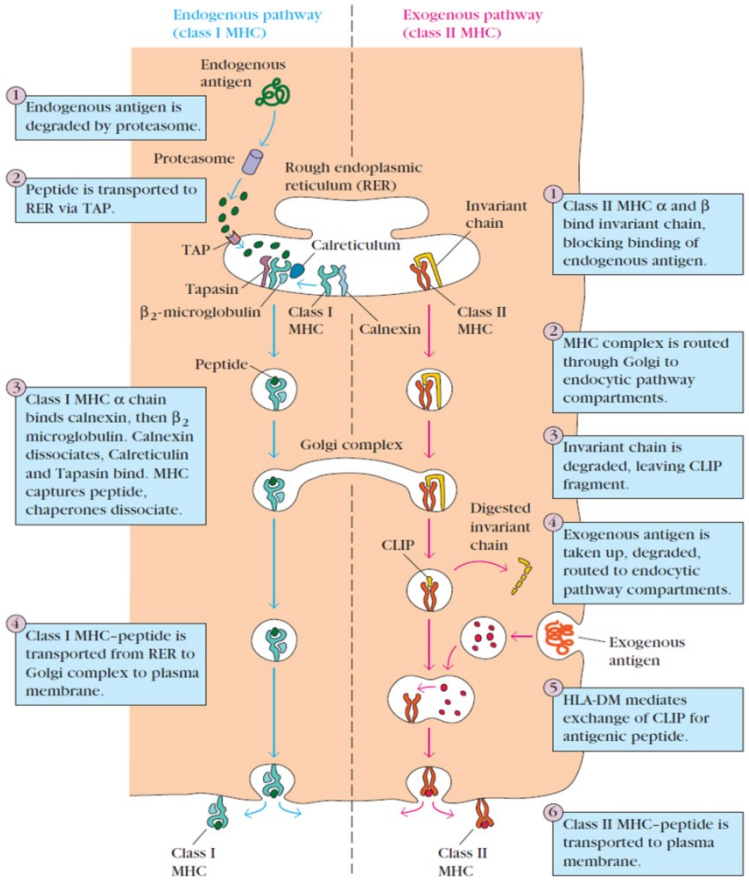
T and B Cell Generation Maturation & Activation



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Major Histocompatibility Complex

- Every mammalian species to date possesses a tightly linked cluster of genes, the major histocompatibility complex (MHC), whose products play roles in intercellular recognition and in discrimination between self and nonself.

- The major histocompatibility complex is a collection of genes arrayed within a long continuous stretch of DNA on chromosome 6 in humans and on chromosome 17 in mice. The MHC is referred to as the HLA complex in humans and as the H-2 complex in mice.
- Class I MHC genes encode glycoproteins expressed on the surface of nearly all nucleated cells; the major function of the class I gene products is presentation of peptide antigens to TC cells.

- Class II MHC genes encode glycoproteins expressed primarily on antigen-presenting cells (macrophages, dendritic cells, and B cells), where they present processed antigenic peptides to TH cells.

- Class III MHC genes encode, in addition to other products, various secreted proteins that have immune
- functions, including components of the complement system and molecules involved in inflammation.

Major Histocompatibility Complex

Mouse H-2 complex

Complex	H-2						
MHC class	I	II		III		I	
Region	K	IA	IE	S		D	
Gene products	H-2K	IA αβ	IE αβ	C′ proteins	TNF-α TNF-β	H-2D	H-2L

Human HLA complex

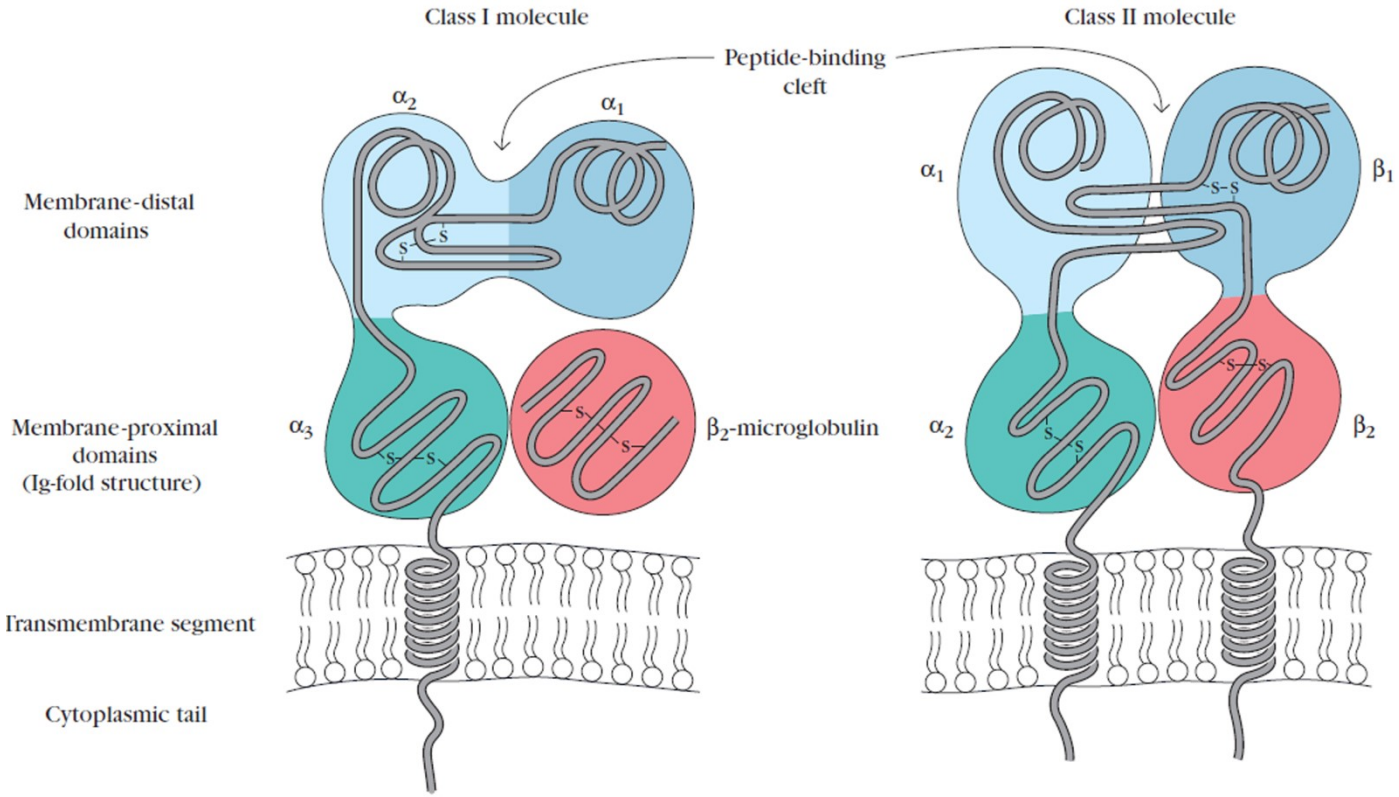
Complex	HLA							
MHC class	II			III		I		
Region	DP	DQ	DR	C4, C2, BF		B	C	A
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A

Simplified organization of the major histocompatibility complex (MHC) in the mouse and human. The MHC is referred to as the H-2 complex in mice and as the HLA complex in humans. In both species the MHC is organized into a number of regions encoding class I (pink), class II (blue), and class III (green) gene products. The class I and class II gene products shown in this figure are considered to be the classical MHC molecules. The class III gene products include complement (C) proteins and the tumor necrosis factors (TNF-alfa and TNF-beta).

Major Histocompatibility Complex

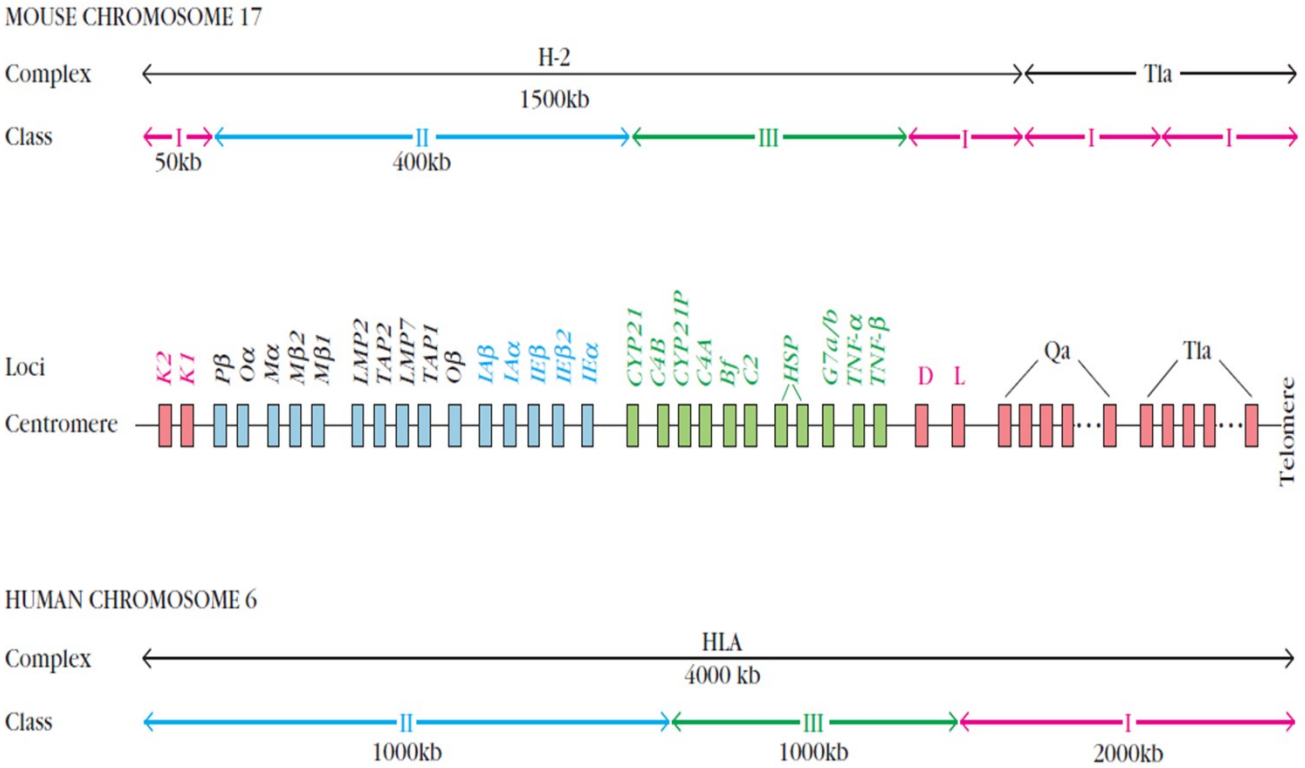
- Class I and class II MHC molecules are membrane-bound glycoproteins that are closely related in both structure and function.
- Class I MHC molecules contain a 45-kilodalton (kDa) α chain associated noncovalently with a 12-kDa β 2-microglobulin molecule.
- Association of the chain with 2-microglobulin is required for expression of class I molecules on cell membranes. The chain is anchored in the plasma membrane by its hydrophobic transmembrane segment and hydrophilic cytoplasmic tail.
- Class II MHC molecules contain two different polypeptide chains, a 33-kDa chain and a 28-kDa chain, which associate by noncovalent interactions. Like class I chains, class II MHC molecules are membrane-bound glycoproteins that contain external domains, a transmembrane segment, and a cytoplasmic anchor segment. Each chain in a class II molecule contains two external domains: α 1 and α 2 domains in one chain and β 1 and β 2 domains in the other.

Major Histocompatibility Complex



Schematic diagrams of a class I and a class II MHC molecule showing the external domains, transmembrane segment, and cytoplasmic tail. The peptide-binding cleft is formed by the membrane-distal domains in both lass I and class II molecules. The membrane-proximal domains possess the basic immunoglobulinfold structure; thus, class I and class II MHC molecules are classified as members of the immunoglobulin superfamily.

Major Histocompatibility Complex



C2, C4A, C4B, Bf **Complement components**
CYP21,CYP21P **Steroid 21-hydroxylases**
G7a/b **Valyl-tRNA synthetase**
HSP **Heat-shock protein**
LMP2, LMP7 **Proteasome-like subunits**
TAP1, TAP2 **Peptide-transporter subunits**
TNF- , TNF- **Tumor necrosis factors alfa and beta.**

Detailed genomic map of the mouse and human MHC, including genes encoding classical and nonclassical MHC molecules. The class I MHC genes are colored red, MHC II genes are colored blue, and genes in MHC III are colored green. Classical class I genes are labeled in red, class II in blue, and the nonclassical MHC genes are labeled in black. The concept of classical and nonclassical does not apply to class III. The functions for certain proteins encoded by the nonclassical class I genes are known. In the mouse, there are nonclassical genes located downstream from Tla that are not shown.

Antigen Processing and Presentation

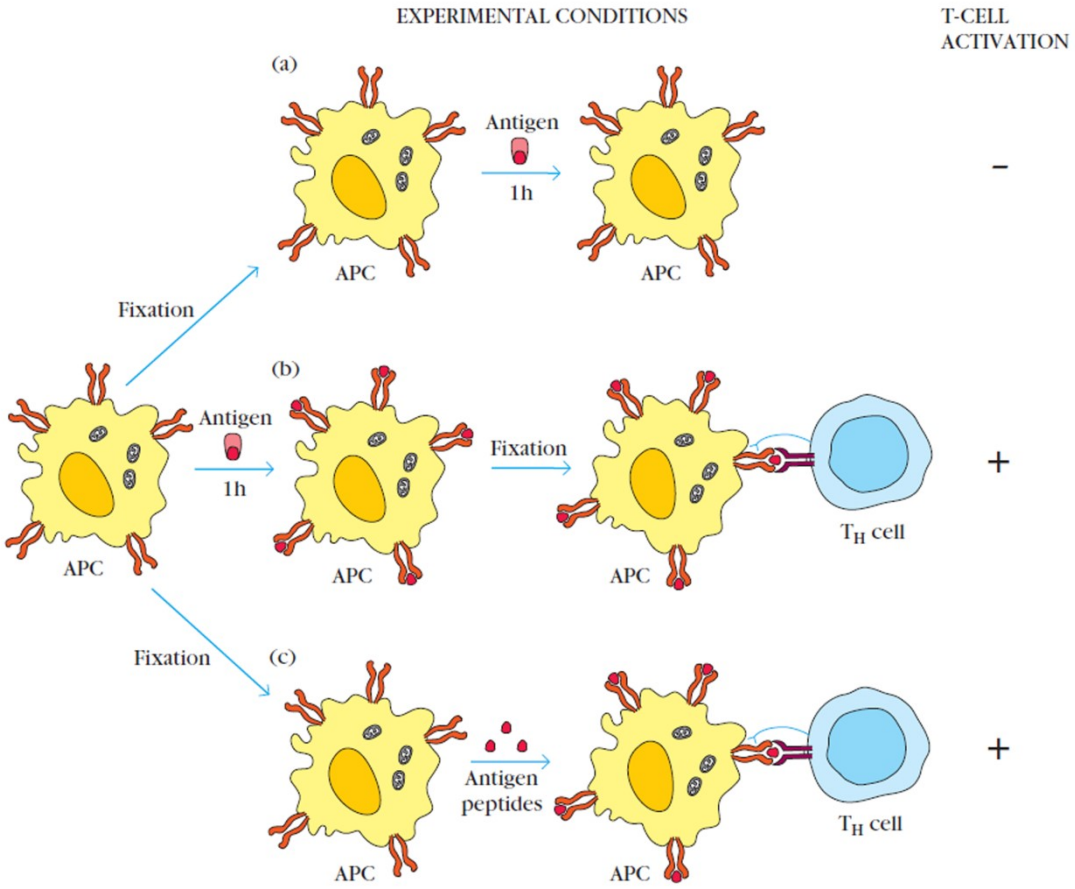
- **Recognition of foreign protein antigens by a T cell requires that peptides derived from the antigen be displayed within the cleft of an MHC molecule on the membrane of a cell. The formation of these peptide-MHC complexes requires that a protein antigen be degraded into peptides by a sequence of events called antigen processing. The degraded peptides then associate with MHC molecules within the cell interior, and the peptide-MHC complexes are transported to the membrane, where they are displayed (antigen presentation).**

- **Class I MHC molecules bind peptides derived from endogenous antigens that have been processed within the cytoplasm of the cell (e.g., normal cellular proteins, tumor proteins, or viral and bacterial proteins produced within infected cells). Class II MHC molecules bind peptides derived from exogenous antigens that are internalized by phagocytosis or endocytosis and processed within the endocytic pathway.**

- **In addition, a third pathway for the presentation of nonpeptide antigens derived from bacterial pathogens is also available.**

Antigen Processing and Presentation

- **Both CD4and CD8T cells can recognize antigen only when it is presented by a self-MHC molecule, an attribute called *self-MHC restriction.***
- **Processing of Antigen Is Required for Recognition by T Cells.**



Experimental demonstration that antigen processing is necessary for TH-cell activation. (a) When antigen-presenting cells (APCs) are fixed before exposure to antigen, they are unable to activate TH cells. (b) In contrast, APCs fixed at least 1 h after antigen exposure can activate TH cells. (c) When APCs are fixed before antigen exposure and incubated with peptide digests of the antigen (rather than native antigen), they also can activate TH cells. TH-cell activation is determined by measuring a specific TH-cell response (e.g., cytokine secretion).

