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Biotechnology

Immunology

Molecules of Adaptive Immunity

Introduction

The adaptive immune system uses a broad range of molecules for its activities. Some of these molecules are also used by theinnate immune system (see Chapter 5). Others, including antigen-specific B cell receptors (BCR) and T cell receptors (TCR)of B and T lymphocytes, are unique to the adaptive immune system. Immunoglobulins are synthesized by and reside withinthe cytoplasm and are present on the surfaces of B lymphocytes. Each B cell synthesizes immunoglobulins of a singlespecificity that bind to a specific molecular structure (epi -tope). The immunoglobulins on the B cell surface serve as the BCRs.

Stimulated B cells may further differentiate into plasma cells that secrete soluble forms of these immunoglobulins. Theimmunoglobulins recognize and bind to the same epitopes that activate the classical complement pathway. T cells express awide variety of membrane-bound TCRs. Each T cell produces single-specificity TCRs that recognize a specific peptide epitopecontained within a major histocompati-bility complex (MHC) molecule. Epitope engagement of BCRs or TCRs leads to theinitiation of signal transduction pathways and the expression of both soluble (cytokines and chemokines) and cell –surface(receptors and adhesion) molecules.

II. Immunoglobulins

Immunoglobulins are synthesized by B lymphocytes (B cells) and are both synthesized and secreted by plasma cells.Plasma cells are B cells that have terminally differentiated. The term antibody is applied to an immunoglobulin molecule withspecificity for an epitope of the molecules that make up antigens (see Chapter 2). Antibodies nonco-valently bind to antigensto immobilize them, render them harmless, or “tag” the antigen for destruction and removal by other components of theimmune system. In doing so, antibodies facilitate the ability of other cells and molecules in the immune system to identify andinteract with antigens. Because antibodies are often in soluble form, they are important components of humoral (soluble)immune responses (see Chapter 11).

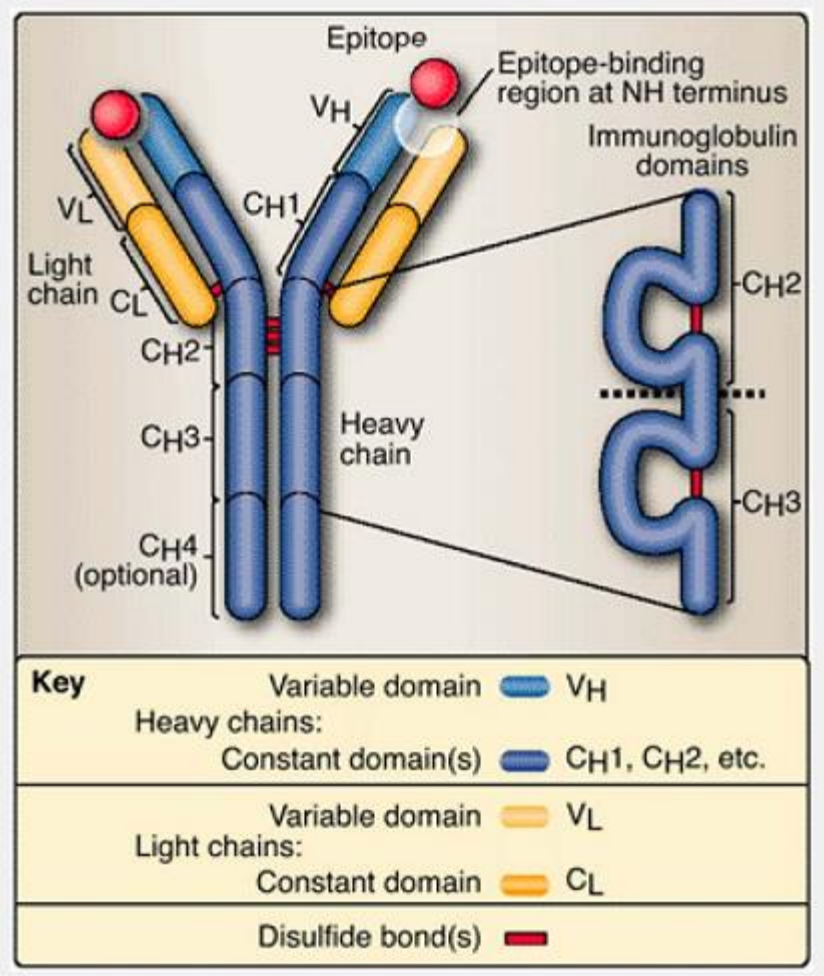

Figure 6.1 Immunoglobulin monomer. An immunoglobulin monomer contains 2 identicallight (L) chains and two identical heavy (H) chains connected by disulfide bonds. Eachchain contains a variable domain and one or more constant domains.

A. Basic structure

Human immunoglobulin contains four polypeptides: two identical light chains and two identical heavy chains linked bydisulfide bonds (Fig. 6.1) to form a monomeric unit. Heavy and light chainsare aligned such that the amino portion (NH terminus) of a single heavy and a single light chain form an epitope-binding site(more about this later in the chapter). Each heavy and light chain may be subdivided into homologous regions termeddomains. Light chains, termed K (kappa) or X (lambda), are encoded on chromosomes 2 and 22, respectively. There are fivetypes of heavy chains, all encoded on chromosome 14, termed mu (n), delta (8), gamma (Y), ep-silon (e), and alpha (a). Thegenetically different forms of light chains (K and X) and of heavy chains (n, 8, y, e, and a) are known as iso-types.

Immunoglobulin class or subclass is determined by the heavy chain isotype.

