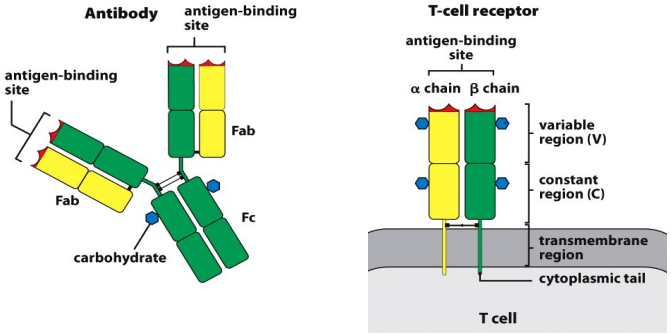
Chapter 4 + 5:

Antigen Recognition by T and B Lymphocytes

Universiteit Utrecht

Antibodies and T-cell receptors have a similar structure



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

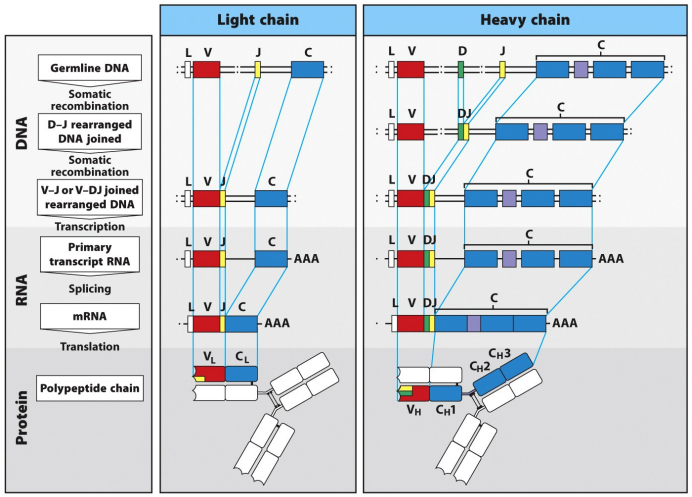


Figure 5.1 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

V-D-J recombination movie:

V-D-J recombination

T cell receptor: V/D/J segments

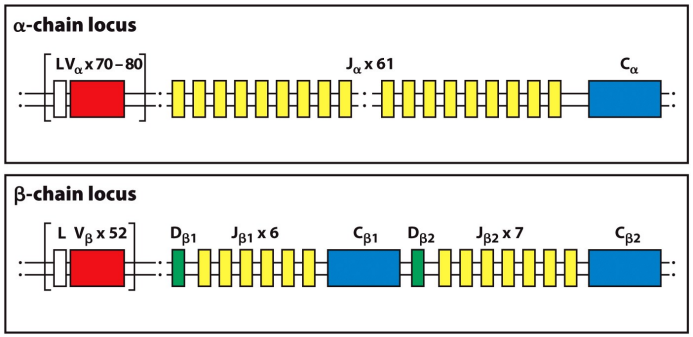


Figure 5.8 Janeway's Immunobiology, 8ed. (© Garland Science 2012)

T-cell receptor diversity is generated by gene rearrangement

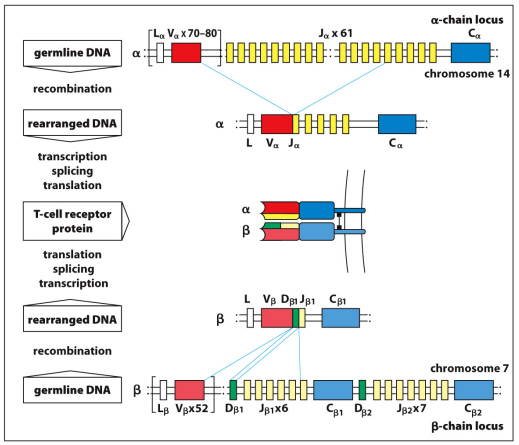


Figure 5.3 The Immune System, 4th ed. (© Garland Science 2015)

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

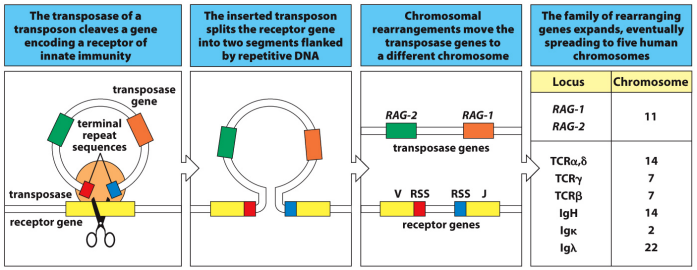


Figure 5.5 The Immune System, 4th ed. (© Garland Science 2015)

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.