Antigen Processing and Presentation

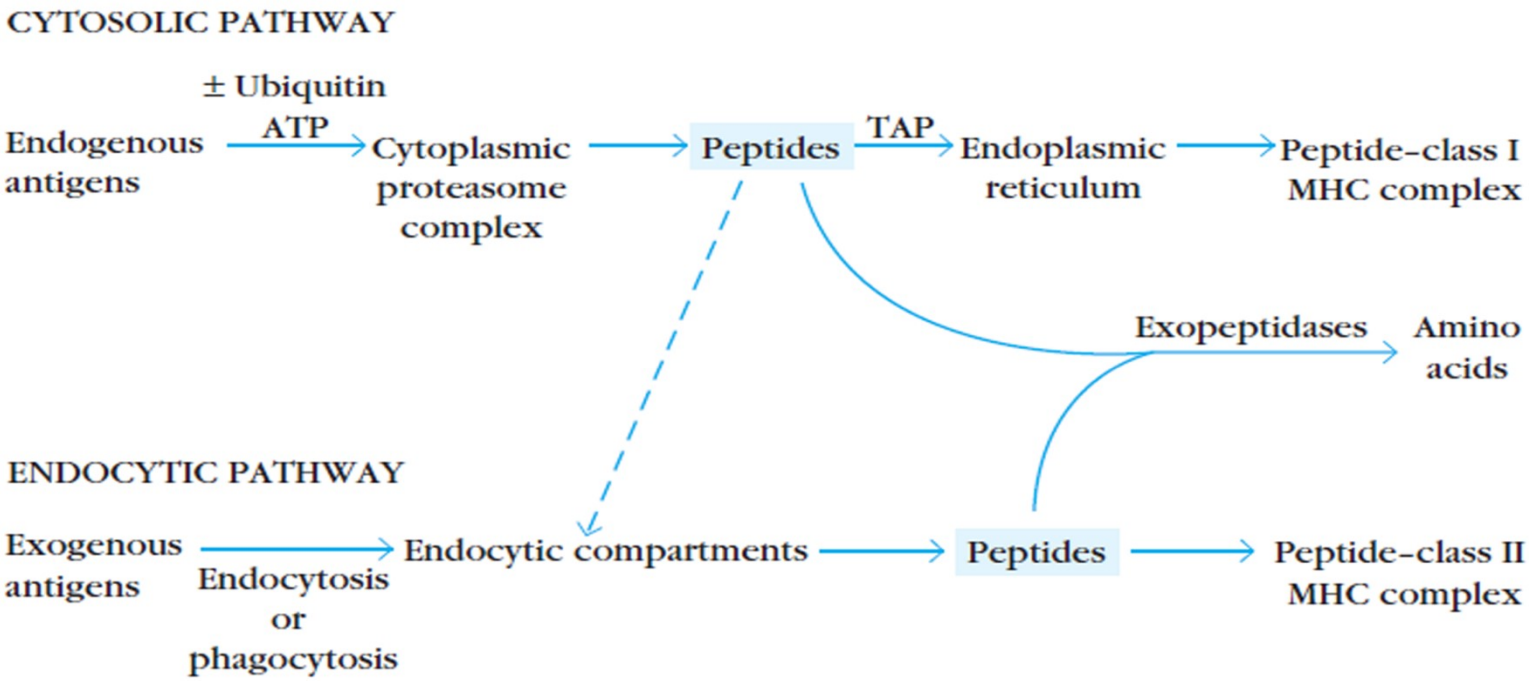
Most Cells Can Present Antigen with Class I MHC; Presentation with Class II MHC Is Restricted to APCs.

Since all cells expressing either class I or class II MHC molecules can present peptides to T cells, strictly speaking they all could be designated as antigen-presenting cells. However, by convention, cells that display peptides associated with class I MHC molecules to CD8 TC cells are referred to as *target cells;* cells that display peptides associated with class II MHC molecules to CD4 TH cells are called antigen-presenting cells (APCs).

TABLE Antigen-presenting cells

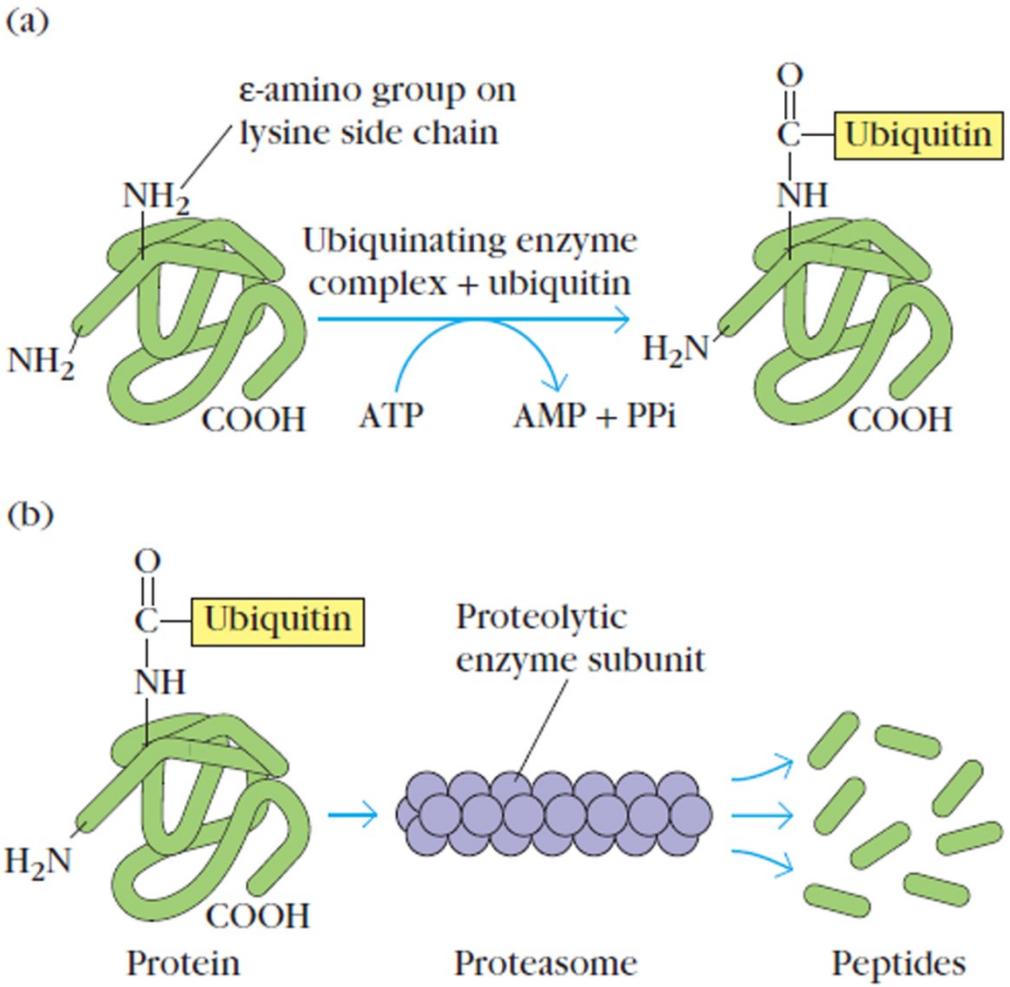
Professional antigen-presenting cells	Nonprofessional antigen-presenting cells	
Dendritic cells (several types)	Fibroblasts (skin)	Thymic epithelial cells
Macrophages	Glial cells (brain)	Thyroid epithelial cells
B cells	Pancreatic beta cells	Vascular endothelial cells

Antigen Processing and Presentation



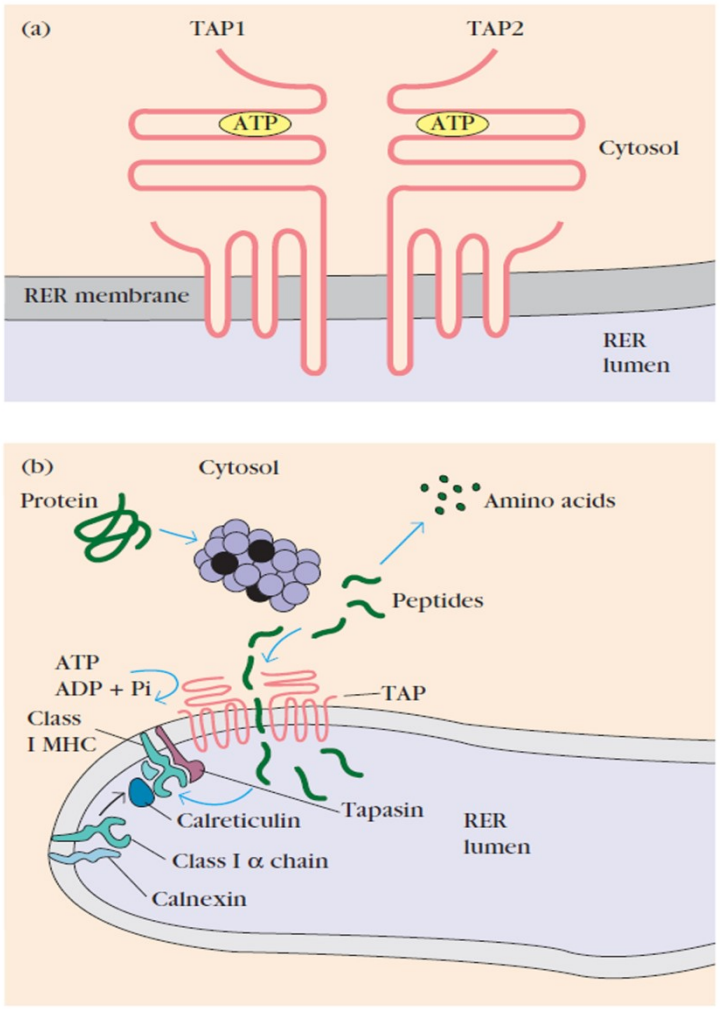
Overview of cytosolic and endocytic pathways for processing antigen. The proteasome complex contains enzymes that cleave peptide bonds, converting proteins into peptides. The antigenic peptides from proteasome cleavage and those from endocytic compartments associate with class I or class II MHC molecules, and the peptide-MHC complexes are then transported to the cell membrane. TAP (*t*ransporter of *a*ntigenic *p*eptides) transports the peptides to the endoplasmic reticulum. It should be noted that the ultimate fate of most peptides in the cell is neither of these pathways, but rather to be degraded completely into amino acids.

Endogenous Antigens: The Cytosolic Pathway



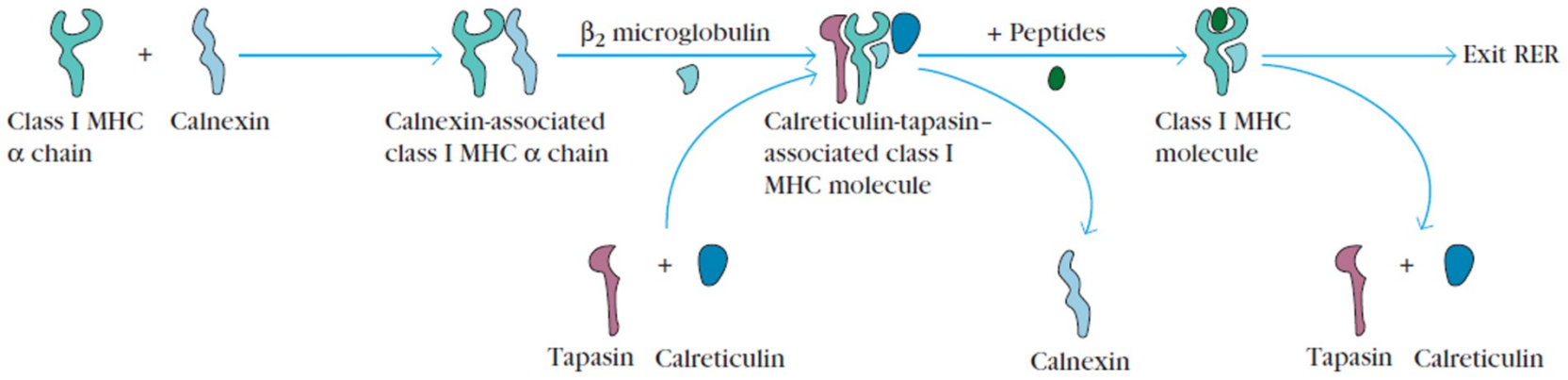
Cytosolic proteolytic system for degradation of intracellular proteins. (a) Proteins to be degraded are often covalently linked to a small protein called ubiquitin. In this reaction, which requires ATP, a ubiquinating enzyme complex links several ubiquitin molecules to a lysine-amino group near the amino terminus of the protein. (b) Degradation of ubiquitin-protein complexes occurs within the central channel of proteasomes, generating a variety of peptides. Proteasomes are large cylindrical particles whose subunits catalyze cleavage of peptide bonds

Endogenous Antigens: The Cytosolic Pathway



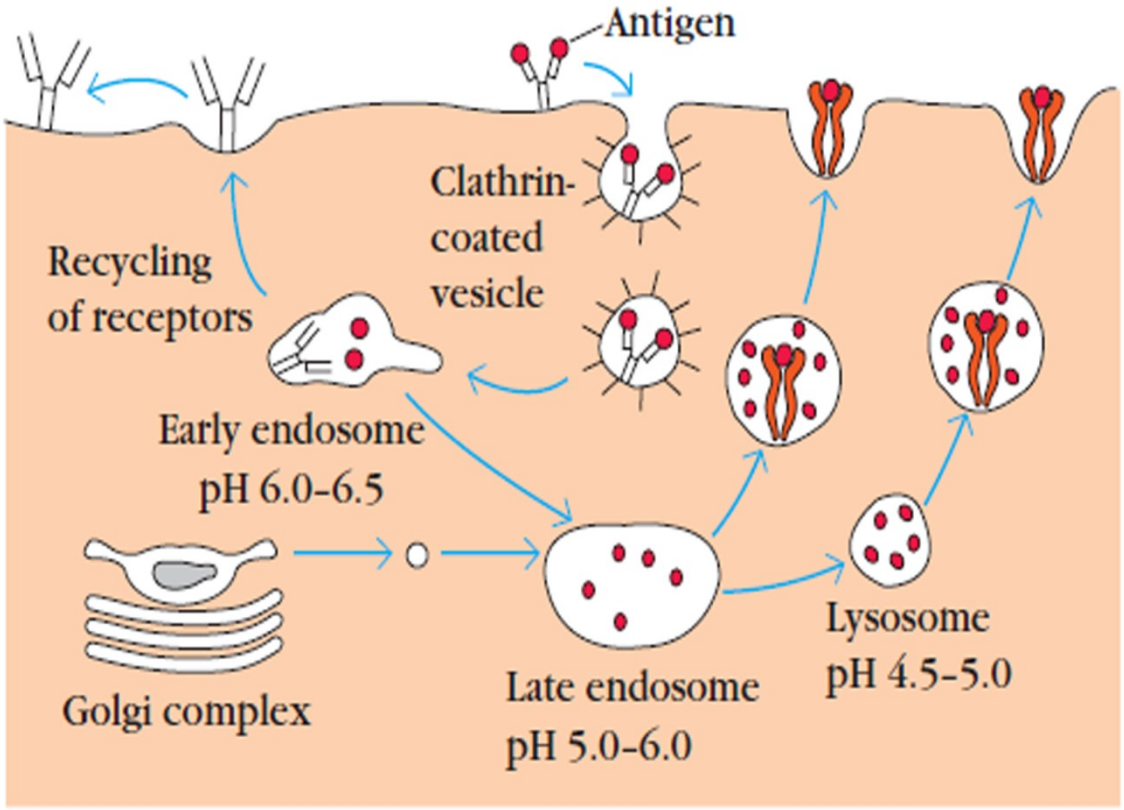
Generation of antigenic peptide–class I MHC complexes in the cytosolic pathway. (a) Schematic diagram of TAP, a heterodimer anchored in the membrane of the rough endoplasmic reticulum (RER). The two chains are encoded by *TAP1* and *TAP2.* The cytosolic domain in each TAP subunit contains an ATP-binding site, and peptide transport depends on the hydrolysis of ATP. (b) In the cytosol, association of LMP2, LMP7, and LMP10 (black spheres) with a proteasome changes its catalytic specificity to favor production of peptides that bind to class I MHC molecules. Within the RER membrane, a newly synthesized class I chain associates with calnexin until 2-microglobulin binds to the chain. The class I chain/2-microglobulin heterodimer then binds to calreticulin and the TAP-associated protein tapasin. When a peptide delivered by TAP is bound to the class I molecule, folding of MHC class I is complete and it is released from the RER and transported through the Golgi to the surface of the cell.