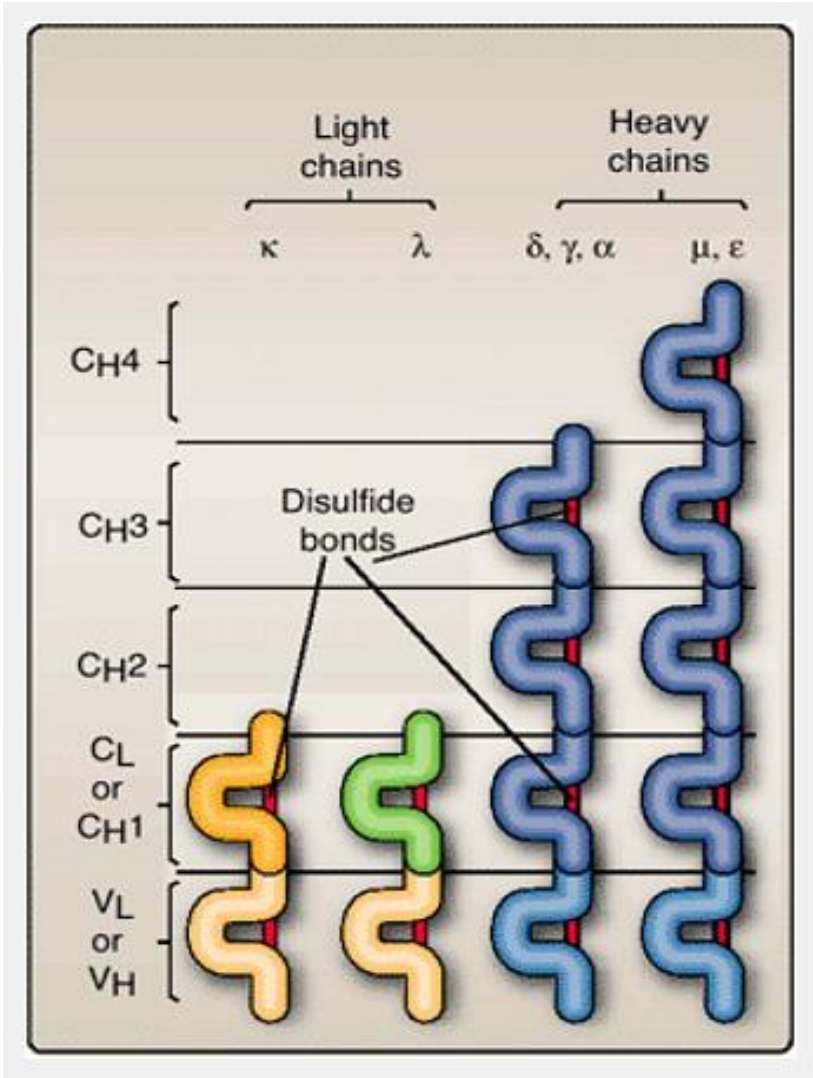

Figure 6.2 Immunoglobulin domains. Light chains are of two types (κ and λ) while there are five types of heavy chains (α, δ, ε, γ, μ). Immunoglobulin light and heavy changes are divisible into domains that consist of approximately 110 amino acids and contain an intrachange disulfide bond (V_L = light chain variable domain, V_H = heavy chain variable domain, C_L = light chain constant domain, C_H = heavy chain constant domain).

1. Light chains

An immunoglobulin monomer contains two identical K or two identical X light chains but never one of each. Light or L chainscontain a variable (V_L) domain and a constant (C_L) domain (Fig. 6.2). Each domain contains about 110 amino acids and anintrachain disulfide bond. Variable regions (in both heavy and light chains) are so named for their variation in amino acidsequences between immunoglobulins synthesized by different B cells.

2. Heavy chains

Heavy chains contain one variable (V_H) and three or four constant (C_H) domains (Fig. 6.2). Heavy (H) chain variable domains(V_H) are extremely diverse, and constant domains (C_H) display a relatively limited variability for members of an isotype. The 8,y, and a heavy chains contain three constant domains (C_H1, C_H2, C_H3), and n and e heavy chains contain a fourth constantdomain (C_H4), making them both longer and heavier than 8, Y, or a heavy chains.

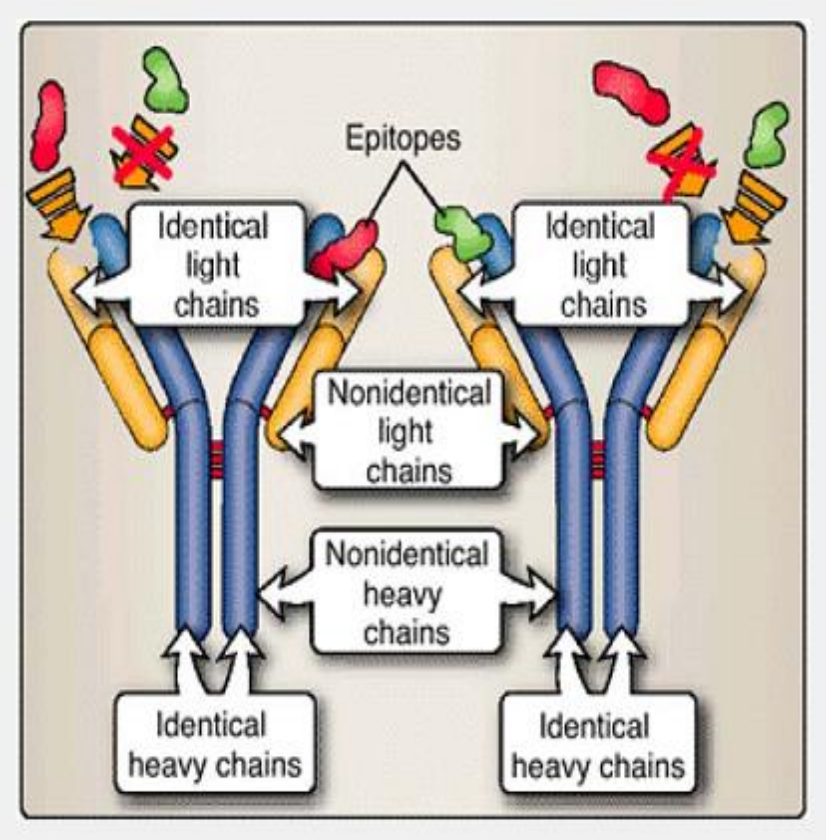

Figure 6.3 Immunoglobulin epitope-binding regions. Two identical epitope-binding regions are formed by pairing of a single V_L domain with a single V_H domain.