How do RAGs work? RSS are essential!

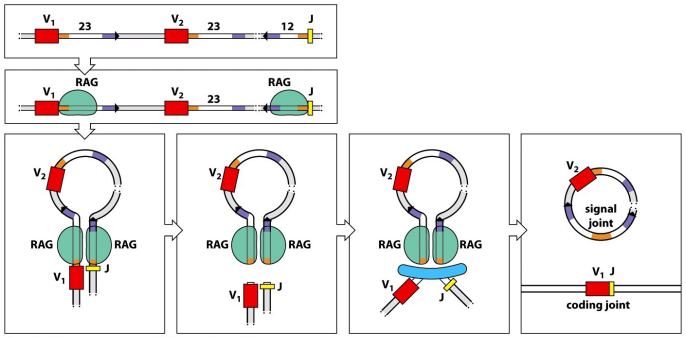


Figure 4.20 The Immune System, 3ed. (© Garland Science 2009)

Generation of junctional diversity

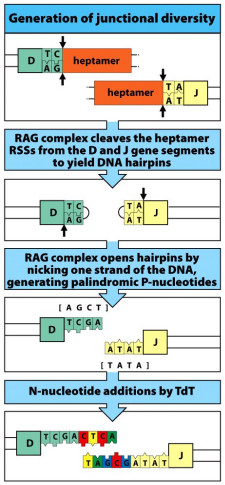


Figure 4.21 part 1 of 2 The Immune System, 3ed. (© Garland Science 2009)

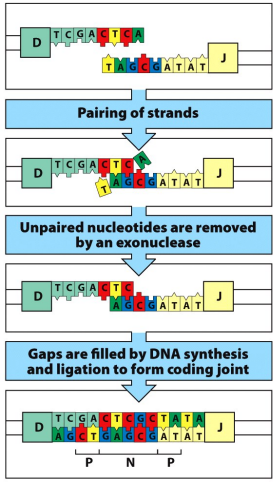


Figure 4.21 part 2 of 2 The Immune System, 3ed. (© Garland Science 2009)

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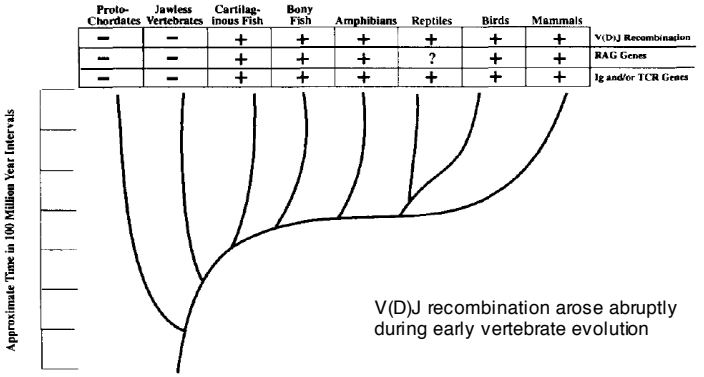
Evolution of RAG reflects the evolution of adaptive immunity



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

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

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

SCID = Severe combined immunodeficiency syndrome

- 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

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Where are the V, D, and J segments (for T cells) coded in our genomes?

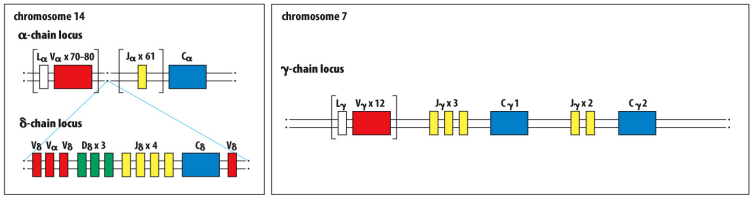

Figure 5.8 The Immune System, 4th ed. (© Garland Science 2015)

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)	23	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, 4th ed. (© Garland Science 2015)

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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
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D segments				
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Somatic recombination results in combinatorial & junctional diversity

Figure 5.9 The Immune System, 4th ed. (© Garland Science 2015)