Endogenous Antigens: The Cytosolic Pathway



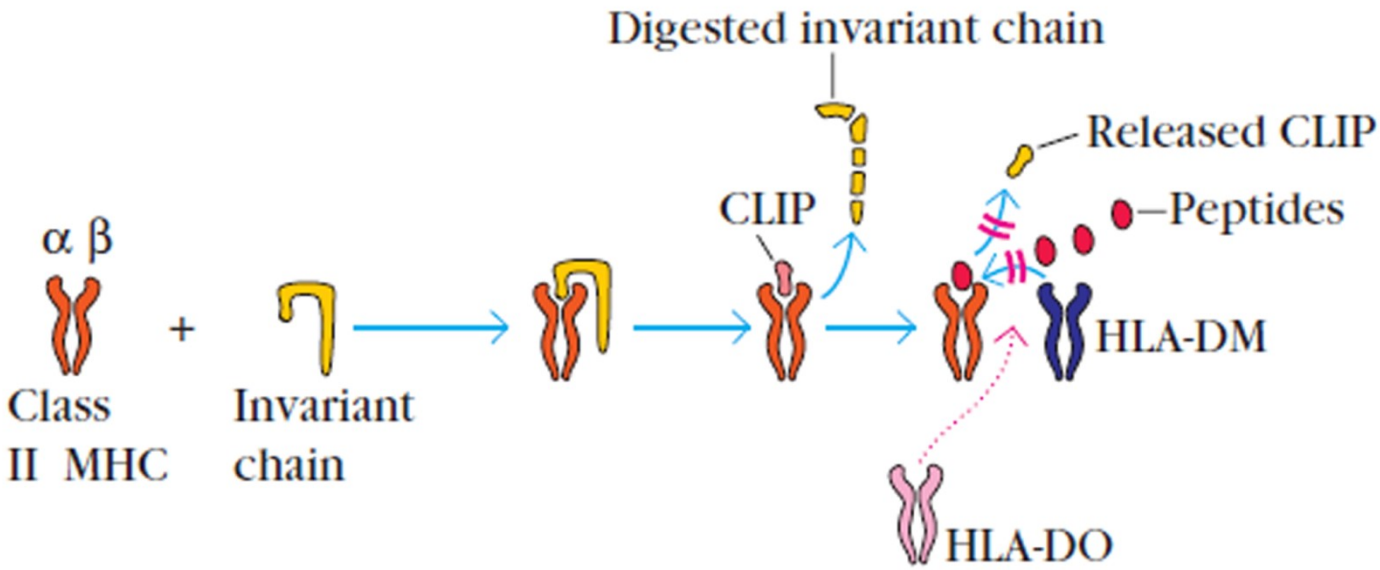
Assembly and stabilization of class I MHC molecules. Newly formed class I chains associate with calnexin, a molecular chaperone, in the RER membrane. Subsequent binding to 2-microglobulin releases calnexin and allows binding to the chaperonin calreticulin and to tapasin, which is associated with the peptide transporter TAP. This association promotes binding of an antigenic peptide, which stabilizes the class I molecule–peptide complex, allowing its release from the RER.

Exogenous Antigens: The Endocytic Pathway



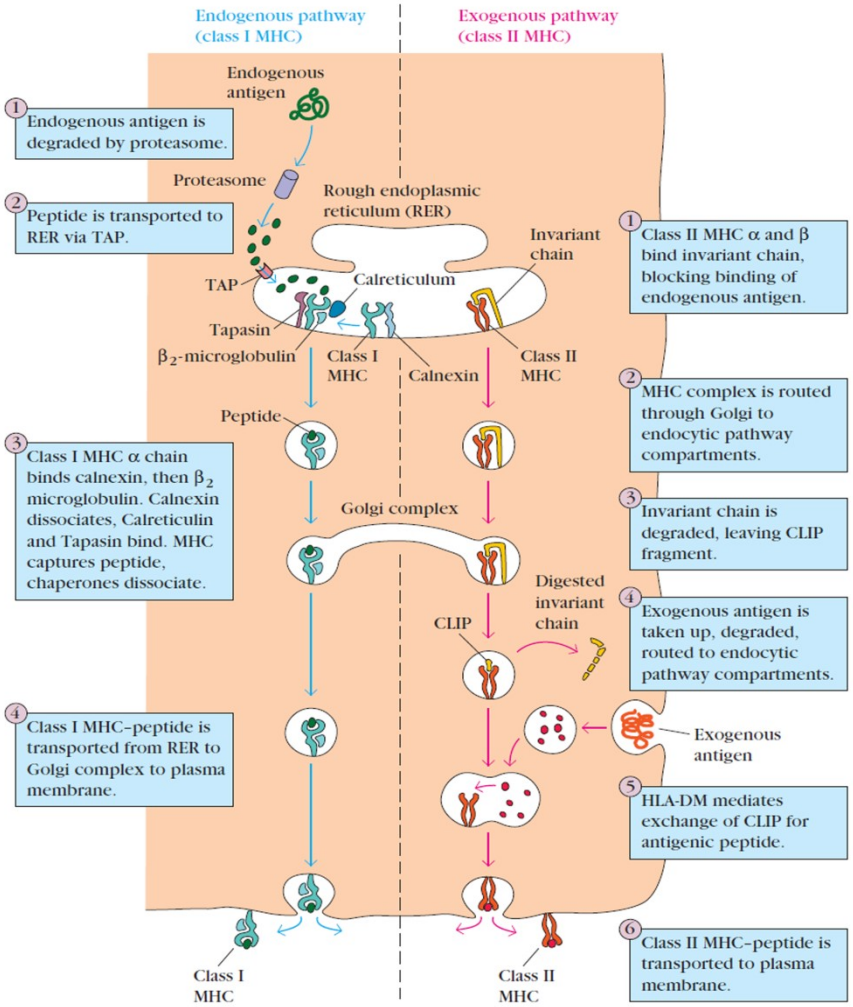
Generation of antigenic peptides in the endocytic processing pathway. Internalized exogenous antigen moves through several acidic compartments, in which it is degraded into peptides that ultimately associate with class II MHC molecules transported in vesicles from the Golgi complex. The cell shown here is a B cell, which internalizes antigen by receptor-mediated endocytosis, with the membrane-bound antibody functioning as an antigen-specific receptor.

Exogenous Antigens: The Endocytic Pathway



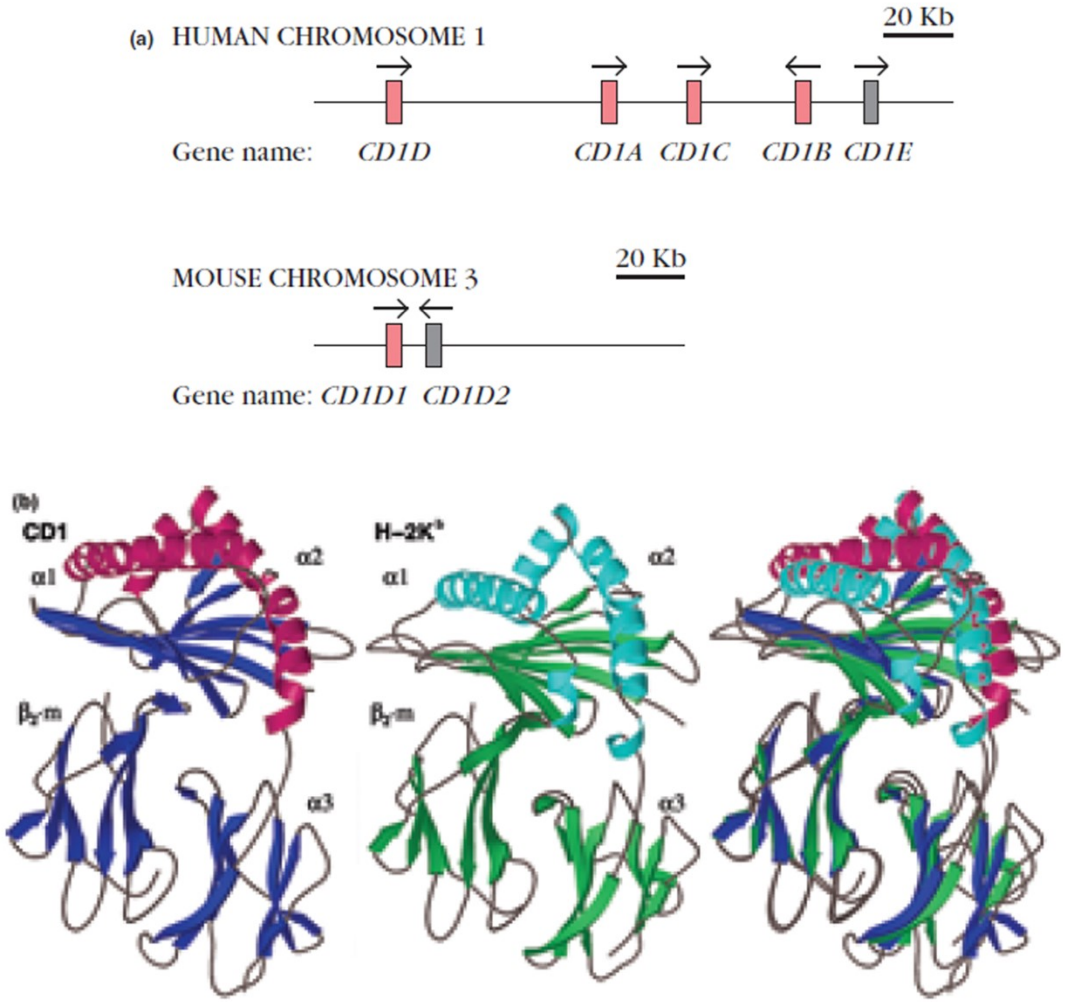
(a) **Assembly of class II MHC molecules. Within the rough endoplasmic reticulum, a newly synthesized class II MHC molecule binds an invariant chain. The bound invariant chain prevents premature binding of peptides to the class II molecule and helps to direct the complex to endocytic compartments containing peptides derived from exogenous antigens. Digestion of the invariant chain leaves CLIP, a small fragment remaining in the binding groove of the class II MHC molecule. HLA-DM, a nonclassical MHC class II molecule expressed within endosomal compartments, mediates exchange of antigenic peptides for CLIP. The nonclassical class II molecule HLA-DO may act as a negative regulator of class II antigen processing by binding to HLA-DM and inhibiting its role in the dissociation of CLIP from class II molecules.**

Antigen Processing and Presentation



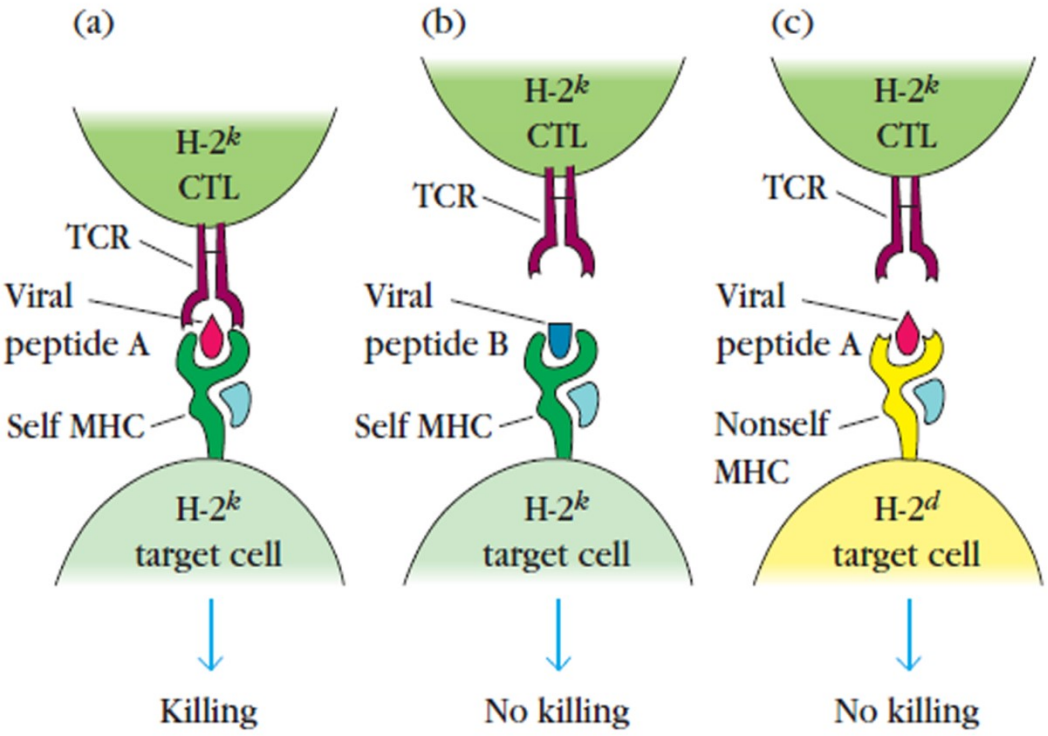
Separate antigen-presenting pathways are utilized for endogenous (green) and exogenous (red) antigens. The mode of antigen entry into cells and the site of antigen processing determine whether antigenic peptides associate with class I MHC molecules in the rough endoplasmic reticulum or with class II molecules in endocytic compartments.

Antigen Processing and Presentation



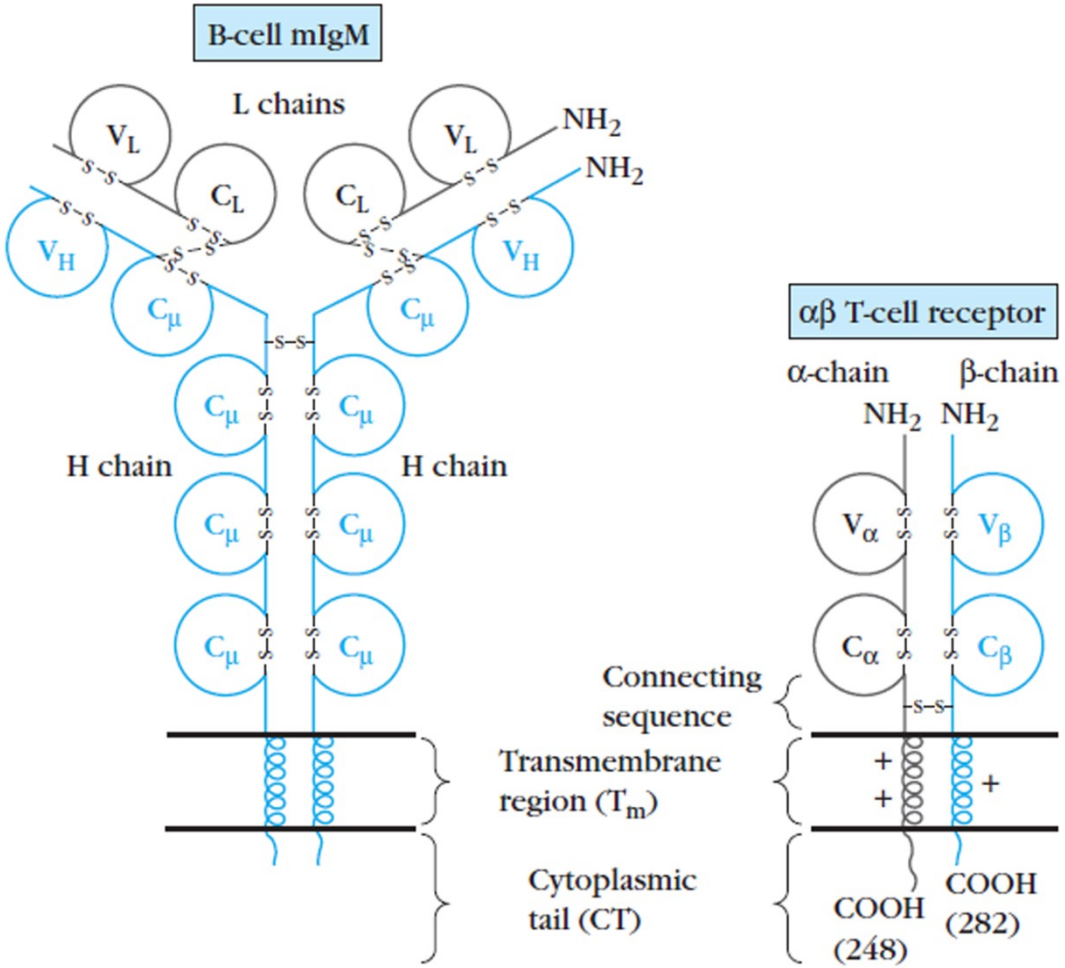
The *CD1* family of genes and structure of a CD1d molecule. (a) The genes encoding the CD1 family of molecules in human (top) and mouse (bottom). The genes are separated into two groups based on sequence identity; *CD1A, B, C,* and *E* are group 1, *CD1D* genes are group 2. The products of the pink genes have been identified; products of grey genes have not yet been detected. (b) Comparison of the crystal structures of mouse nonclassical CD1 and classical class I molecule H-2*kb*.