3. Antigen-binding sites

A light chain variable domain and a heavy chain variable domain together form a pocket that constitutes the antigen(epitope)-binding region of the immunoglobulin molecule. Because an immunoglobulin monomer contains two identical lightchains and two identical heavy chains, the two binding sites found in each monomeric immunoglobulin are also identical (Fig.6.3). The variability in the amino acid sequences of the V_L and V_H domains, together with the random pairing of light andheavy chain that occurs from one B cell to another, creates a pool of binding sites capable of recognizing a very large numberof different epitopes.

4. Immunoglobulin landmarks

Immunoglobulin molecules can be enzymatically cleaved into discrete fragments by either pepsin or papain (Fig. 6.4).Disulfide bonds join the heavy chains at or near a proline-rich hinge region, which confers flexibility on the immunoglobulinmolecule.

The fragments of immunoglobulin are as follows:

- Fab or antigen (epitope)-binding fragment, produced by papain cleavage of the immunoglobulin molecule, contains V_H, C_H1, V_L, and C_L. Two Fab fragments are produced by papain cleavage of an immunoglobulin monomer; each fragment has an epitope-binding site.
- Fc or constant (crystallizable) fragment is produced by cleavage of the immunoglobulin molecule with papain. The Fc portion contains the C_H2, C_H3, and (sometimes) C_H4 regions of the immunoglobulin molecule. It is responsible for many biologic activities that occur following engagement of an epitope.

- Fd is the heavy chain (V_H, C_H1) portion of Fab.
- Fd' is a heavy chain (V_H, C_H1) portion of Fab. The prime (′) mark denotes extra amino acids due to a pepsin cleavagesite.
- F(ab')2 is a dimeric molecule produced by pepsin cleavage. An immunoglobulin monomer will produce a single F(ab')2fragment containing two (V_H, C_H1') segments joined by disulfide bonds. An $F(ab')_2$ contains two epitope-binding sites.

B. Isotypes

Heavy chain isotypes (μ, δ, γ, α, and ε) also determine immunoglobulin isotype or class (IgM, IgD, IgG, IgA, and IgE,respectively) (Table 6.1). Normally humans produce all five immunoglobulin isotypes. Of the two light chain isotypes, anindividual B cell will produce only κ or λ chains, never both. B cells express surface-bound immunoglobulin monomers asepitope-specific receptors; B cells produce and display only one isotype, with the exception that unstimulated B cells expressboth IgM and IgD. When secreted into the body fluids, soluble IgG and IgE remain monomeric, soluble IgM forms a pentamer,and soluble IgA can be found in either a monomeric or dimeric form.

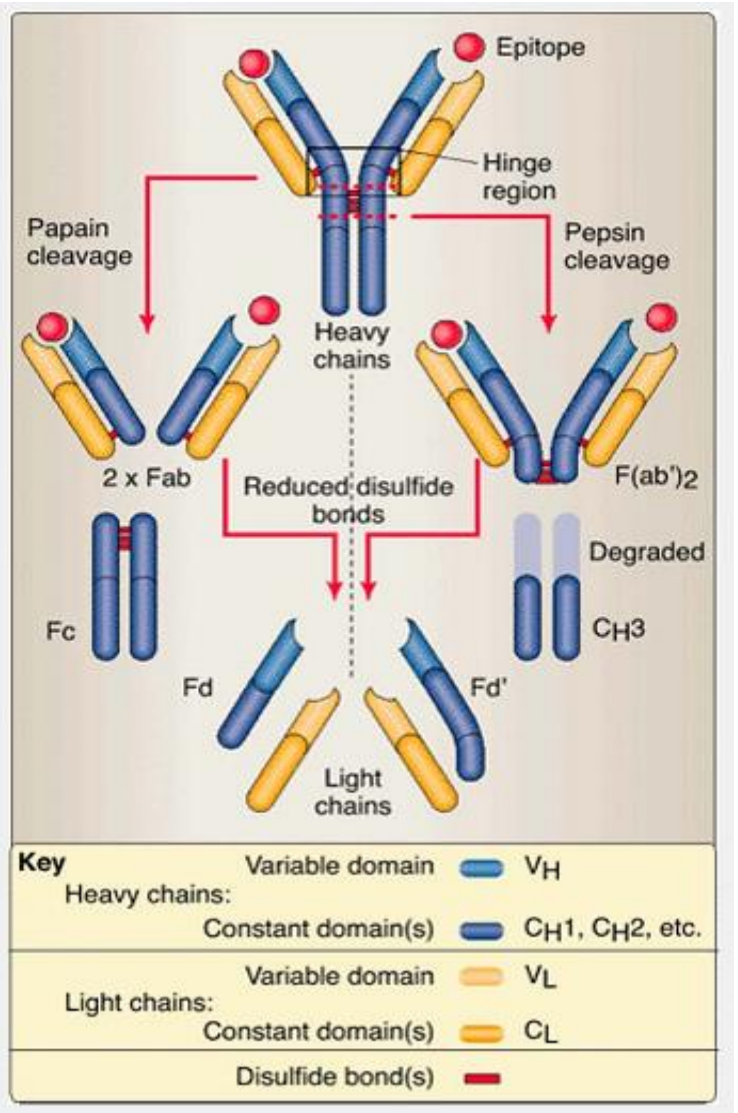

Figure 6.4 Enzyme cleavage of immunoglobulin determines landmarks. Papain cleavesheavy chains to form two identical Fab fragments (each containing one binding site) andone Fc fragment. Pepsin cleaves heavy chains at a point that produces an $F(ab')_2$fragment containing two linked binding sites and remaining heavy chain material that isdegraded and eliminated.

•IgM is found either as a cell -surface-bound monomer (2μ + 2κ or 2λ) or as a secreted pentamer with 10 H and L chains linked by disulfide bonds and a J ("joining") chain [five monomers + J, i.e., 5 x (2μ + 2κ or 2λ) + J]. Most B cells display IgM on their cell surfaces. In general, IgM is the first immunoglobulin to be formed following antigenic stimulation. IgM is effective both at immobilizing antigen (agglutination; see Chapter 20, Fig. 20.2) and in activating the classical pathway of complement.

