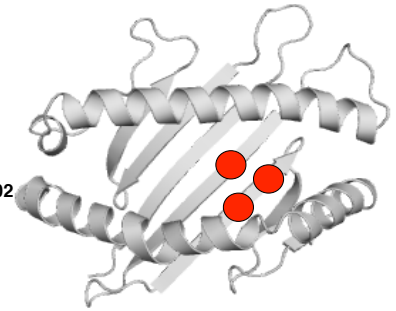
A great variety of binding motifs…

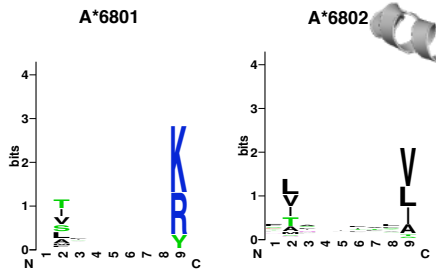


39

Seemingly small differences may have a big impact on the peptide binding motif!

A*6801 and A*6802 have very different peptide binding motifs.





40

T cell recognition of antigens is MHC restricted

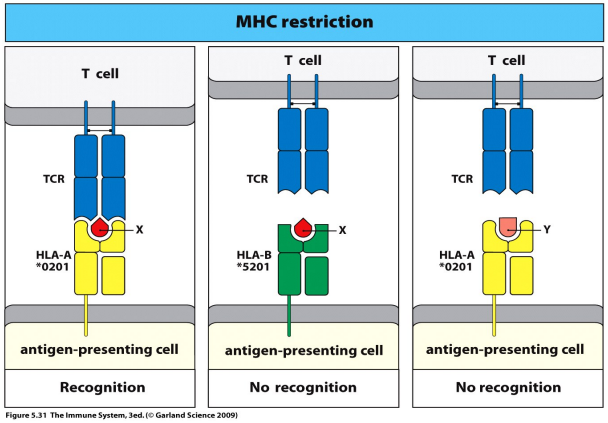


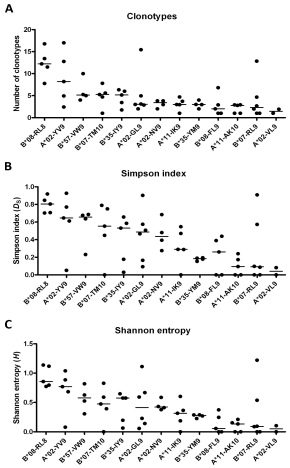
Figure 5.31 The Immune System, 3ed. (© Garland Science 2009)

But: Some T cells are alloreactive => problem for organ and bone marrow transplantations!

Nobel Prize Medicine 1996

Peter Doherty (1940 -) and Rolf Zinkernagel (1944 -)

Peptide determines TCR diversity



MHC molecules are expressed in a codominant fashion.

Which consequences does that have for an individual?

Heterozygous individuals are able to present a more diverse set of peptides to their T cells

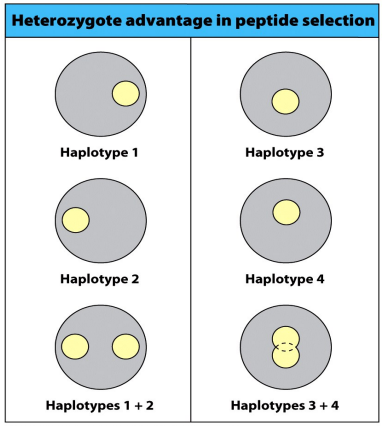
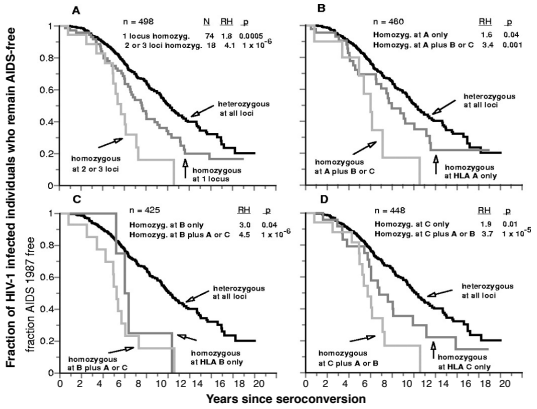