T-Cell Receptor



Self-MHC restriction of the T-cell receptor (TCR). A particular TCR is specific for both an antigenic peptide and a self-MHC molecule. In this example, the H-2*k* CTL is specific for viral peptide A presented on an H-2*k* target cell (a). Antigen recognition does not occur when peptide B is displayed on an H-2*k* target cell (b) nor when peptide A is displayed on an H-2*d* target cell (c).

T-Cell Receptor



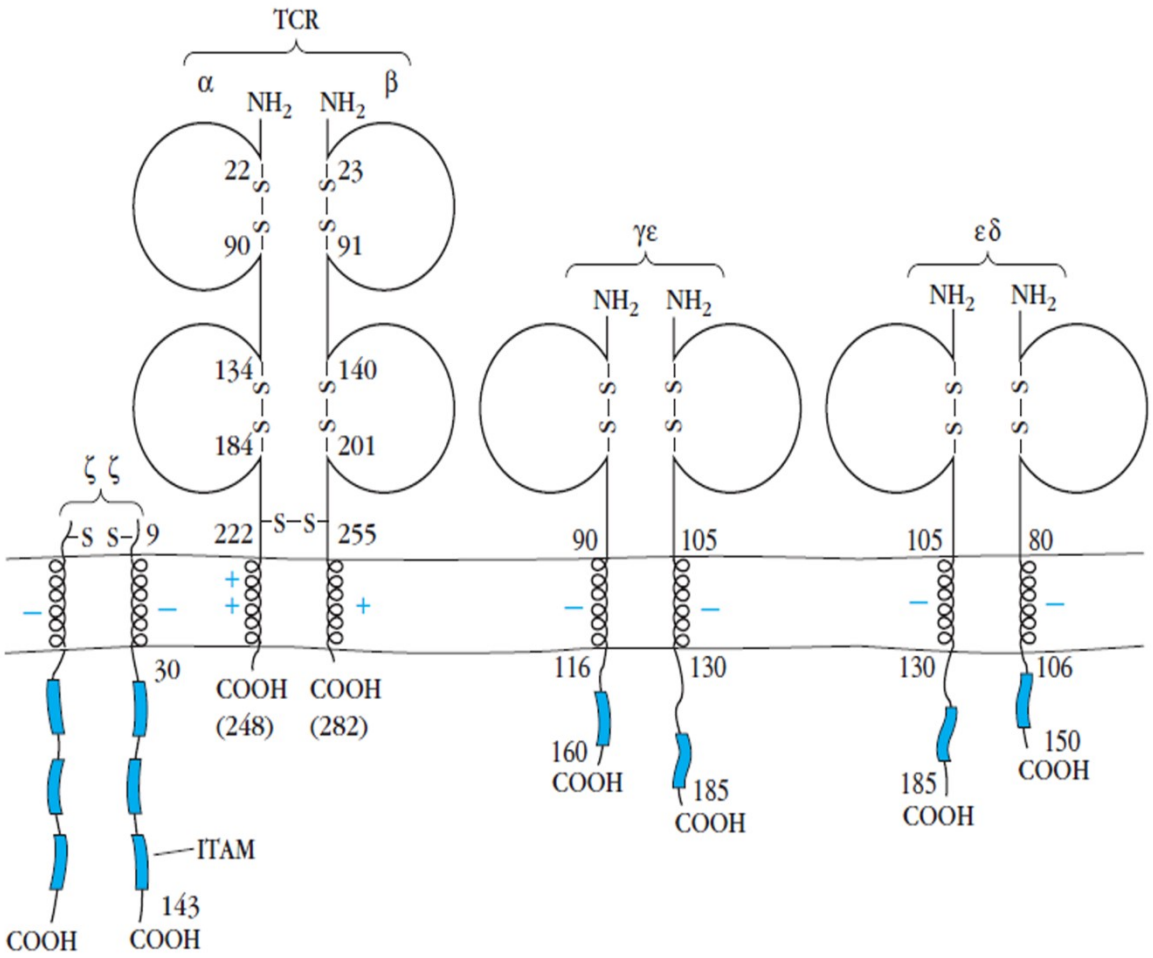
Schematic diagram illustrating the structural similarity between the T-cell receptor and membrane-bound IgM on B cells. The TCR α and β chain each contains two domains with the immunoglobulin-fold structure. The amino-terminal domains (Vα and Vβ) exhibit sequence variation and contain three hypervariable regions equivalent to the CDRs in antibodies. The sequence of the constant domains (Ca and Cb) does not vary. The two TCR chains are connected by a disulfide bond between their constant sequences; the IgM H chains are connected to one another by a disulfide bond in the hinge region of the H chain, and the L chains are connected to the H chains by disulfide links between the C termini of the L chains and the Cμ region. TCR molecules interact with CD3 via positively charged amino acid residues (indicated by) in their transmembrane regions. Numbers indicate the length of the chains in the TCR molecule. Unlike the antibody molecule, which is bivalent, the TCR is monovalent.

T-Cell Receptor

TABLE Comparison of αβ and γδ T cells

Feature	αβ T cells	γδ T cells
Proportion of $CD3^+$ cells	90–99%	1–10%
TCR V gene germ-line repertoire	Large	Small
CD4/CD8 phenotype		
$CD4^+$	~60%	<1%
$CD8^+$	~30%	~30%
$CD4^+CD8^+$	<1%	<1%
$CD4^-CD8^-$	<1%	~60%
MHC restriction	$CD4^+$: MHC class II	No MHC restriction
	$CD8^+$: MHC class I	
Ligands	Peptide + MHC	Phospholipid antigen

T-Cell Receptor Complex: TCR-CD3

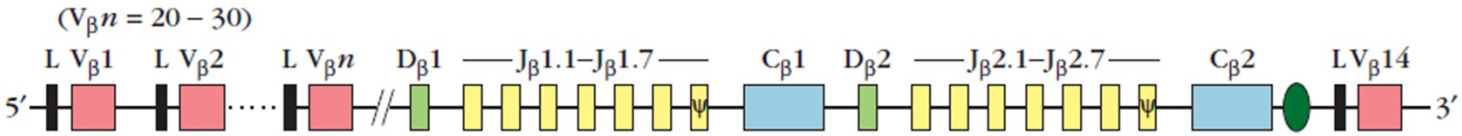


Schematic diagram of the TCR-CD3 complex, which constitutes the T-cell antigen-binding receptor. The CD3 complex consists of the zeta ζζ homodimer (alternately, a zeta eta ζη heterodimer) plus gamma and epsilon γε and delta and epsilon δε heterodimers. The external domains of the γ, δ and ε chains of CD3 are similar to the immunoglobulin fold, which facilitates their interaction with the T-cell receptor and each other. Ionic interactions also may occur between the oppositely charged transmembrane regionsin the TCR and CD3 chains. The long cytoplasmic tails of the CD3 chains contain a common sequence, the immunoreceptor tyrosine-based activation motif (ITAM), which functions in signal transduction.

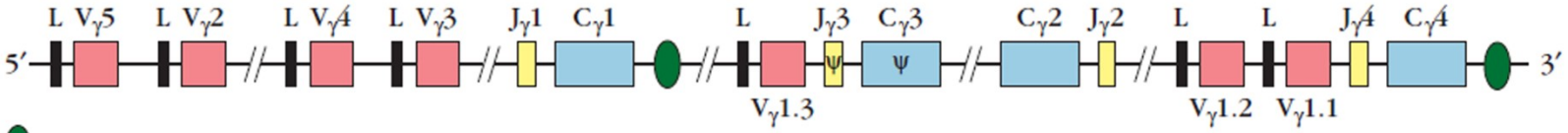
T-Cell Receptor

Mouse TCR α-chain and δ-chain DNA (chromosome 14)

Mouse TCR β-chain DNA (chromosome 6)



Mouse TCR γ-chain DNA (chromosome 13)



= Enhancer

ψ = pseudogene

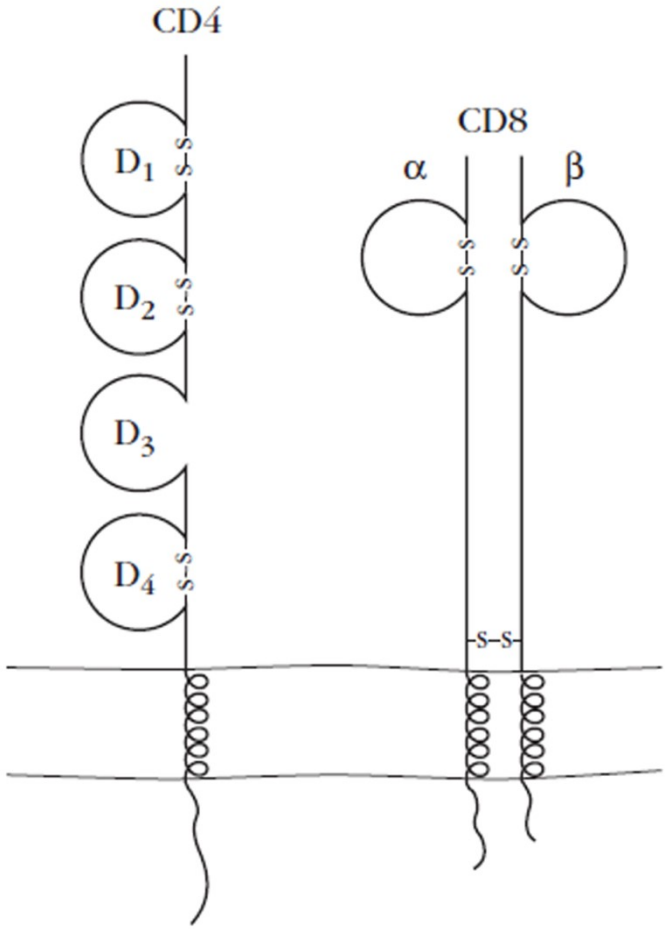
Germ-line organization of the mouse TCR

T-Cell Accessory Membrane Molecules

TABLE Selected T-cell accessory molecules

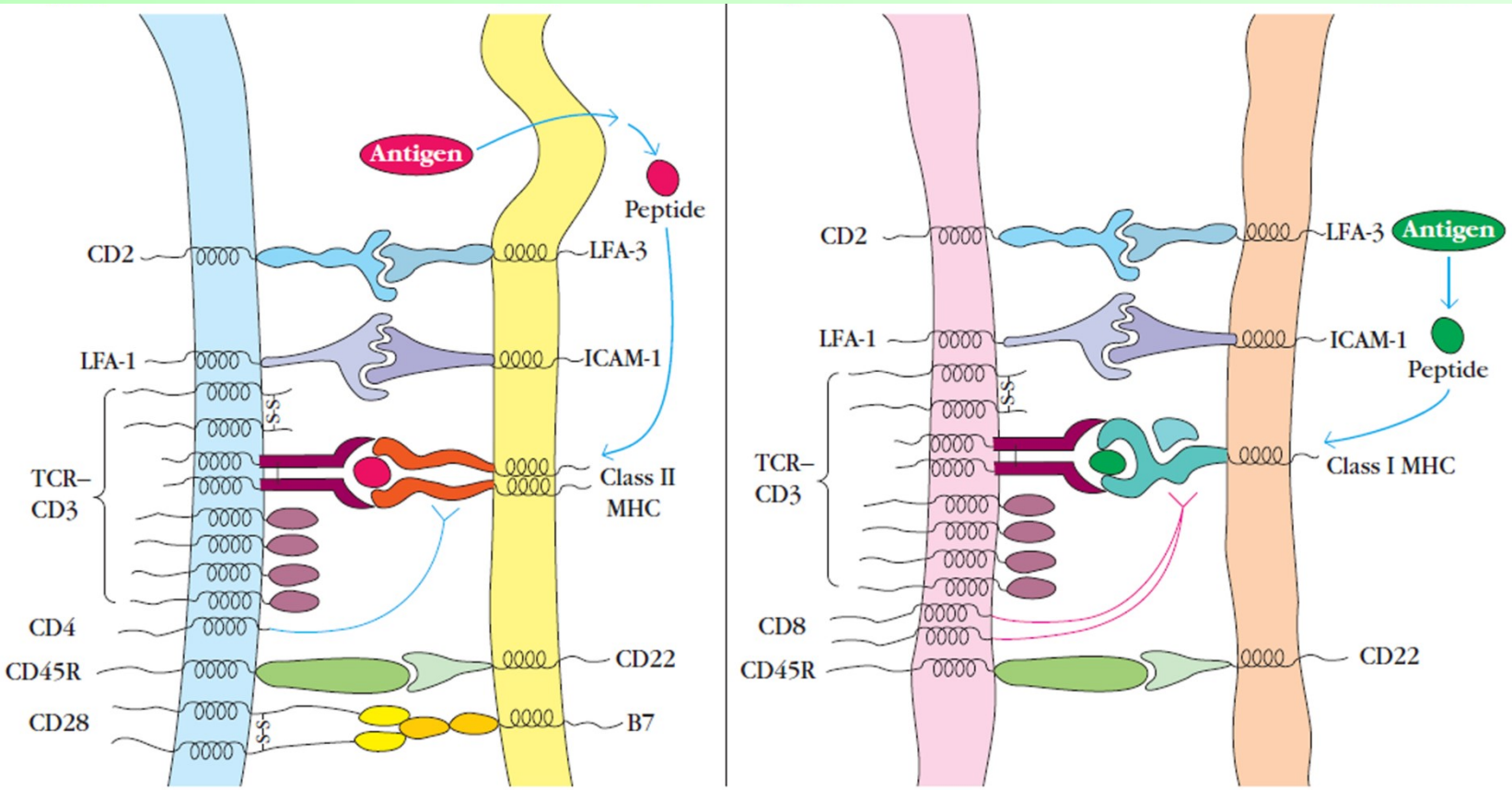
Name	Ligand	FUNCTION		
		Adhesion	Signal transduction	Member of Ig superfamily
CD4	Class II MHC	+	+	+
CD8	Class I MHC	+	+	+
CD2 (LFA-2)	CD58 (LFA-3)	+	+	+
LFA-1 (CD11a/CD18)	ICAM-1 (CD54)	+	?	+/(−)
CD28	B7	?	+	+
CTLA-4	B7	?	+	−
CD45R	CD22	+	+	+
CD5	CD72	?	+	−

T-Cell Accessory Membrane Molecules



General structure of the CD4 and CD8 coreceptors. CD8 may take the form of an heterodimer, or an homodimer. The monomeric CD4 molecule contains four Ig-fold domains; each chain in the CD8 molecule contains one.

T-Cell Accessory Membrane Molecules

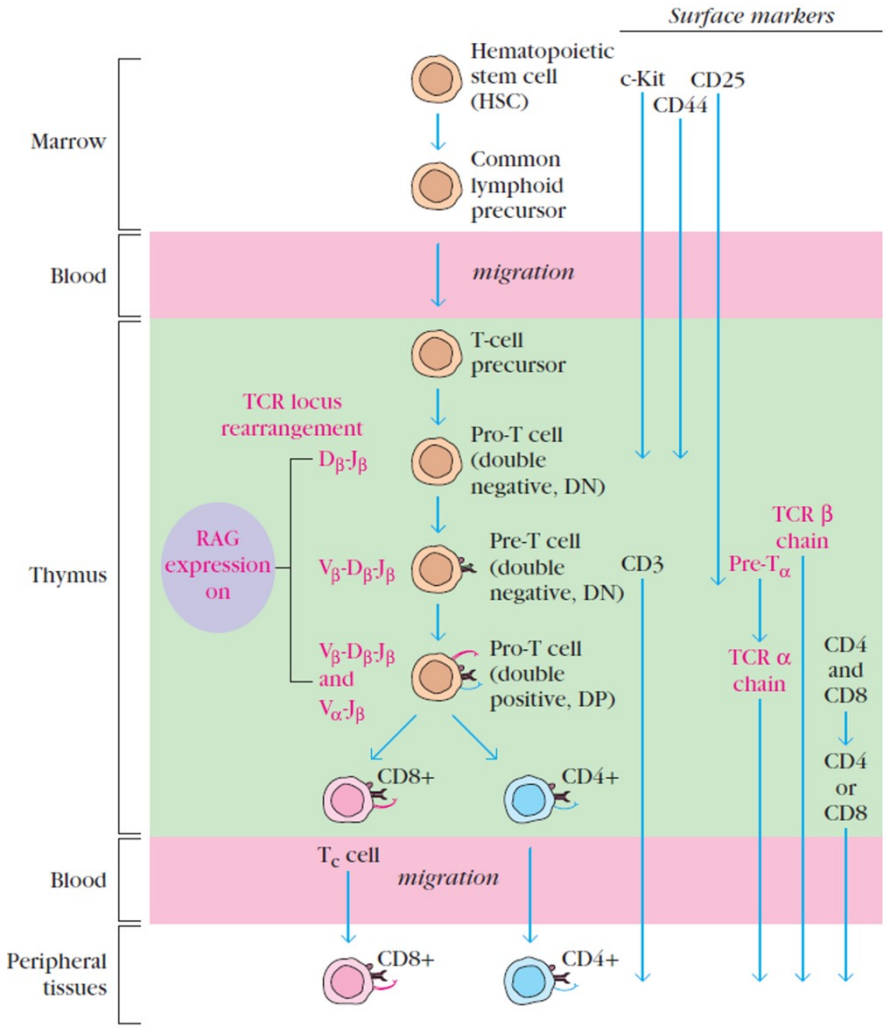


Schematic diagram of the interactions between the T-cell receptor and the peptide-MHC complex and of various accessory molecules with their ligands on an antigen-presenting cell (*left*) or target cell (*right*). Binding of the coreceptors CD4 and CD8 and the other accessory molecules to their ligands strengthens the bond between the interacting cells and/or facilitates the signal transduction that leads to activation of the T cell.