•IgD has a monomeric structure (2δ + 2κ or 2λ) and is almost exclusively displayed on B cell surfaces. Little is known of its function.

•IgG exists as both surface and secreted monomeric (2γ + 2κ or 2λ) molecules. Four subclasses (γ1, γ2, γ3, and γ4) of γ heavy chains account for the four human IgG subclasses, IgG1, IgG2, IgG3, and IgG4. Collectively, IgG subclasses make up the greatest amount of immunoglobulin in the serum. Many IgG antibodies are effective in activating complement (see below), opsonizing and neutralizing microorganisms and viruses, and initiating antibody-dependent cell -mediated cytotoxicity, and they function in a wide variety of hypersensitivity functions.

•IgA is present in both monomeric and dimeric forms. Monomeric IgA (2α + 2κ or 2λ) is found in the serum. The addition of a J or joining chain to two IgA monomers forms a dimer. Epithelial cells use a specialized receptor to transport the IgA dimer to mucosal surfaces. This specialized receptor becomes an accessory molecule that binds to the IgA dimers is known as secretory component (SC) [2 x (2α + 2κ or 2λ) + J + SC]. Secretory IgA dimers are found in mucus, saliva, tears, breast milk, and gastrointestinal secretions. The SC provides increased resistance to enzymatic degradation. Two isoforms of IgA (α1 and α2) show slightly different functions.

IgA1predominates in the serum and in secretions above the diaphragm. Secretory IgA2 accounts for the majority of IgAfound in the lumen of the lower portion of the gastrointestinal tract. Large amounts of IgA are synthesized and secreteddaily at the mucosal surfaces of the GI tract, respiratory tracts, and other secretory ep-ithelia. More IgA is produceddaily than all the other isotypes combined.

Table 6.1 Immunoglobulin Isotypes

Isotype	Heavy Chains[a]	Heavy Chain Subclass	Additional Chains	Formulaa	Number of Monomers[b]	Subclass
IgM	μ			$2\mu^{d} + 2\kappa$ or 2λ	1	
		μ	J chain	$5[2\mu + 2\kappa \text{ or } 2\lambda] + J$	5	IgM
IgD	δ			$2\delta + 2\kappa$ or 2λ	1	
IgG	γ			$2\gamma + 2\kappa$ or 2λ	1	
		γ1		$2\gamma_1 + 2\kappa$ or 2λ	1	IgG1
		γ2		$2\gamma_2 + 2\kappa$ or 2λ	1	IgG2
		γ3		$2\gamma_3 + 2\kappa$ or 2λ	1	IgG3

		γ4		$2\gamma_4$ + 2κ or 2λ	1	IgG4
IgA	α			2α + 2κ or 2λ	1	
		α_1		$2\alpha_1$ + 2κ or 2λ	1 — serum	IgA1
			J chain & SC[f]	2[$2\alpha_1$ + 2κ or 2λ] + J + SC[f]	2 — external[g] upper body and GI	sIgA1
		α_2		$2\alpha_2$ + 2κ or 2λ	1 — serum	IgA2
			J chain & SC[f]	2[$2\alpha_2$ + 2κ or 2λ] + J + SC[f]	2 — external[g]	sIgA2
IgE	ε			2ε + 2κ or 2λ	1	

[a]All monomers contain two identical heavy (μ, δ, γ, α, or ε) and two light (κ or λ) chains.

[b]Number of monomeric subunits expressed on the surface of the B cell (always 1) or in the form secreted by a plasma cell.

[c]Molecular weight.

[d]The carboxyl-terminal cytoplasmic tail portion of the μ chain of the surface-bound IgM monomer differs significantly from the μ chain present in the pentameric secreted form of IgM.

Valence	MW[c]	Half Life (days)	Serum Level (mg/dl)	Percent	Stick Figure

2	180,000				
10	900,000	1	45–150[e]	5–8	
2	180,000	2.8	3	<1	
2	150,000	23	720-1500[e]	75-85	
2	150,000	23	430-1050		
2	150,000	23	100-300		
2	150,000	8	30-90		
2	150,000	23	15-60		
	170,000	5.8	90-325	10-16	
2	170,000	5.8	80-290		
4	390,000	na	na		
2	170,000	5.8	10-35		
4	390,000	n.a.	n.a.		
2	190,000	2.5	0.03	<1	

[e]Serum level for all members of this class.

[f]Secretory component.

ggThe dimeric form is transported across specialized epithelial cells tothe external environment. sIgA1 is found in tears, nasal secretions,saliva and milk. sIgA2 is found in the gastrointestinal system.

IgE is present in relatively low serum concentration; most is adsorbed onto the surfaces of mast cells, monocytes, andeosinophils. Its basic structural formula is (2ε + 2κ or 2λ). Mast cells and basophils have isotype-specific receptors(FcRε, CD23) for the Fc portion of free IgE molecules. Cross-linking of IgE on mast cell surfaces by antigen triggersthe release of histamine and other inflammatory mediators, leading to immediate hypersensitivity (allergic) responses.

IV. Major Histocompatibility Molecules

The major histocompatibility complex (MHC), also called the human leukocyte antigen (HLA) complex, is a segment ofchromosome 6 containing several genes that are critical to immune function (Fig. 6.7). These include genes encoding a varietyof enzymes and structural molecules needed for the activation and function of B and T cells. The encoded molecules fall intothree groups or classes known as MHC (or HLA) class I, II, and III molecules. MHC class III molecules include complementcomponents C4, Bf, and C2. MHC class I and II molecules serve entirely different functions.

A. MHC class I molecules

Codominantly expressed 45-kDa MHC class I molecules, in association with β2 microglobulin (β2m, 12 kDa), are found on thesurfaces of all nucleated cells. Three genetic loci, HLA-A, -B, and -C, are highly polymorphic, with over 100 alleles at eachlocus (see Fig. 6.7). Altogether, up to six different class I molecules (if heterozygous at all three loci) can be displayed oneach cell.