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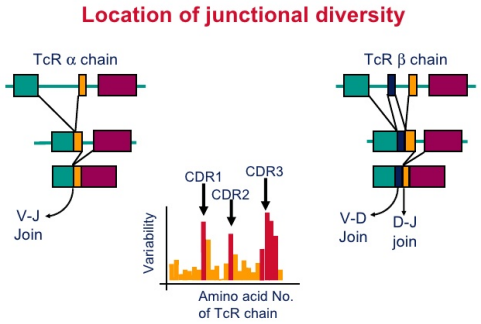
Recombination process generates diversity



CDR = Complemantarity determining region

Figure courtesy of Dr. Hewit

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CDR regions on TCR

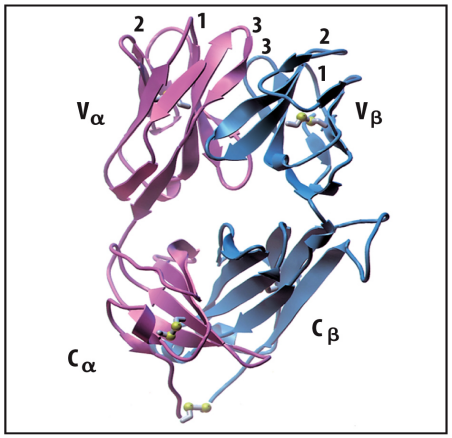


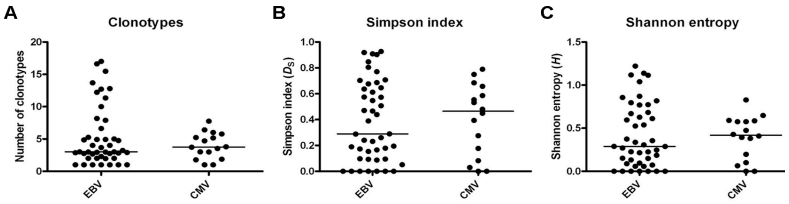
Figure 5.2 The Immune System, 4th ed. (© Garland Science 2015)

CDR3β analysis of specific T-cells against different viruses

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

Koning, et al JI 2013

T cell responses against different viruses



The composition of the T cell receptor complex

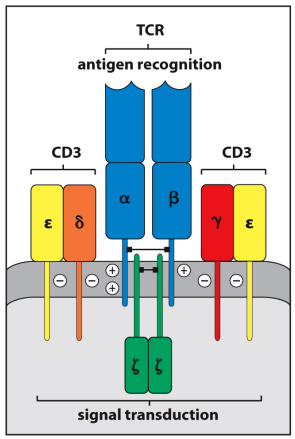


Figure 5.6 The Immune System, 4th ed. (© Garland Science 2015)

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

T cells function by interacting with other cells

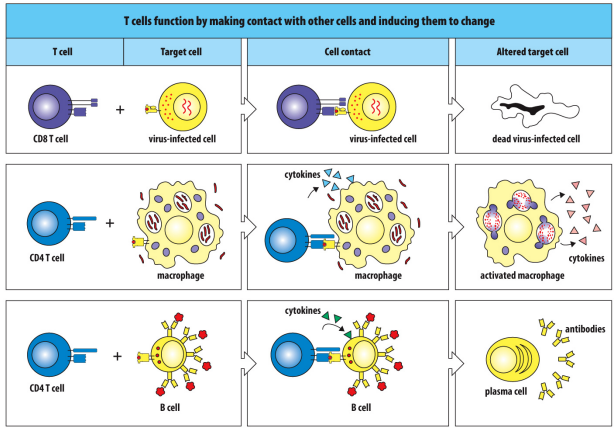


Figure 5.13 The Immune System, 4th ed. (© Garland Science 2015)

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

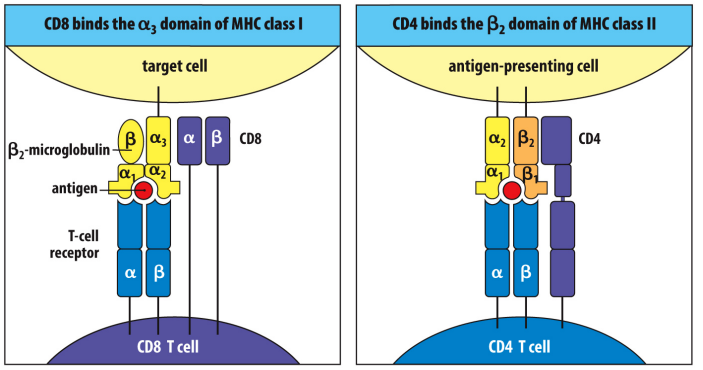


Figure 5.15 The Immune System, 4th ed. (© Garland Science 2015)

MHC = major histocompatibility complex
Structure of MHC class I and class II are similar!