T-Cell Maturation, Activation, and Differentiation

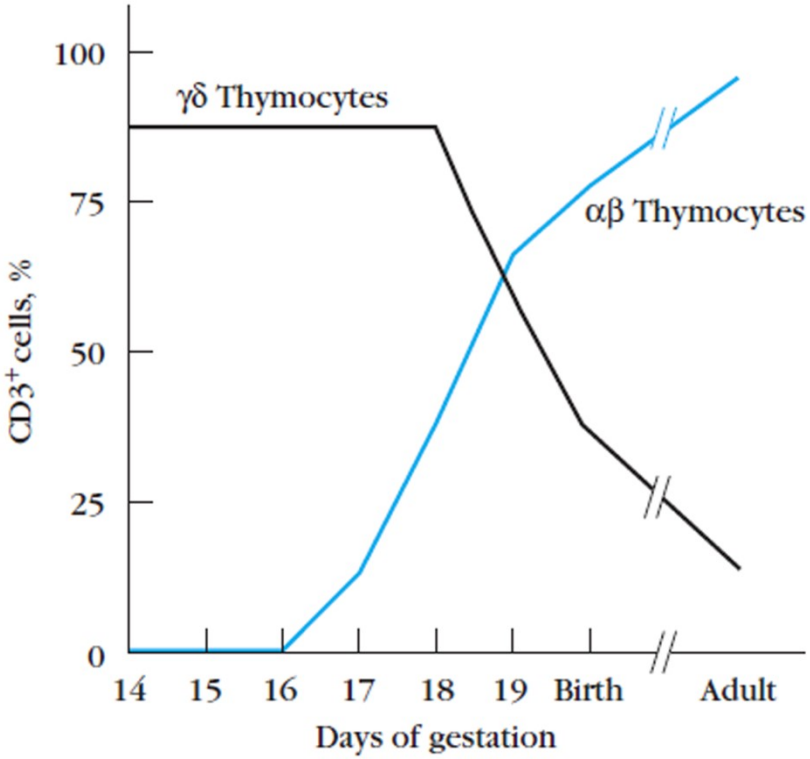
- **Progenitor T cells from the early sites of hematopoiesis begin to migrate to the thymus at about day 11 of gestation in mice and in the eighth or ninth week of gestation in humans. In a manner similar to B-cell maturation in the bone marrow, Tcell maturation involves rearrangements of the germ-line TCR genes and the expression of various membrane markers. In the thymus, developing T cells, known as thymocytes, proliferate and differentiate along developmental pathways that generate functionally distinct subpopulations of mature T cells.**

T-Cell Maturation and the Thymus



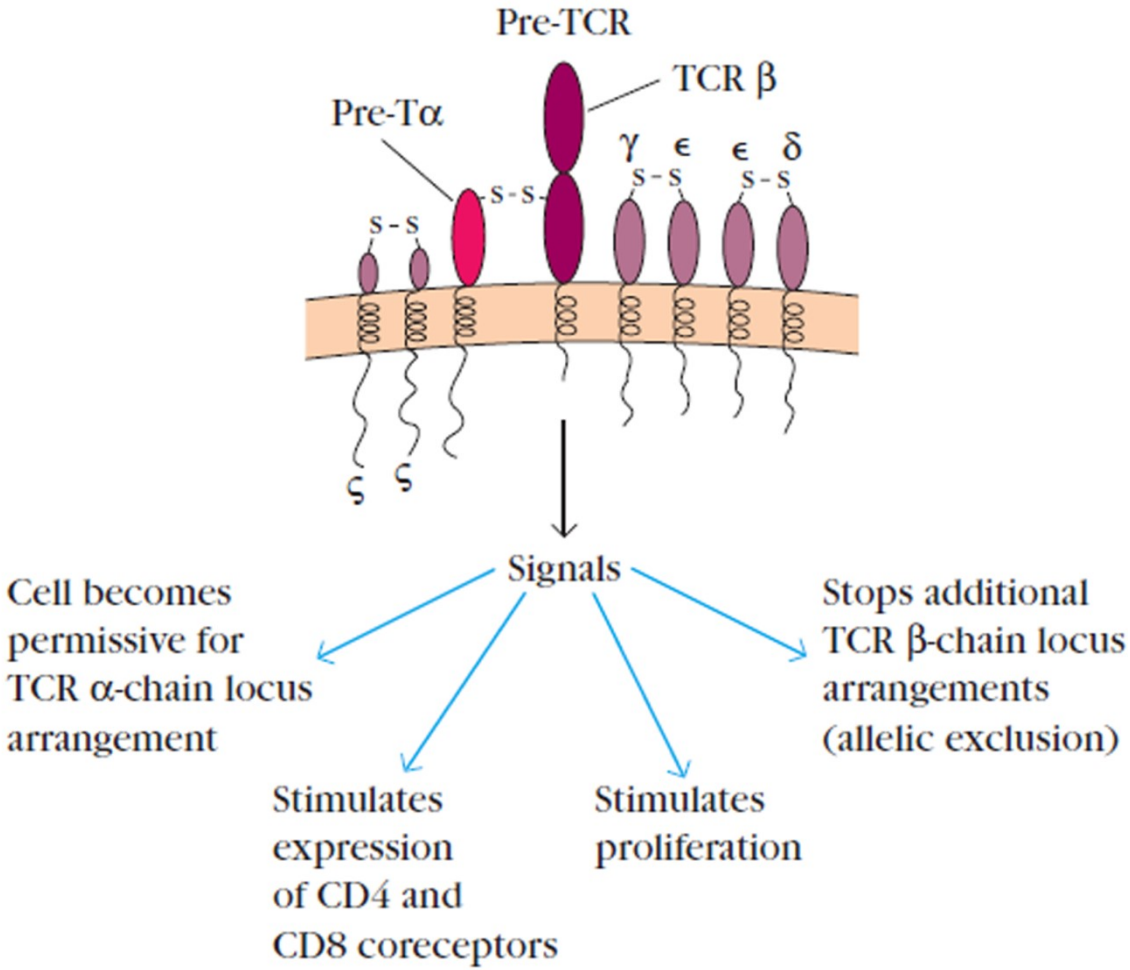
Development of T cells in the mouse. T-cell precursors arrive at the thymus from bone marrow via the bloodstream, undergo development to mature T cells, and are exported to the periphery where they can undergo antigen-induced activation and differentiation into effector cells and memory cells. Each stage of development is characterized by stage-specific intracellular events and the display of distinctive cell-surface markers.

T-Cell Maturation and the Thymus



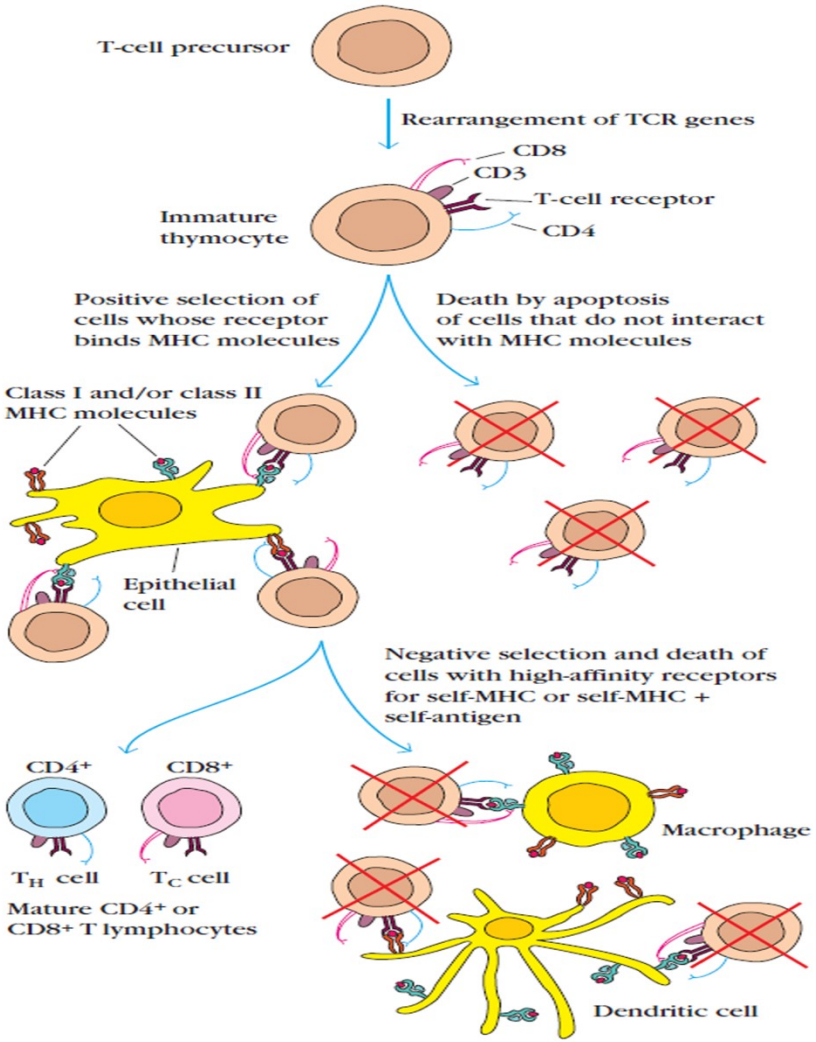
Time course of appearance of γδ thymocytes and αβ thymocytes during mouse fetal development. The graph shows the percentage of CD3 cells in the thymus that are double-negative (CD4-8-) and bear the γδ T-cell receptor (black) or are doublepositive (CD4+8+) and bear the αβ T-cell receptor (blue).

T-Cell Maturation and the Thymus



Structure and activity of the pre–T-cell receptor (pre-TCR). Binding of ligands yet to be identified to the pre-TCR generates intracellular signals that induce a variety of processes.

T-Cell Maturation and the Thymus



Positive and negative selection of thymocytes in the thymus. Thymic selection involves thymic stromal cells (epithelial cells, dendritic cells, and macrophages), and results in mature T cells that are both self-MHC restricted and self-tolerant.

TH-Cell Activation

- **The central event in the generation of both humoral and cellmediated immune responses is the activation and clonal expansion of TH cells. Thcell activation is initiated by interaction of the TCR-CD3 complex with a processed antigenic peptide bound to a class II MHC molecule on the surface of an antigen-presenting cell. This interaction and the resulting activating signals also involve various accessory membrane molecules on the TH cell and the antigen-presenting cell. Interaction of a TH cell with antigen initiates a cascade of biochemical events that induces the resting TH cell to enter the cell cycle, proliferating and differentiating into memory cells or effector cells.**

- **Many of the gene products that appear upon interaction with antigen can be grouped into one of three categories depending on how early they can be detected after antigen recognition**
- ***Immediate genes,* expressed within half an hour of antigen recognition, encode a number of transcription factors, including c-Fos, c-Myc, c-Jun, NFAT, and NFk-B**
- ***Early genes,* expressed within 1–2 h of antigen recognition, encode IL-2, IL-2R (IL-2 receptor), IL-3,**
- **IL-6, IFN-γ, and numerous other proteins *Late genes,* expressed more than 2 days after antigen recognition, encode various adhesion molecules.**

- **These profound changes are the result of signal-transduction pathways that are activated by the encounter between the TCR and MHC-peptide complexes.**

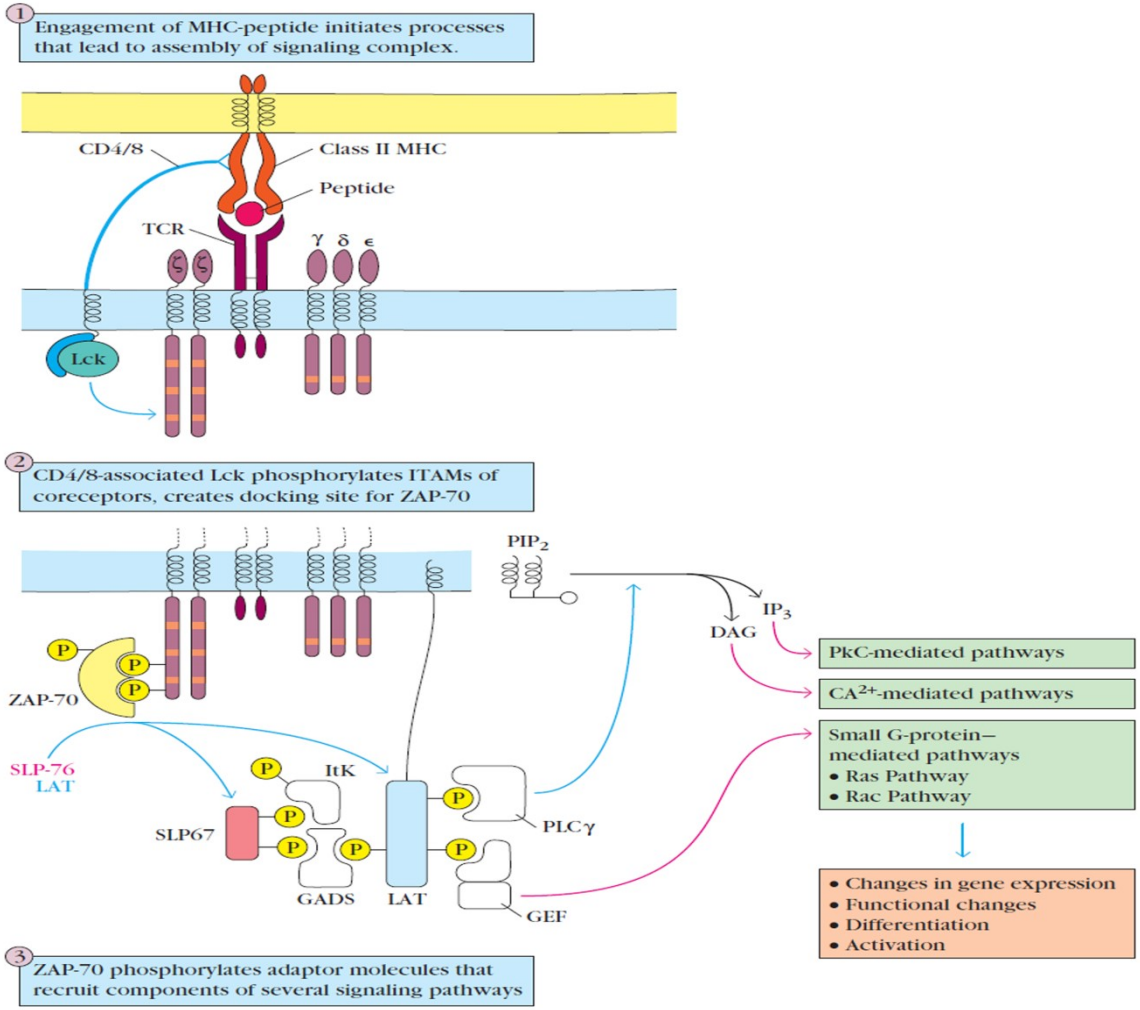
TH-Cell Activation

TABLE Time course of gene expression by T_H cells following interaction with antigen