MHC class I molecules fold to form a cleft between the α1 and α2 domains that noncovalently binds an eight- to nine-amino-acid peptide (Fig. 6.8). Because of slight structural variations in thebinding cleft (or binding groove) among the different allelic forms, different peptides may preferentially fit into clefts of someMHC class I molecules better than others. Additional ("nonclassical") class I molecules (e.g., those encoded by the HLA-E, -F,-G, -H loci) show limited variability and tissue distribution and may function to present carbohydrate and peptide fragments toγδ T cells.

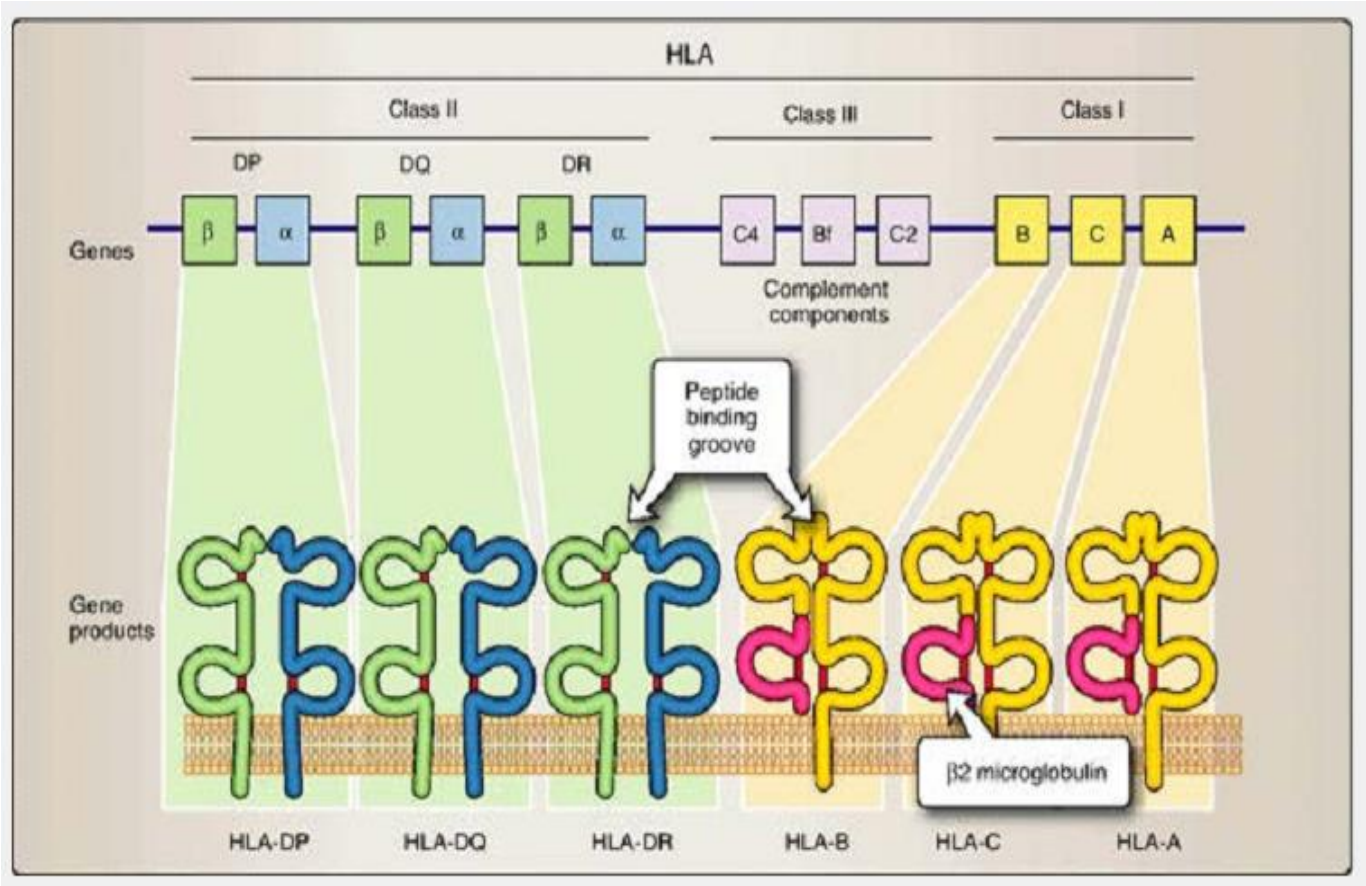

Figure 6.7 Genetic and protein organization of MHC class I, II, and III. Located onchromosome 6, HLA (human leukocyte antigen) genes are arranged as shown. They aregrouped into Class I, Class II, and Class III based on structural and functionalcharacteristics.

B. MHC class II molecules

MHC class II molecules are normally only expressed on dendritic-, macrophage-, and B cell surfaces; on some activated Tcells; and on some specialized epithelial cells in the thymus and intestine. Codom-inantly expressed as non covalentheterodimers, a 32- to 38-kDa α chain and a 29- to 32-kDa β chain form a binding groove (α1 and β1 domains) that can accommodate peptides of 18- to 20-amino-acid length (see Fig. 6.8). Encoded within the HLA-DP, -DQ, and -DR regions (see Fig. 6.7) are both α and β loci (DPα, DPβ, DQα, DQβ, etc.). After synthesis, MHC class II α and β chains combine only with others encoded within the same region (e.g., DPα associates only with DPβ but never with DQβ or DRβ). However, within each of these regions, α chains can combine with β chains encoded on the same chromosome (cis) or on the other member of the chromosome pair (trans). Termed cis-trans complementation, this allows individuals that are heterozygous at one or more of the class II loci to produce a greater variety of class II dimers than would be possible if they were homozygous. The range of different MHC class I and II molecules expressed can affect the overall immune capacity of an individual.