MHC molecules bind a variety of peptides

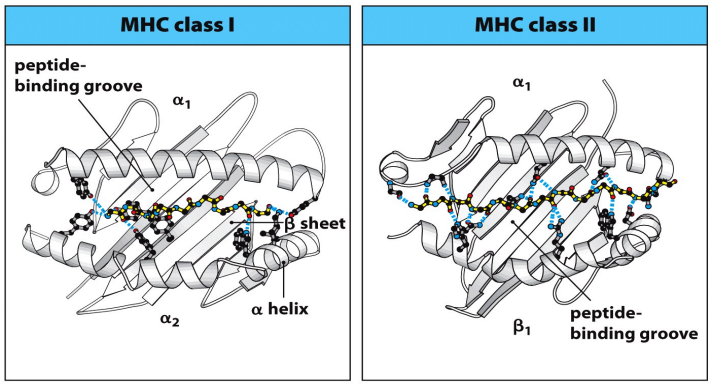
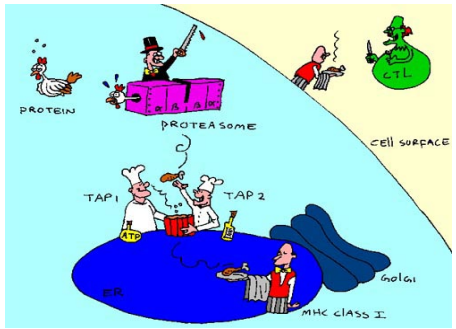
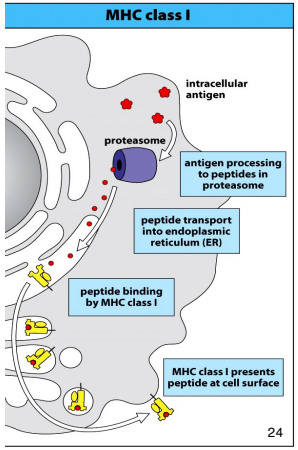


Figure 5.15 The Immune System, 3ed. (© Garland Science 2009)

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

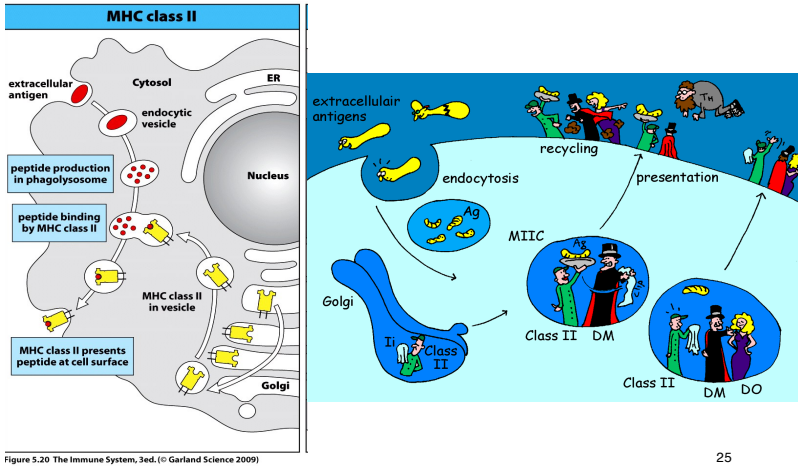
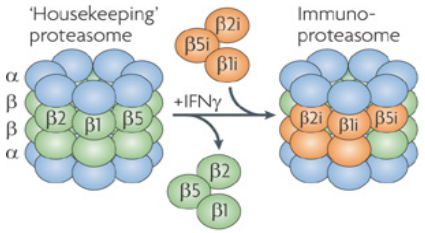


Figure 5.20 The Immune System, 3ed. (© Garland Science 2009)