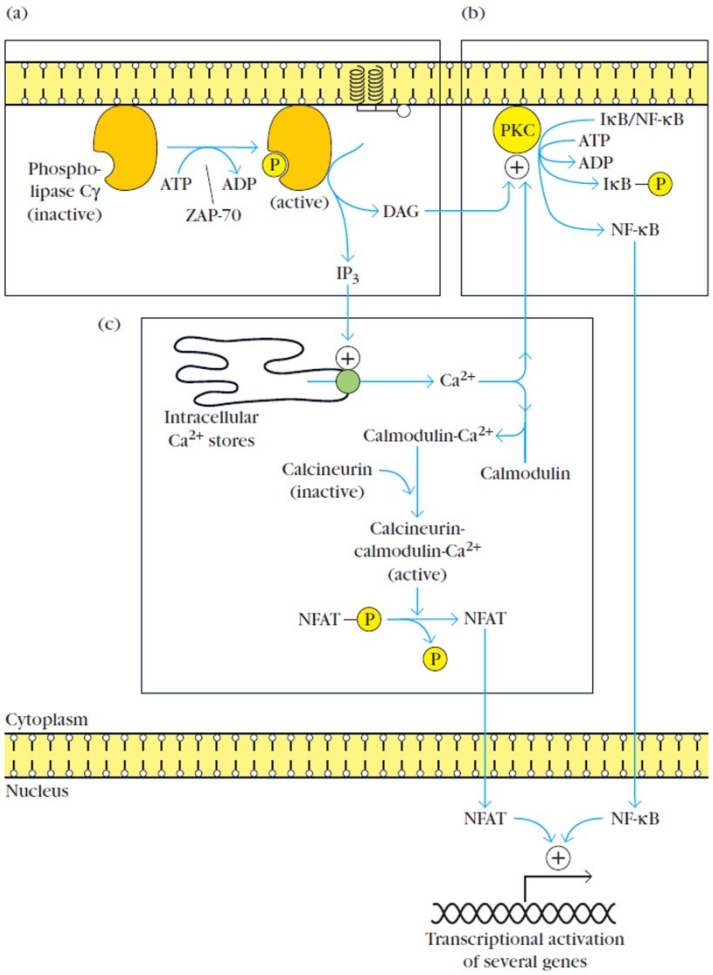
Gene product	Function	Time mRNA expression begins	Location	Ratio of activated to nonactivated cells
		IMMEDIATE		
c-Fos	Protooncogene; nuclear-binding protein	15 min	Nucleus	> 100
c-Jun	Cellular oncogene; transcription factor	15–20 min	Nucleus	?
NFAT	Transcription factor	20 min	Nucleus	50
c-Myc	Cellular oncogene	30 min	Nucleus	20
NF-κB	Transcription factor	30 min	Nucleus	> 10
		EARLY		
IFN-γ	Cytokine	30 min	Secreted	> 100
IL-2	Cytokine	45 min	Secreted	> 1000
Insulin receptor	Hormone receptor	1 h	Cell membrane	3
IL-3	Cytokine	1–2 h	Secreted	> 100
TGF-β	Cytokine	< 2 h	Secreted	> 10
IL-2 receptor (p55)	Cytokine receptor	2 h	Cell membrane	> 50
TNF-β	Cytokine	1–3 h	Secreted	> 100
Cyclin	Cell-cycle protein	4–6 h	Cytoplasmic	> 10
IL-4	Cytokine	< 6 h	Secreted	> 100
IL-5	Cytokine	< 6 h	Secreted	> 100
IL-6	Cytokine	< 6 h	Secreted	> 100
c-Myb	Protooncogene	16 h	Nucleus	100
GM-CSF	Cytokine	20 h	Secreted	?
		LATE		
HLA-DR	Class II MHC molecule	3–5 days	Cell membrane	10
VLA-4	Adhesion molecule	4 days	Cell membrane	> 100
VLA-1, VLA-2, VLA-3, VLA-5	Adhesion molecules	7–14 days	Cell membrane	> 100, ?, ?, ?

SOURCE: Adapted from G. Crabtree, *Science* **243**:357.

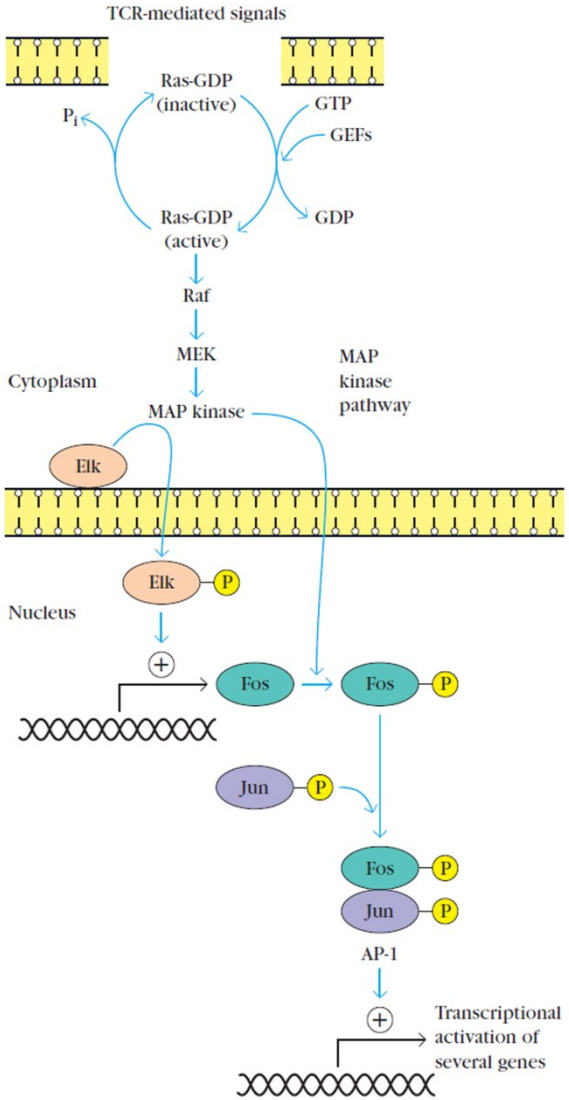
Multiple Signaling Pathways Are Initiated by TCR Engagement



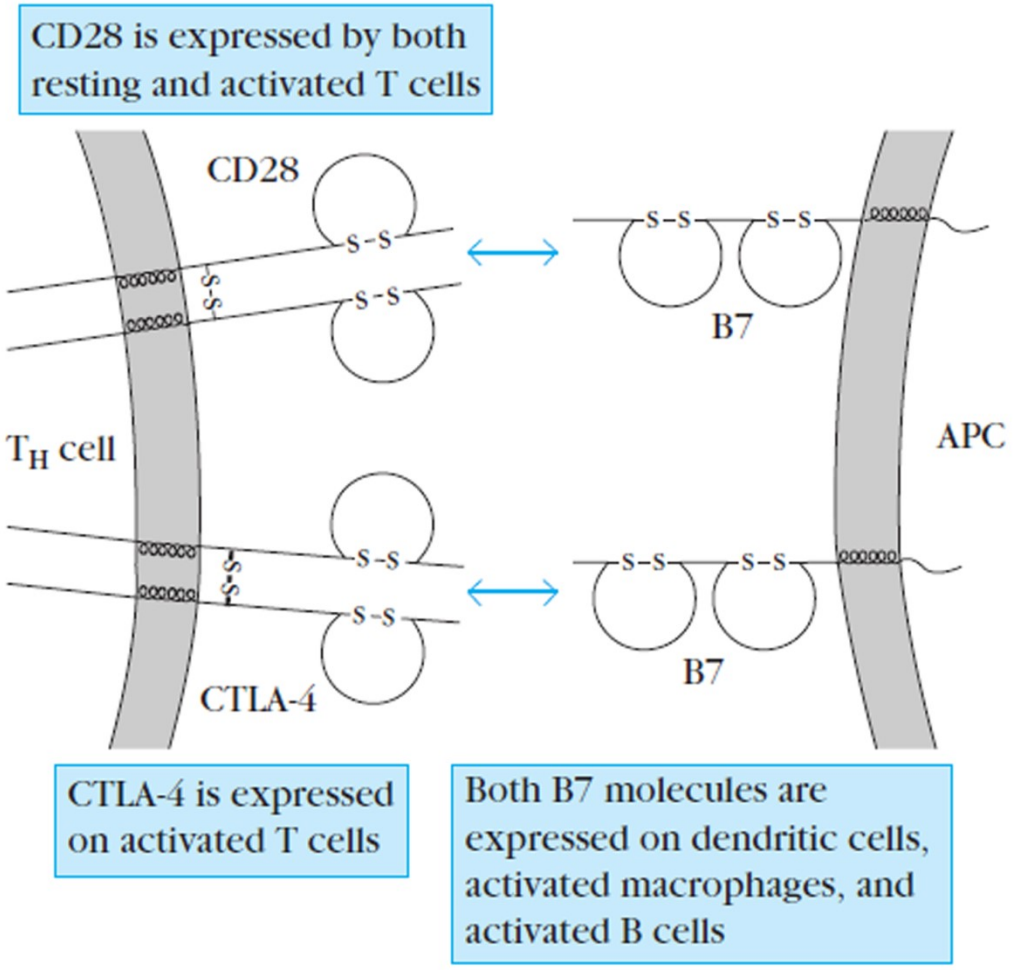
Multiple Signaling Pathways Are Initiated by TCR Engagement



Multiple Signaling Pathways Are Initiated by TCR Engagement

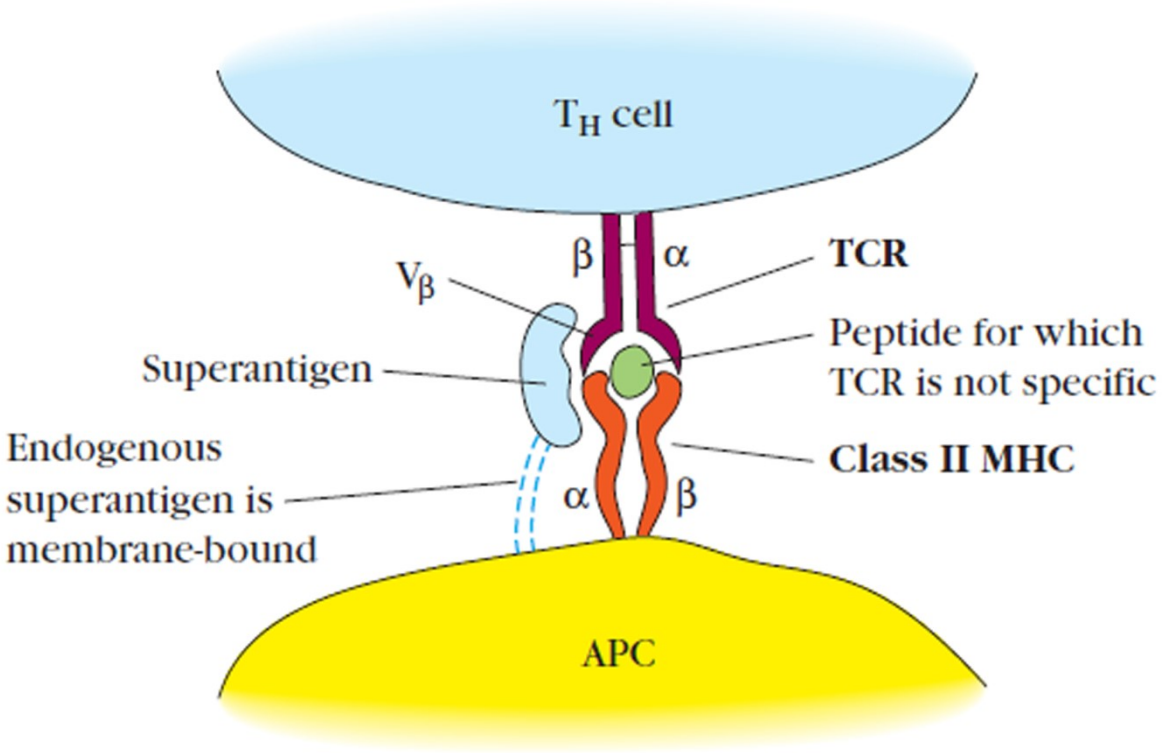


Co-Stimulatory Signals Are Required for Full T-Cell Activation



TH-cell activation requires a co-stimulatory signal provided by antigen-presenting cells (APCs). Interaction of B7 family members on APCs with CD28 delivers the co-stimulatory signal. Engagement of the closely related CTLA-4 molecule with B7 produces an inhibitory signal. All of these molecules contain at least one immunoglobulin-liké domain and thus belong to the immunoglobulin superfamily.

Superantigens Induce T-Cell Activation by Binding the TCR and MHC II Simultaneously



Superantigen-mediated crosslinkage of T-cell receptor and class II MHC molecules. A superantigen binds to all TCRs bearing a particular Vβ sequence regardless of their antigenic specificity. Exogenous superantigens are soluble secreted bacterial proteins, including various exotoxins. Endogenous superantigens are membrane-embedded proteins produced by certain viruses; they include Mls antigens encoded by mouse mammary tumor virus.

Superantigens Induce T-Cell Activation by Binding the TCR and MHC II Simultaneously

TABLE Exogenous superantigens and their V_β specificity

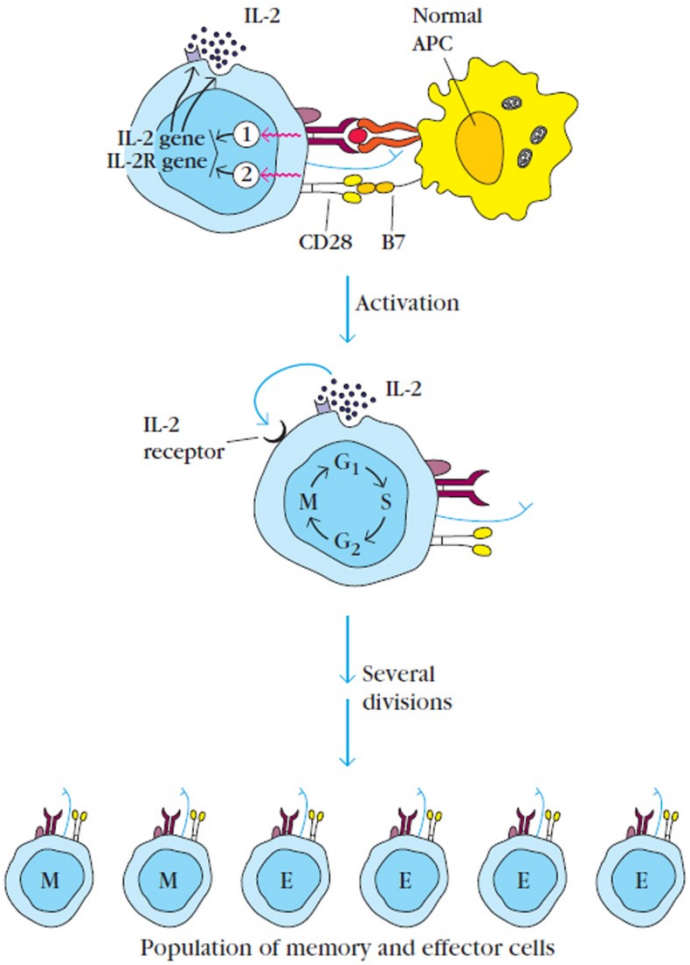
Superantigen	Disease*	V_β SPECIFICITY: Mouse	V_β SPECIFICITY: Human
Staphylococcal enterotoxins			
SEA	Food poisoning	1, 3, 10, 11, 12, 17	nd
SEB	Food poisoning	3, 8.1, 8.2, 8.3	3, 12, 14, 15, 17, 20
SEC1	Food poisoning	7, 8.2, 8.3, 11	12
SEC2	Food poisoning	8.2, 10	12, 13, 14, 15, 17, 20
SEC3	Food poisoning	7, 8.2	5, 12
SED	Food poisoning	3, 7, 8.3, 11, 17	5, 12
SEE	Food poisoning	11, 15, 17	5.1, 6.1–6.3, 8, 18
Toxic-shock-syndrome toxin (TSST1)	Toxic-shock syndrome	15, 16	2
Exfoliative-dermatitis toxin (ExFT)	Scalded-skin syndrome	10, 11, 15	2
Mycoplasma-arthritidis supernatant (MAS)	Arthritis, shock	6, 8.1–8.3	nd
Streptococcal pyrogenic exotoxins (SPE-A, B, C, D)	Rheumatic fever, shock	nd	nd

*Disease results from infection by bacteria that produce the indicated superantigens.

T-Cell Differentiation

- CD4 and CD8 T cells leave the thymus and enter the circulation as resting cells in the G0 stage of the cell cycle. There are about twice as many CD4 T cells as CD8 T cells in the
- periphery. T cells that have not yet encountered antigen (naive T cells) are characterized by condensed chromatin, very little cytoplasm, and little transcriptional activity. Naïve T cells continually recirculate between the blood and lymph systems. During recirculation, naive T cells reside in secondary lymphoid tissues such as lymph nodes. If a naive cell does not encounter antigen in a lymph node, it exits through the efferent lymphatics, ultimately draining into the thoracic duct and rejoining the blood. It is estimated that each naive T cell recirculates from the blood to the lymph nodes and back again every 12–24 hours. Because only about 1 in 10^5 naive T cells is specific for any given antigen, this large-scale recirculation increases the chances that a naive T cell will encounter appropriate antigen.