Figure 5.32 The Immune System, 3ed. (© Garland Science 2009)

HLA heterozygosity delays the progression to AIDS



Carrington et al. Science 1999;283:1748-1752

Exposure to pathogens shapes MHC gene frequencies

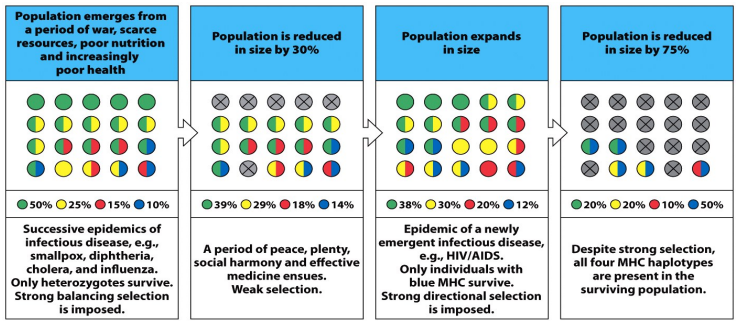
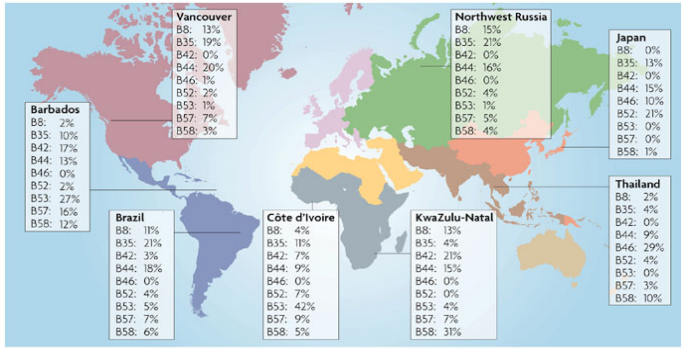


Figure 5.33 The Immune System, 3ed. (© Garland Science 2009)

=> Balancing selection maintains diversity of HLA allotypes in populations

Worldwide HLA class I diversity

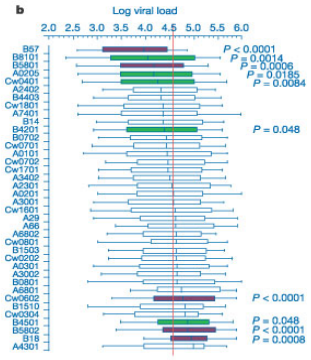


Nature Reviews | Immunology

Goulder & Watkins (2008) Nat Rev Imm. 8:619-630

HLA-association with HIV-1 disease outcome

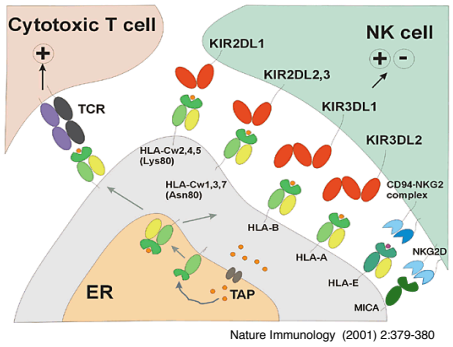
- HIV-1 viral load roughly predicts speed of disease progression
- Specific HLA class I molecules have been associated with either slow or fast progression to AIDS



Kiepiela *et al.* (2004) *Nature* 432:769-75

Another important role of MHC class I molecules?

Another important role of MHC class I molecules?



Nature Immunology (2001) 2:379-380

Some of them serve as ligands for NK cell receptors.

NK cell receptor genes cluster in two different regions of the human genome

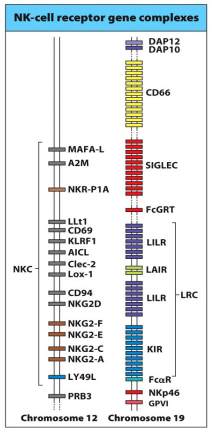


Figure 10.33 The Immune System, 3ed. (© Garland Science 2009)

Humans possess more than 30 different NK cell receptor genes.