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

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

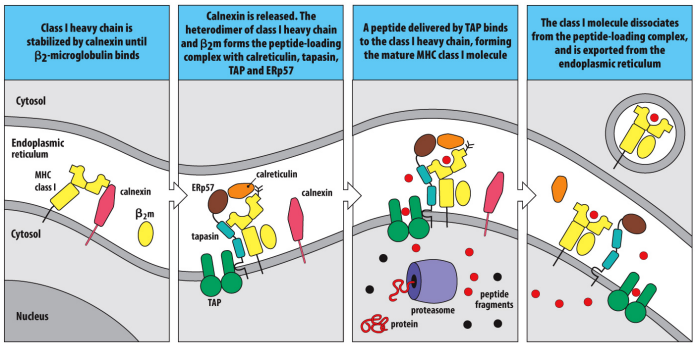


Figure 5.20 The Immune System, 4th ed. (© Garland Science 2015)

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

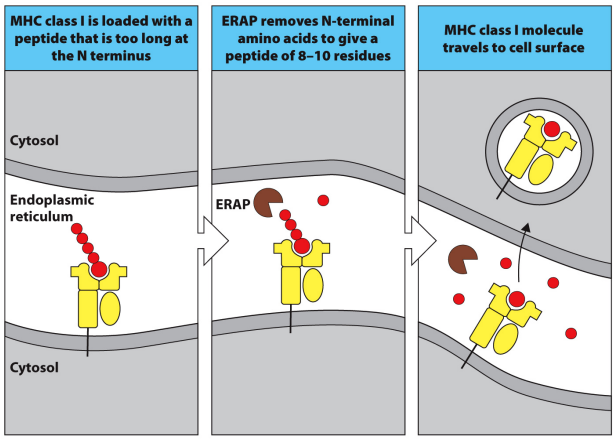


Figure 5.21 The Immune System, 4th ed. (© Garland Science 2015)

The MHC class II antigen processing pathway

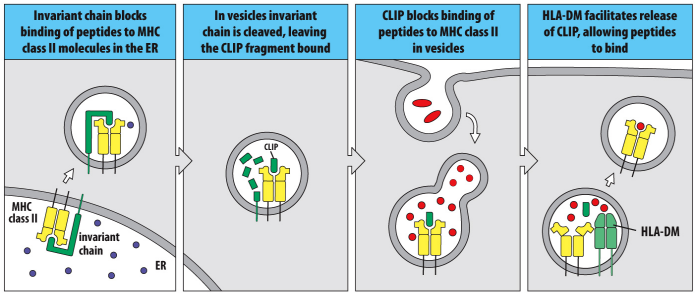
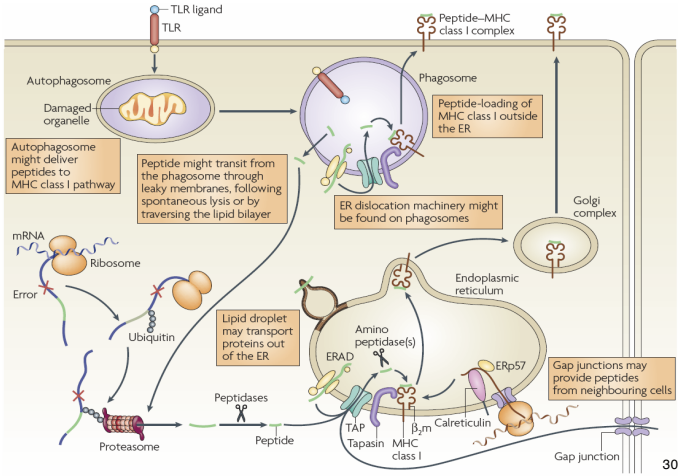


Figure 5.23 The Immune System, 4th ed. (© Garland Science 2015)

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

CLIP = class II-associated invariant-chain peptide

Cross-presentation by dendritic cells



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

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		
Liver hepatocytes	+	–
Kidney epithelium	+	–
Brain	+	–†

Figure 5.25 The Immune System, 4th ed. (© Garland Science 2015)

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

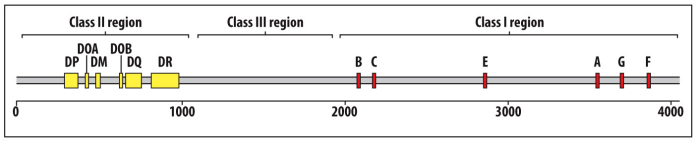


Figure 5.30 The Immune System, 4th ed. (© Garland Science 2015)