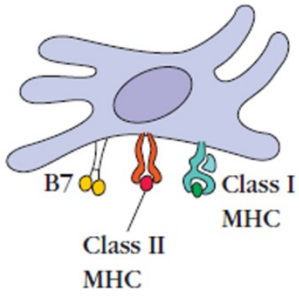
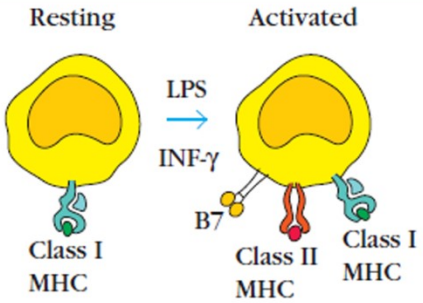
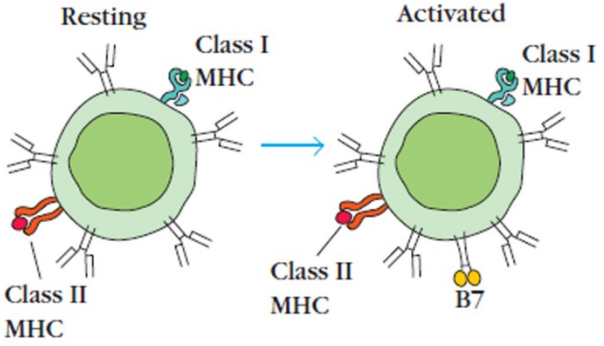
T-Cell Differentiation



If a naive T cell recognizes an antigen-MHC complex on an appropriate antigen-presenting cell or target cell, it will be activated, initiating a *primary response*. About 48 hours after activation, the naive T cell enlarges into a blast cell and begins undergoing repeated rounds of cell division.

Activation of a TH cell by both signal 1 and costimulatory signal 2 up-regulates expression of IL-2 and the highaffinity IL-2 receptor, leading to the entry of the T cell into the cell cycle and several rounds of proliferation. Some of the cells differentiate into effector cells, others into memory cells.

T-Cell Differentiation

	Dendritic cell	Macrophage		B Lymphocyte	
					
Antigen uptake	Endocytosis phagocytosis (by Langerhans cells)	Phagocytosis	Phagocytosis	Receptor-mediated endocytosis	Receptor-mediated endocytosis
Class II MHC expression	Constitutive (+++)	Inducible (–)	Inducible (++)	Constitutive (++)	Constitutive (+++)
Co-stimulatory activity	Constitutive B7 (+++)	Inducible B7 (–)	Inducible B7 (++)	Inducible B7 (–)	Inducible B7 (++)
T-cell activation	Naive T cells Effector T cells Memory T cells	(–)	Effector T cells Memory T cells	Effector T cells Memory T cells	Naive T cells Effector T cells Memory T cells

T-Cell Differentiation

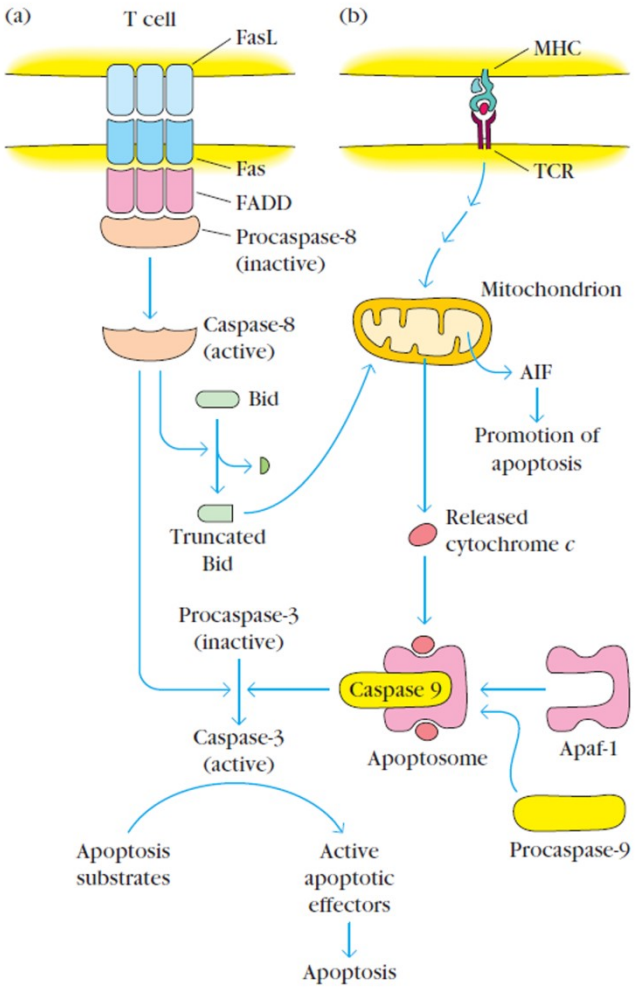
- The various *effector T cells* carry out specialized functions such as cytokine secretion and B-cell help (activated CD4 TH cells) and cytotoxic killing activity (CD8 CTLs).

- Effector cells are derived from both naive and memory cells after antigen activation. Effector cells are short-lived cells, whose life spans range from a few days to a few weeks. The effector and naive populations express different cell-membrane molecules,which contribute to different recirculation patterns.

- CD4 effector T cells form two subpopulations distinguished by the different panels of cytokines they secrete. One population, called the TH1 subset, secretes IL-2, IFN-γ, and TNF-β. The TH1 subset is responsible for classic cell-mediated functions, such as delayed-type hypersensitivity and the activation of cytotoxic T lymphocytes. The other subset, called the TH2 subset, secretes IL-4, IL-5, IL-6, and IL-10. This subset functions more effectively as a helper for B-cell activation.

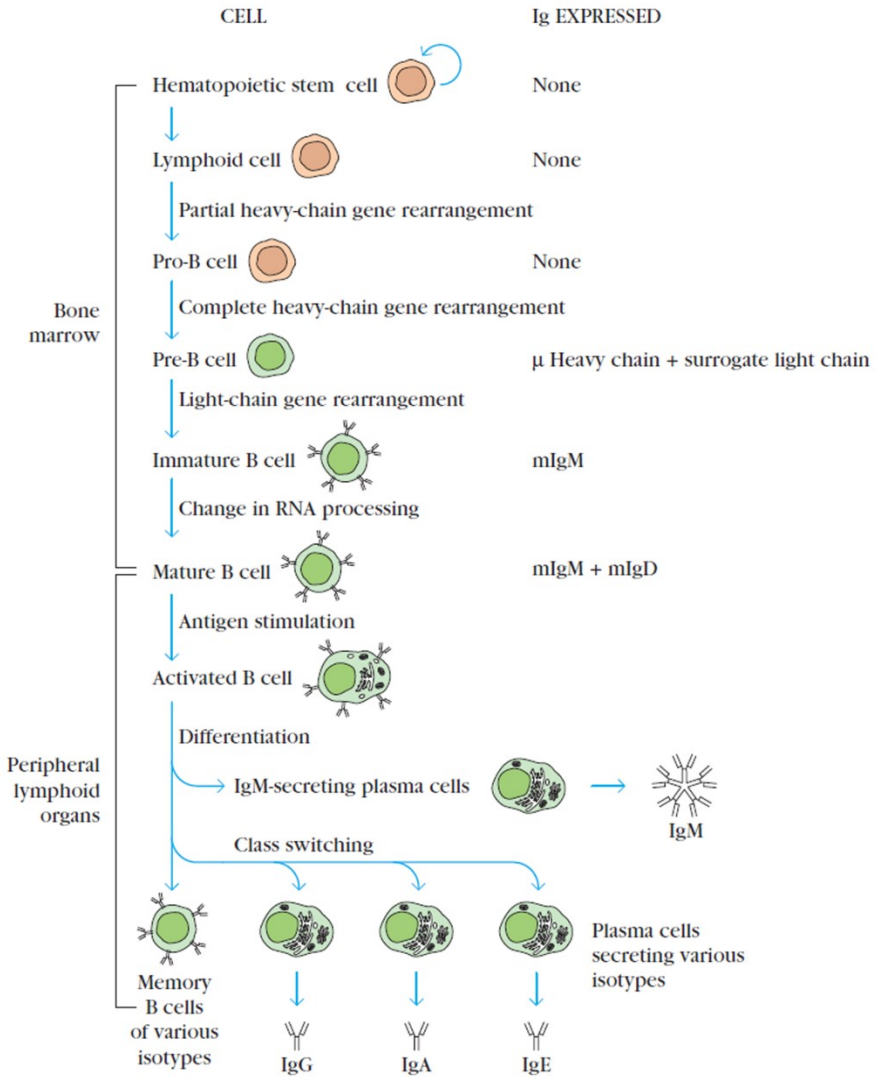
- The *memory T-cell* population is derived from both naïve T cells and from effector cells after they have encountered antigen. Memory T cells are antigen-generated, generally long-lived, quiescent cells that respond with heightened reactivity to a subsequent challenge with the same antigen, generating a *secondary response.*

Cell Death and T-Cell Populations



Cell death is an important feature of development in all multicellular organisms. During fetal life it is used to mold and sculpt, removing unnecessary cells to provide shape and form. It also is an important feature of lymphocyte homeostasis, returning T- and B-cell populations to their appropriate levels after bursts of antigen-induced proliferation. Apoptosis also plays a crucial role in the deletion of potentially autoreactive thymocytes during negative selection and in the removal of developing T cells unable to recognize self (failure to undergo positive selection).

Organization and Expression of Immunoglobulin Genes



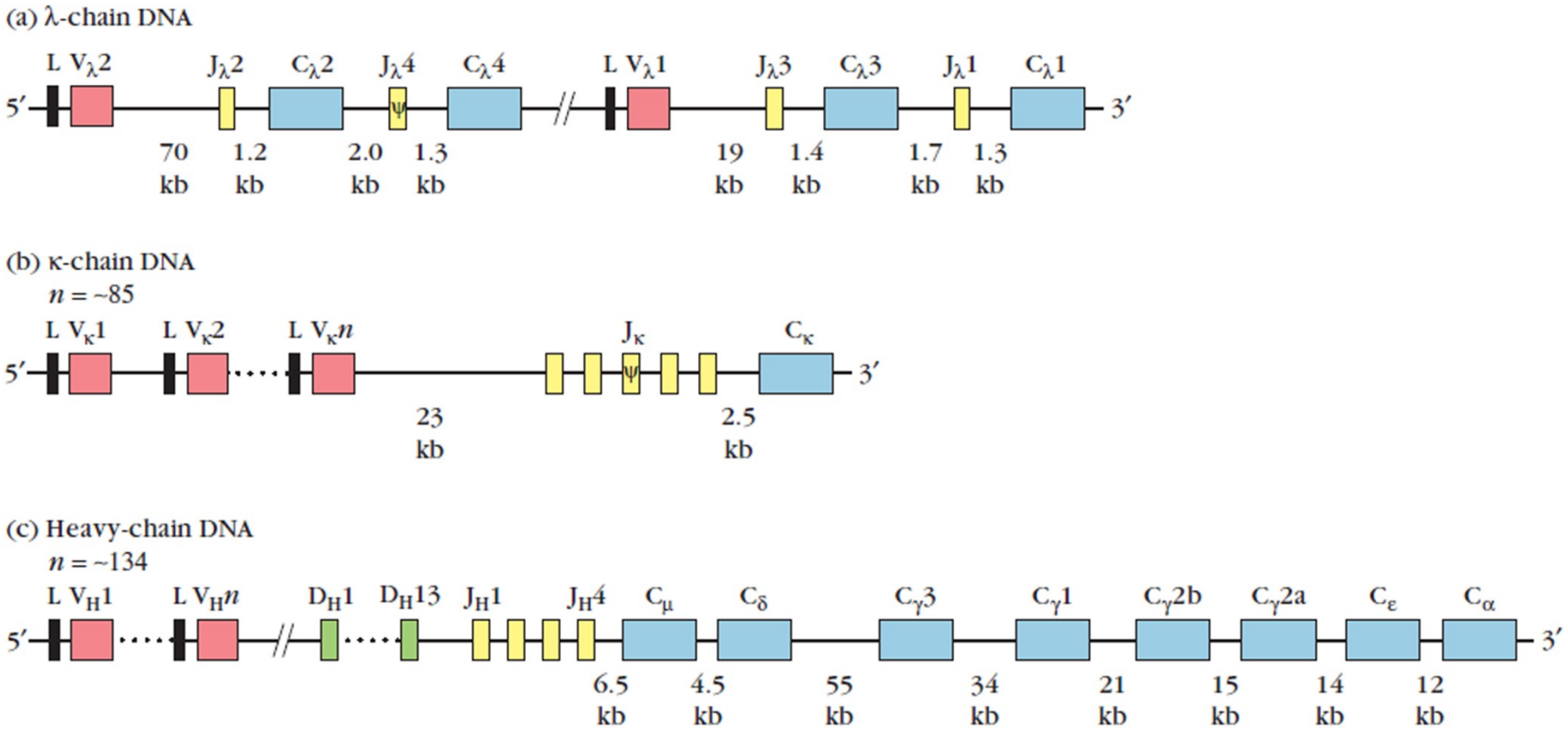
Overview of B-cell development. The events that occur during maturation in the bone marrow do not require antigen, whereas activation and differentiation of mature B cells in peripheral lymphoid organs require antigen. The labels mIgM and mIgD refer to membrane-associated Igs. IgG, IgA, and IgE are secreted immunoglobulins.

Organization and Expression of Immunoglobulin Genes

TABLE Chromosomal locations of immunoglobulin genes in human and mouse

Gene	CHROMOSOME	
	Human	Mouse
λ Light chain	22	16
κ Light chain	2	6
Heavy chain	14	12

Organization and Expression of Immunoglobulin Genes



Organization of immunoglobulin germ-line gene segments in the mouse: (a) light chain, (b) light chain, and (c) heavy chain. The and light chains are encoded by V, J, and C gene segments. The heavy chain is encoded by V, D, J, and C gene segments. The distances in kilobases (kb) separating the various gene segments in mouse germ-line DNA are shown below each chain diagram.

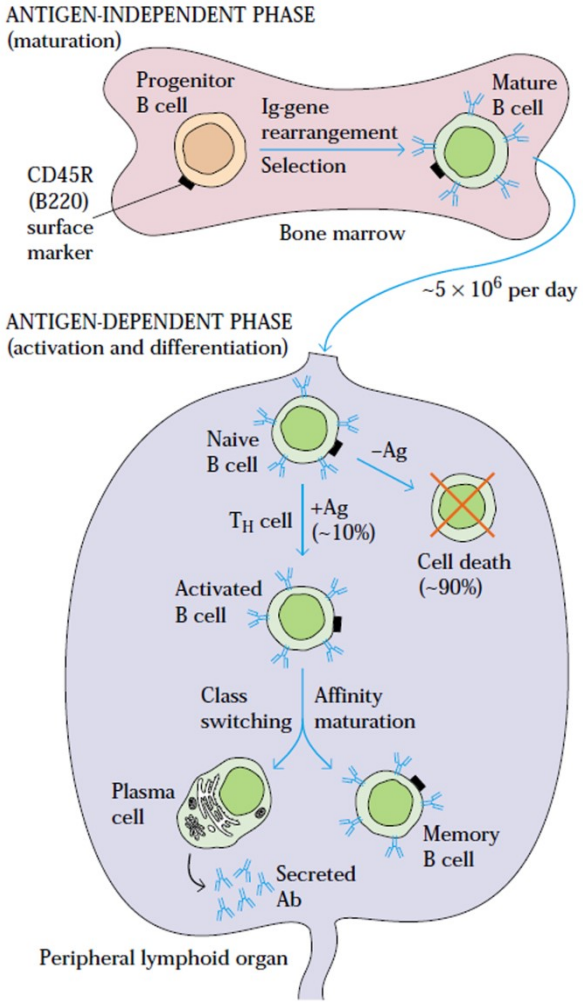
B-Cell Generation, Activation, and Differentiation

- The developmental process that results in production of plasma cells and memory B cells can be divided into three broad stages: generation of mature, immunocompetent B cells (maturation), activation of mature B cells when they interact with antigen, and differentiation of activated B cells into plasma cells and memory B cells. In many vertebrates, including humans and mice, the bone marrow generates B cells. This process is an orderly sequence of Ig-gene rearrangements, which progresses in the absence of antigen. This is the antigenindependent phase of B-cell development.