Individual NK cells express different combinations of receptors.

NKC – natural killer complex:
lectin-like NK cell receptors

LRC – leukocyte receptor complex:
immunoglobulin-like receptors

A variety of inhibitory and activating receptors allows NK cells to identify infected cells.

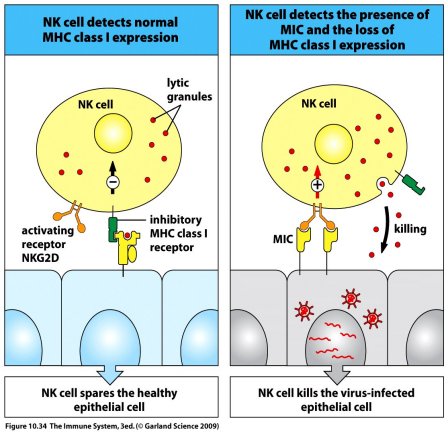


Figure 10.34 The Immune System, 3ed. (© Garland Science 2009)

53

CD94:NKG2A recognizes HLA-E in complex with a peptide derived from the leader sequence of HLA-A, -B or -C molecules.

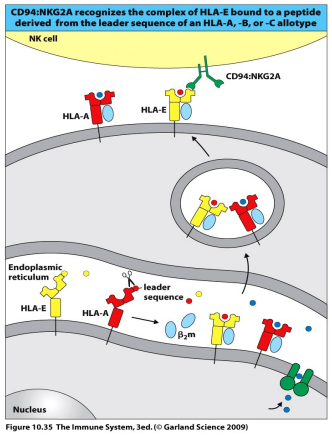


Figure 10.35 The Immune System, 3ed. (© Garland Science 2009)

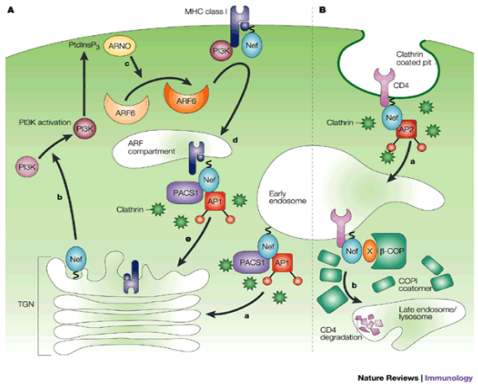
HLA-E is non-polymorphic and has a restricted specificity for peptides

HLA-E exclusively binds a peptide derived from the leader sequence of HLA-A, -B, and -C molecules.

The amount of HLA-E on the cell-surface is a measure of the amount of HLA-A, -B, and -C produced by the cell.

54

Clever viral evasion of NK cell response



Nature Reviews | Immunology

- HIV: HLA-A and -B are down regulated, but HLA-C not
  - (Adnan et al, Blood, 2006, 3414).
- EBV: HLA-A and -B are down regulated, but HLA-E is upregulated
  - (Dutta, et al, Cancer, 2006, 1685)

Adapted from Peterlin &Trono, Nat. Rev. Immunol, 2003, 97.

Special function of NK cells: detect missing self

KIR bind to the same face of the MHC class I molecules as the T cell receptor

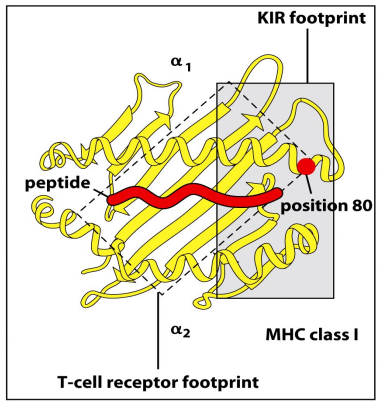


Figure 10.36 The Immune System, 3ed. (© Garland Science 2009)

56