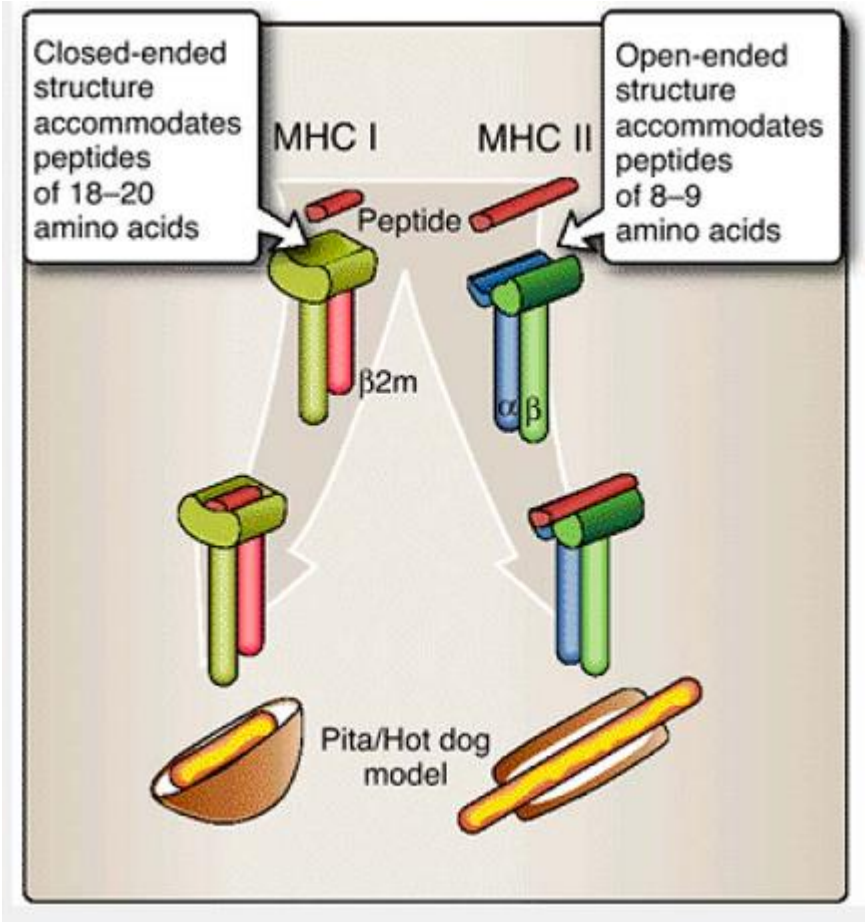

Figure 6.8 Peptide-binding clefts of MHC class I and class II molecules. MHC class Imolecules (HLA-A, HLA-B, or HLA-C), in association with β2 microglobulin (β2m), formpeptide binding clefts that are closed at the ends and bind peptides of 8-9 amino acids inlength. MHC class II molecules (HLA-DP, HLA-DQ, or HLA-DR) are α chain - β chainheterodimers that form open-ended peptide binding clefts that bind peptides of 18-20amino acids in length.

V. T Cell Receptors

The antigen-specific T cell receptor (TCR) is an αβ or a γδ heterodimer polypeptide pair. (Note: Despite the similarity interminology, αβ TCR loci/molecules and MHC class II αβ loci/molecules are genetically and molecularly distinct.) Eachpolypeptide of the TCR contains variable and constant domains that are genetically and molecularly distinct fromimmunoglobulins. The choice of whether to express an αβ or γδ heterodimer is made early in T cell development, and clonaldescendants retain the same type of TCR.

A. Basic structure

The TCR is bound to the membrane of the T cell. The short cytoplasmic tails of αβ or γδ polypeptide chains lack signalingsequences or immunoreceptor tyrosine activation motifs (ITAMs) to initiate activation signals to the nucleus (see Chapter8). These signals are provided by the CD3 complex molecules [(CD3δ, CD3γ, CD3ε, and CD247 (ζ chain)] that noncovalentlyassociate with the TCR. Unlike antibodies, TCRs cannot bind soluble epitopes. They bind only to fragments of largermolecules that fit within the binding grooves of MHC class I or class II molecules as peptide-MHC (pMHC) complexes.

Interaction of the TCR with pMHC is stabilized by the associated interaction of CD4 or CD8 with constantdomains of MHC class II or MHC class I molecules, respectively (Fig. 6.9).

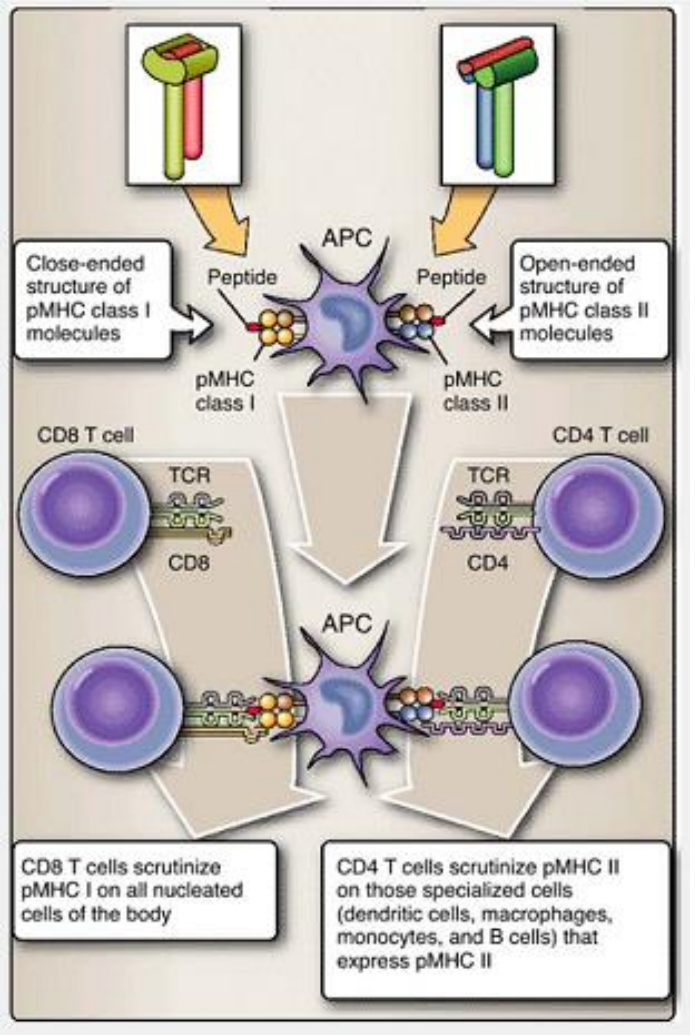

Figure 6.9 CD4+ and CD8+ T cells only interact with peptides bound to MHC class II orclass I molecules.