Diversity of HLA class I molecules in human population is caused by **polymorphism**

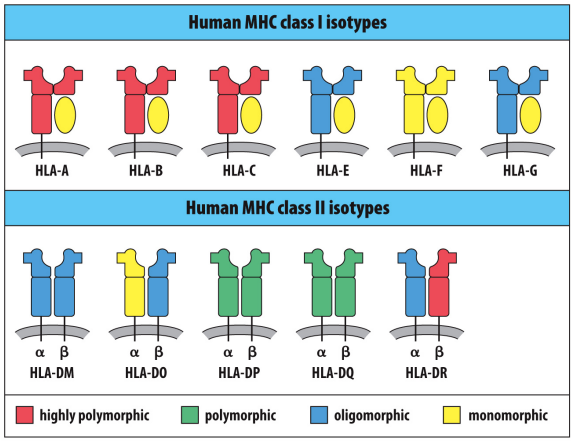
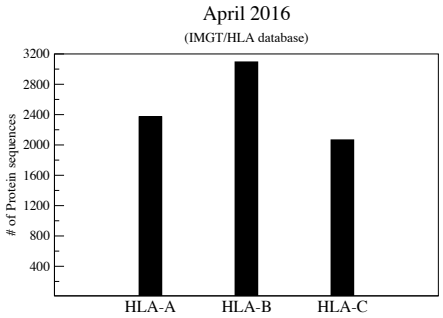


Figure 5.28 The Immune System, 4th ed. (© Garland Science 2015)

HLA polymorphism		
MHC class	HLA locus	Number of allotypes
MHC class I	A	1939
	B	2577
	C	1595
	E	6
	F	4
	G	16
MHC class II	DMA	4
	DMB	7
	DOA	3
	DOB	5
	DPA1	17
	DPB1	286
	DQA1	32
	DQB1	399
	DRA	2
	DRB1	1158
	DRB3	46
	DRB4	8
	DRB5	17

Figure 5.29 The Immune System, 4th ed. (© Garland Science 2015)

How many MHC molecules do we find in the human population?



What are the functional differences between different MHC molecules?

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

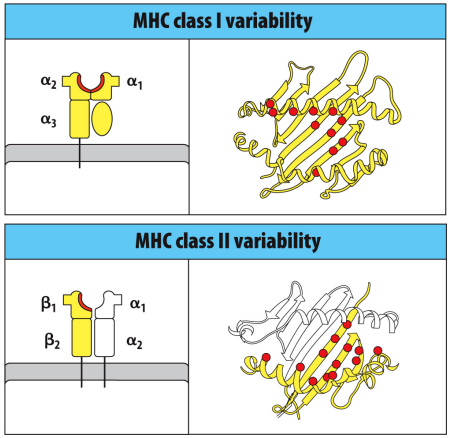


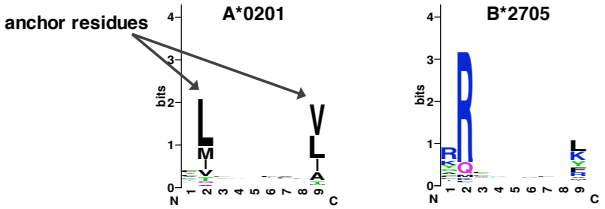
Figure 5.33 The Immune System, 4th ed. (© Garland Science 2015)

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

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 L/M V V/L	
		Bound peptide I L K E P Y 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	Transferrin receptor

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



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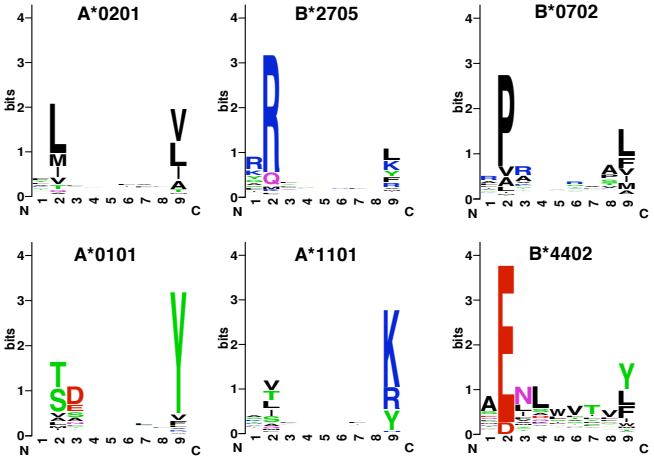
A great variety of binding motifs…