B. Variable and constant regions

Each polypeptide chain of the TCR pair contains a variable (Vα or Vβ, Vγ or Vδ) and a constant (Cα or Cβ, Cγ or Cδ) regiondomain. Together, variable regions of α and β (or γ and δ) chains form hypervariable or complementarity-determining regions (CDRs) that interact with pMHC. Similar to immunoglobulins, each T cell expresses a unique TCR. Unlike immunoglobulins, T cells must "see" pMHC and do not recognize soluble peptides.

VI. Molecules of Cellular Interaction

Many adaptive and innate immune responses require leukocyte-to-leukocyte interaction. These interactions take place by direct cell -to-cell contact or by the sending and receiving of signals via soluble molecules. Leukocytes respond to these signals by upregulatingor downregulating their functions, by migrating to specific anatomic sites, or by making life-or-death decisions about the fate of a cell within the body.

A. Cytokines

Cytokines are low-molecular -weight soluble protein messengers that are involved in all aspects of the innate and adaptiveimmune response, including cellular growth and differentiation, inflammation, and repair. Originally called lymphokines and monokines to reflect lymphocytic or monocytic origin, we now recognize that these substances are produced by a wide varietyof leukocytes and nonleuko-cytes. A large number of cytokines have been identified, although the roles of many of them are not yet fully understood (Table 6.2). Many cytokines are crucial in regulating lymphocyte development and in determining the types of immune responses evoked by specific responses.

B. Chemokines

Low-molecular -weight cytokines known as chemokines (chemoat-tractant cytokines) stimulate leukocyte movement.Leukocytes are guided by chemokine concentration gradients to the site of an infection or inflammation (a process calledhoming). They are divided into four types based on the presence of certain structural motifs involving the numbers andintervals between cystine residues: C, CC, CXC, and CX3C (Table 6.3).

C. Adhesion molecules

Often, leukocytes must interact directly to contact other cells under somewhat adverse conditions, such as during rapid fluidflow within the circulatory system or under weak ligand-receptor binding. Adhesion molecules provide stable cell -to-cellcontact necessary for both innate and adaptive immune responses as well as for many other intercellular activities. While aseemingly simple activity, the ability of cells to examine the surface of other cells and to establish stable contact with them isvital. For cells to communicate and for cell -surface receptors and ligands to interact, the cells must be able to establish and maintain relatively prolonged surface-to-surface contact.

Types of adhesion molecules include integrins, selectins, and addressins.

1. Integrins are found on the surfaces of many types of leukocytes. Integrins are heterodimers consisting of variouscombinations of α and β chains (e.g., α5β1 on monocytes and macrophages). They interact with other molecules thatare based on the Ig su-perfamily motif (found on a wide variety of cells and has the generalized intrachain disulfidebond domain, e.g., Fig. 6.2) and with extracellular matrix. Their main function is to strengthen contact betweenleukocytes and many types of cells (e.g., vascular endothelium) so that more extensive interactions can then takeplace. Individual integrins and their activities are discussed in upcoming chapters in the more detailed descriptions ofvarious immune responses.

2. Selectins and addressins are limited in their tissue distribution and are designed to identify particular tissues and tofacilitate the interactions of particular cell combinations. For example, newly differentiated lymphocytes need to migrateto lymph nodes to undergo their next stage of development. This migration is accomplished by interactions betweenselectin molecules found on the lymphocytes (e.g., CD62L, also known as L-selectin) and ad-dressin molecules (e.g.,GlyCAM-1) located on the high vascular endothelium of blood vessels passing through lymph nodes. Other selectinsand addressins assist in the movement of lymphocytes and other cells to the gut, epithelium, and sites of tissueinflammation. Individual selectins and adhesions and their activities are discussed in upcoming chapters in the moredetailed descriptions of various immune responses.

Table 6.2 Cytokines

Cytokine	Cellular Source†	Targets†	Function	Receptor
IL-1α				
IL-1β	M, B	T, B, M, End, other	Leukocyte activation, increase endo-thelium adhesion.	CD121a or CD121b
IL-2	T	T, B, NK, M, oligo	T cell proliferation, regulation	CD122/CD25
IL-3	T*, Mas, Eos, NK, End	Ery, G	Proliferation and differentiation of hematopoietic precursors	CD123/CDw131
IL-4	Mas, T, M	B, T, End	Differentiation of Th2 and B cells	CD124/CD132
IL-5	Mas, T, Eos	Eos, B	Growth differentiation of B cells and eosinophils	CD125/CDw131
IL-6	T, B, M, Astrocytes, End	T, B, others	Hematopoiesis, differentiation, inflammation	CD126/CD130

IL-7	Bone marrow and thymic stroma	pB, pT	Pre/pro-B cell proliferation, T cell, upregulation of pro-inflammatory cytokines	CD127/CD132
IL-8	M, L, others	PMN, Bas, L	Chemoattractant	CD128
IL-9	Th2*	T, B	Potentiates production of IgM, IgG, IgE	
IL-10	CD8+ T, Th2, (B) M	T, B, Mas, M	Inhibits IFN-γ, TNF-β, IL-2 by TH1 cells, DTH, stimulates Th2	CD210
IL-11		Bone marrow	Osteoclast formation	
IL-12	DC, B, T	T, NK	Potentiates IFN-γ and TNF-α production by T and NK, down-regulates IL-10	CD212
IL-13	Th2*, Mas, NK	Th2, B, M	Th2 modulator, down-regulated IL-1, IL-6, IL-8, IL-10, IL-12	
IL-14	T	B*	Stimulates proliferation, inhibits Ig secretion	
IL-15	M, Epi	T, B*	Proliferation	
IL-16	Eos, $CD8^+$ T	$CD4^+$ T	$CD4^+$ chemoattractant	
IL-17	(T)	Epi, End, others	Osteoclastogenesis, angiogenesis	
IL-18	M	Th1, NK	Induces IFN-γ production, enhances NK activity	

†Abbreviation key: Activated cells (*), B cells (B), basophils (Bas), dendritic cells (DC),endothelium (End), eosinophil (Eos), epithelium (Epi), erythrocytes (Ery),granulocytes (G), lymphocytes (L), macrophage (M), mast cells (Mas), myeloid (Mye),natural killer cells (NK), neutrophils (PMN), oligodendrocytes (oligo), parenthesis(cellular subset), and T cell (T). Within the table, parentheses are used to indicatewhen only a subset of the designated cell types produce the cytokine.