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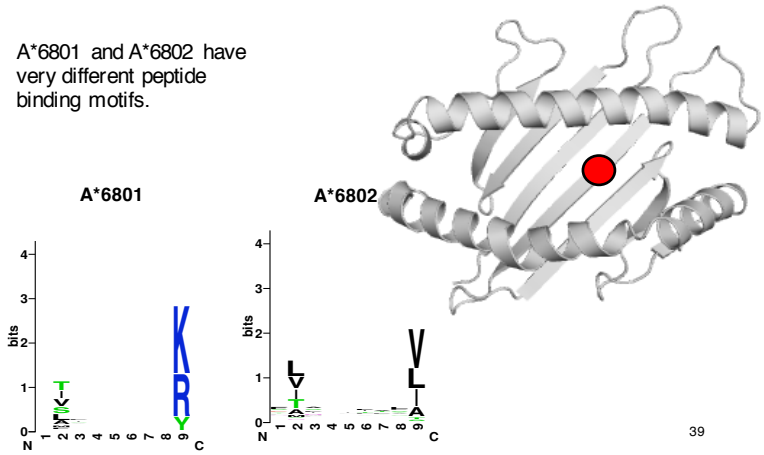
Seemingly small differences may have a big impact on the peptide binding motif!

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



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T cell recognition of antigens is MHC restricted

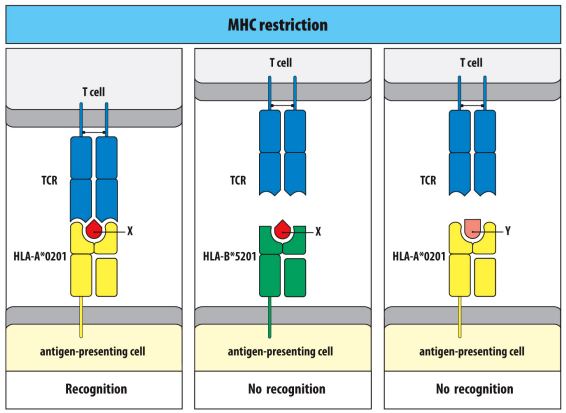

Figure 5.35 The Immune System, 4th ed. (© Garland Science 2015)

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

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Nobel Prize Medicine 1996

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

41

MHC molecules are expressed in a codominant fashion.

Which consequences does that have for an individual?

42

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

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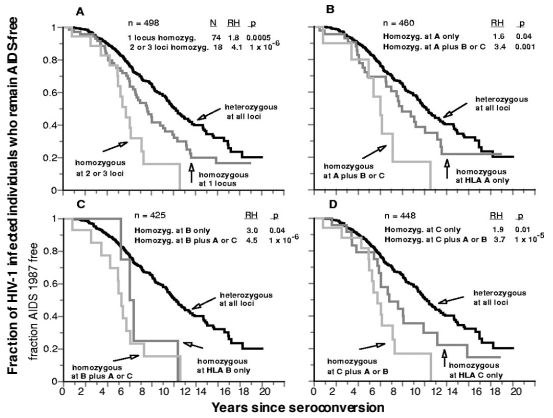
HLA heterozygosity delays the progression to AIDS



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

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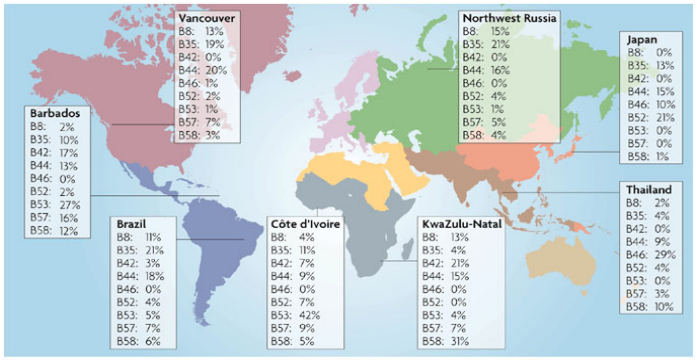
Exposure to pathogens shapes MHC gene frequencies

Figure 5.37 The Immune System, 4th ed. (© Garland Science 2015)

=> 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