TGF-β	Eos, others?	Many cell types	Anti-inflammatory, promotes wound healing	
TNF-α	M*, PMN, T, B, NK	M, PMN, T, End, others	Mediator of inflammatory reactions	CD120a and CD120b
TNF-β	L	Wide variety	Mediator of inflammatory reactions	CD120a and CD120b
IFN-α	L, Epi, fibroblasts	Wide variety	Upregulates MHC class I, inhibits viral proliferation	
IFN-β	Epi, fibroblasts	Wide variety	Upregulates MHC class I, inhibits viral proliferation	
IFN-γ	$CD8^{+*}$, ($CD4^{+*}$), NK	T, B, M, NK, End	Antiviral, antiparasite, inhibits proliferation, enhances MHC class I and II expression	CD119
M-CSF	L, M, G, End, Epi, others	M	Growth and differentiation of macrophages	CD115
G-CSF	T*, M, End	G	Growth and differentiation of granulocytes	
GM-CSF	T, M, End, Mas	PG, pMye	Stimulates growth and differentiation of granulocytes and myeloid lineage cells	CD116
MIF	M	M	Antiapoptotic activity for macrophages, promotes macrophage survival	

Table 6.3 Chemokines and their Receptors

Chemokine family	Chemokine receptors	Ligand	Chemokines
C	XCR1	XCL1, XCL2	ATAC, Lymphotactin, SCM-1
CC	CCR1	CCL3, CCL5, CCL14, CCL15, CCL16, CCL23	HCC-1, HCC-2, HCC-4, LD78α, Lkn-1, MCP-4, LEC, MIP-1α, MPIR-1, RANTES
	CCR2	CCL2, CCL7, CCL8	MCP-1, MCP-2, MCP-3, MCP-4, MCAF
	CCR3	CCL5, CCL7, CCL16, CCL24, CCL26	Eotaxin, Eotaxin-3, HCC-2, HCC-4, LEC, Lkn-1, MIP-1α, MCP-3, RANTES, MPIF-2
	CCR4	CCL17, CCL22	MDC, STCP-1, TARC
	CCR5	CCL3, CCL4, CCL5, CCL8	LD78α, MCP-2, MIP-1α, MIP-1β, RANTES
	CCR6	CCL20	exodus-1, LARC, MIP-3α,
	CCR7	CCL19, CCL21	6Ckine, ELC, exodus-3, exodus-2, MIP-3β, SLC
	CCR8	CCL1	I-309
	CCR9	CCL25	TECK
	CCR10	CCL27	TACK, ILC
CXC	CXCR1	CXCL1, CXCL2, CXCL3, CXCL6, CXCL7, CXCL8	GCP-2, GROα, GROβ, IL-8, MCSA-α, MGSA-β, MGSA-γ, NAP-2

	CXCR2	CXCL5, CXCL6, CXCL7, CXCL8	ENA-78, GCP-2, IL-8, NAP-2
	CXCR3A	CXCL9, CXCL10, CXCL11	I-TAC, Mig
	CXCR3B	CXCL4, CXCL9, CXCL10, CXCL11	IP-10, Mig, PF4
	CXCR4	CXCL12	SDF-1α, SDF-1β
	CXCR5	CXCL13	BCA-1, BLC
CX_3C	CX3CR1	CX3CL1	Fractalkine

Source: http://www.nchi.nlm.nih.gov/

D. Cluster of differentiation molecules

Cluster of differentiation (CD) molecules populate the surfaces of many cell types and often serve as indicators of thefunctional capacities of leukocytes and other cells. It is beyond the scope of this book to describe more than just a few of theover 250 CD molecules thathave been identified so far. Fortunately, for a basic understanding of the underlying mechanisms of the adaptive immuneresponse, you need to know only a few of these. Among those that you will frequently encounter are the following:

• CD3 complex contains several molecules associated with the TCR. It is composed of six polypeptides (2 CD3ε + 1CD3γ + 1 CD3δ + 1 CD247 ζ-ζ homodimer). Its functions are to support the TCR and to transduce transmembrane signaling when the TCR is engaged.

• CD4 is a single-chain member of the immunoglobulin supergene family and is expressed on the surfaces of approximately two thirds of mature T cells. CD4 molecules recognize a nonpeptide-binding portion of MHC class II molecules. As a result, CD4+ T cells, also known as helper T (Th) cells, are “restricted” to the recognition of pMHC class II complexes.

• CD8 is a two-chain cell -surface molecule expressed as a homodimer (αα) or heterodimer (αβ) by about one third of mature T cells. CD8 molecules recognize the nonpeptide-binding portion of MHC class I molecules. CD8+ T cells,“restricted” to the recognition of pMHC I complexes, are also known as cytotoxic T (Tc) and suppressor T (Ts) cells.

E. Signal transduction molecules

Leukocytes use their cell -surface receptors to sense their extracellular environment. Binding of certain ligands causes aconformational change in the receptor or its accessory molecules. This change is then communicated inside the cell via thereceptor's cytoplasmic tail (the part that is inside the cell), initiating a signal transduction cascade within the cell. Suchcascades usually involve the binding of one or more specific intracellular signal transduction proteins. Receptor engagementoften initiates a series of chemical signals that regulate gene transcription in the nucleus and alteration of cellular activity. Twostylized, tyrosine-kinase pathways cascades are described.