- A mature B cell leaves the bone marrow expressing membrane-bound immunoglobulin (mIgM and mIgD) with a single antigenic specificity. These naive B cells, which have not encountered antigen, circulate in the blood and lymph and are carried to the secondary lymphoid organs,most notably the spleen and lymph nodes. If a B cell is activated by the antigen specific to its membrane-bound antibody, the cell proliferates (clonal expansion) and differentiates to generate a population of antibody-secreting plasma cells and memory B cells.

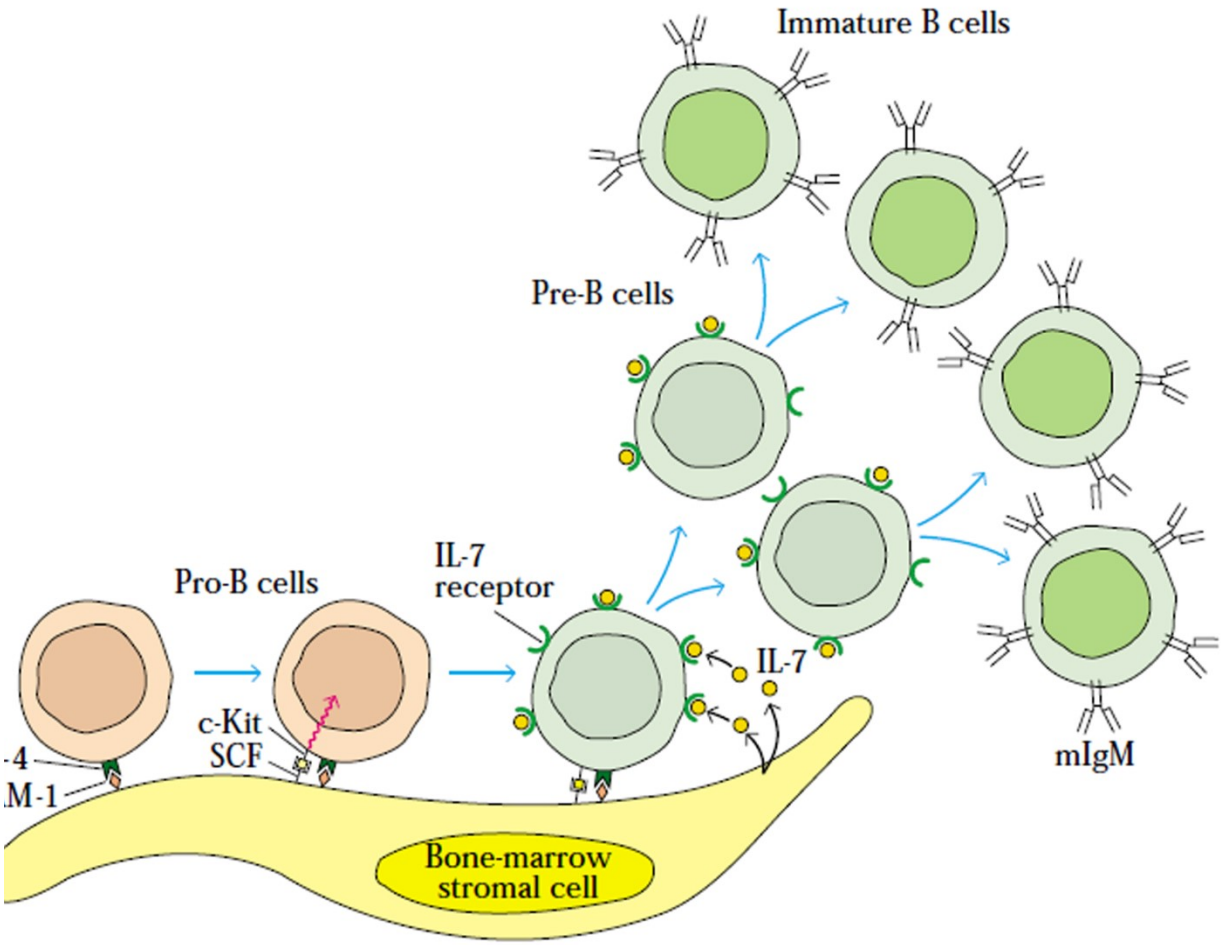
- In this activation stage, affinity maturation is the progressive increase in the average affinity of the antibodies produced and class switching is the change in the isotype of the antibody produced by the B cell from to γ, α, or ε. Since B cell activation and differentiation in the periphery require antigen, this stage comprises the antigendependent phase of B-cell development.

B-Cell Generation, Activation, and Differentiation



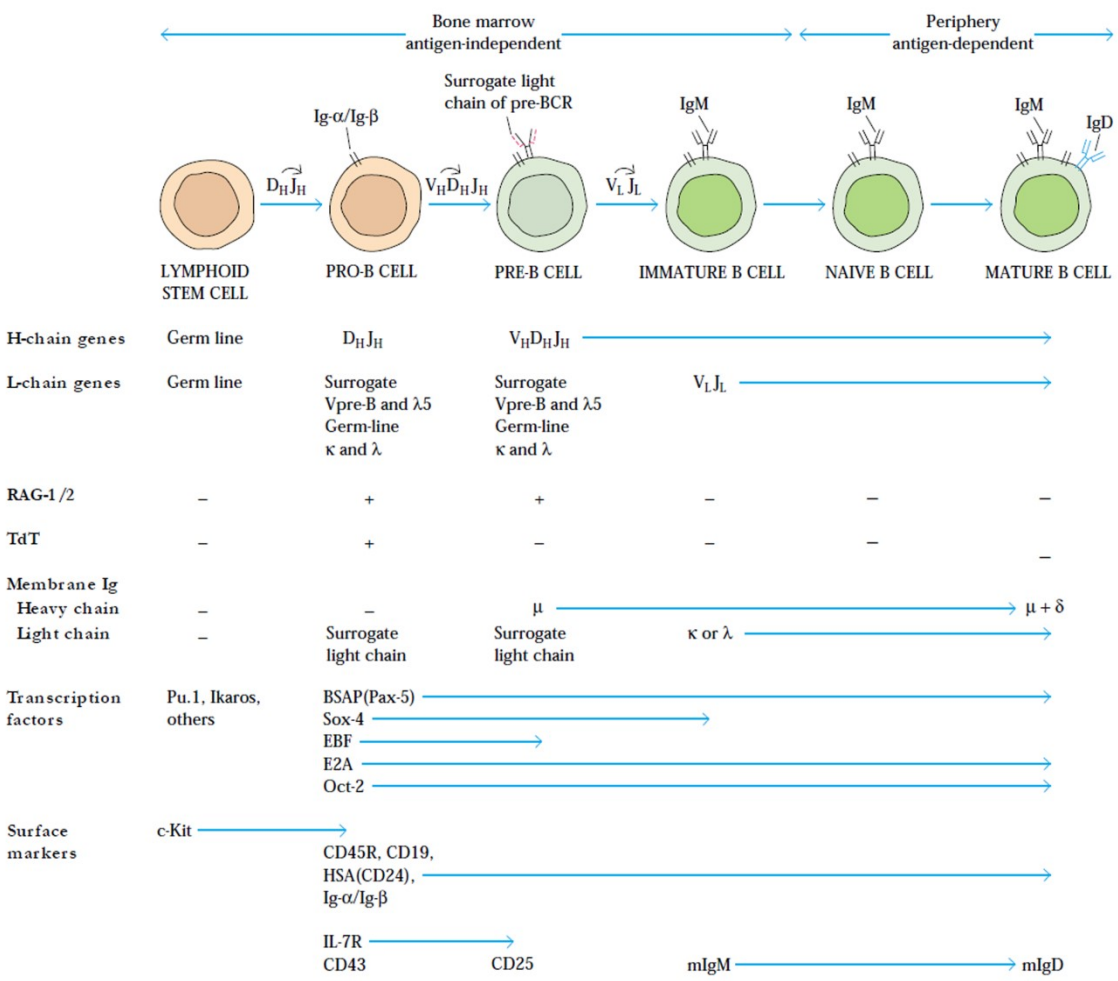
Overview of B-cell development. During the antigen-independent maturation phase, immunocompetent B cells expressing membrane IgM and IgD are generated in the bone marrow. Only about 10% of the potential B cells reach maturity and exit the bone marrow. Naive B cells in the periphery die within a few days unless they encounter soluble protein antigen and activated TH cells. Once activated, B cells proliferate within secondary lymphoid organs. Those bearing high-affinity mIg differentiate into plasma cells and memory B cells, which may express different isotypes because of class switching. The numbers cited refer to B-cell development in the mouse, but the overall principles apply to humans as well.

B-Cell Maturation



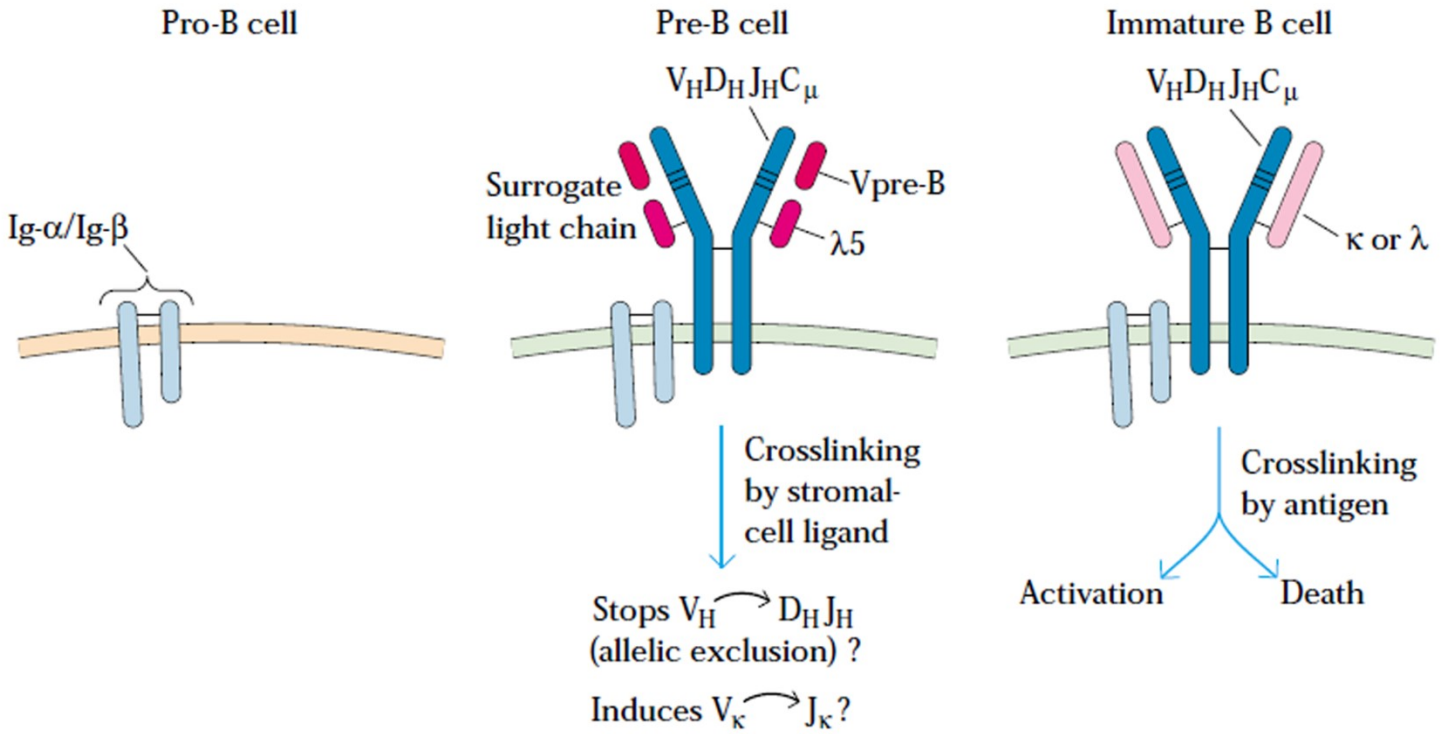
Bone-marrow stromal cells are required for maturation of progenitor B cells into precursor B cells. Pro-B cells bind to stromal cells by means of an interaction between VCAM-1 on the stromal cell and VLA-4 on the pro-B cell. This interaction promotes the binding of c-Kit on the pro-B cell to stem cell factor (SCF) on the stromal cell, which triggers a signal, mediated by the tyrosine kinase activity of c-Kit, that stimulates the pro-B cell to express receptors for IL-7. IL-7 released from the stromal cell then binds to the IL-7 receptors, inducing the pro-B cell to mature into a pre-B cell. Proliferation and differentiation venutally produces immature B cells.

B-Cell Maturation



Sequence of events and characteristics of the stages in B-cell maturation in the bone marrow. The pre-B cell expresses a membrane immunoglobulin consisting of a heavy (H) chain and surrogate light chains, Vpre-B and 5. Changes in the RNA processing of heavy-chain transcripts following the pre-B cell stage lead to synthesis of both membrane-bound IgM and IgD by mature B cells. RAG-1/2 = two enzymes encoded by recombination-activating genes; TdT = terminal deoxyribonucleotidyl transferase. A number of B-cell–associated transcription factors are important at various stages of B-cell development; some are indicated here.

B-Cell Maturation



Schematic diagram of sequential expression of membrane immunoglobulin and surrogate light chain at different stages of B-cell differentiation in the bone marrow. The pre–B-cell receptor contains a surrogate light chain consisting of a Vpre-B polypeptide and a 5 polypeptide, which are noncovalently associated. The immature B cell no longer expresses the surrogate light chain and instead expresses the or light chain together with the heavy chain.

B-Cell Activation and Proliferation

- **Depending on the nature of the antigen, B-cell activation proceeds by two different routes, one dependent upon TH cells, the other not. The B-cell response to thymus-dependent (TD) antigens requires direct contact with TH cells, not simply exposure to TH-derived cytokines.Antigens that can activate B cells in the absence of this kind of direct participation by TH cells are known as thymus-independent (TI) antigens.**

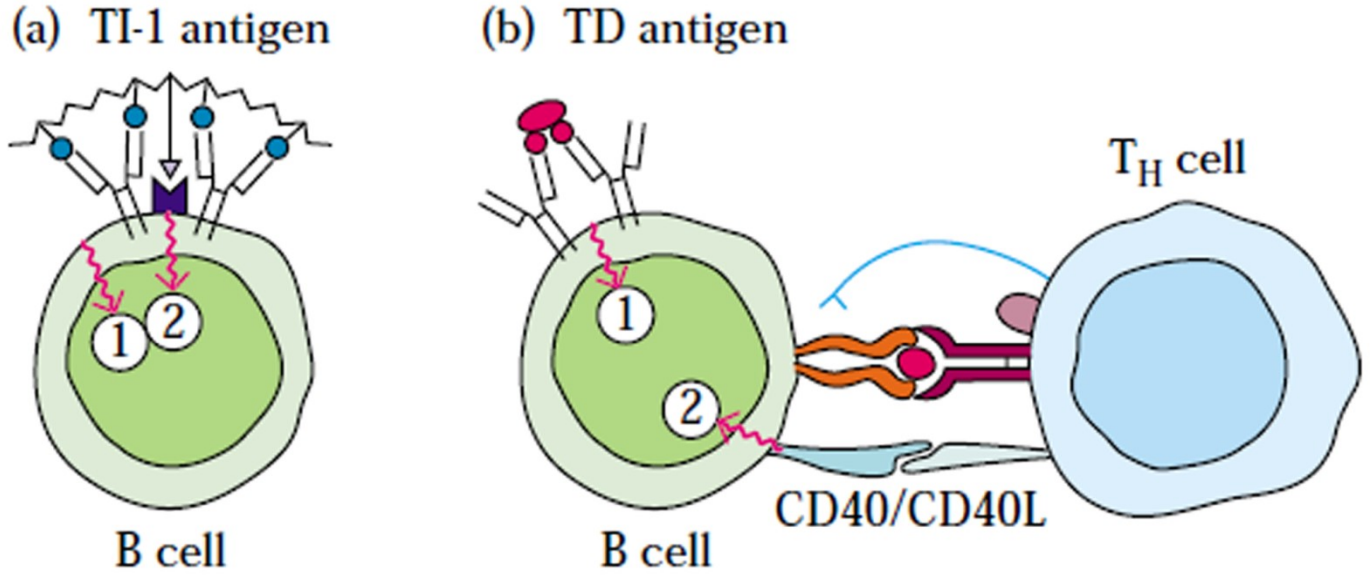
- **TI antigens are divided into types 1 and 2, and they activate B cells by different mechanisms. Some bacterial cell-wall components, including lipopolysaccharide (LPS), function as *type 1 thymus-independent (TI-1) antigens. Type 2 thymus-independent (TI-2) antigens* are highly repetitious molecules such as polymeric proteins (e.g., bacterial flagellin) or bacterial cell-wall polysaccharides with repeating polysaccharide units.**

B-Cell Activation and Proliferation

TABLE Properties of thymus-dependent and thymus-independent antigens

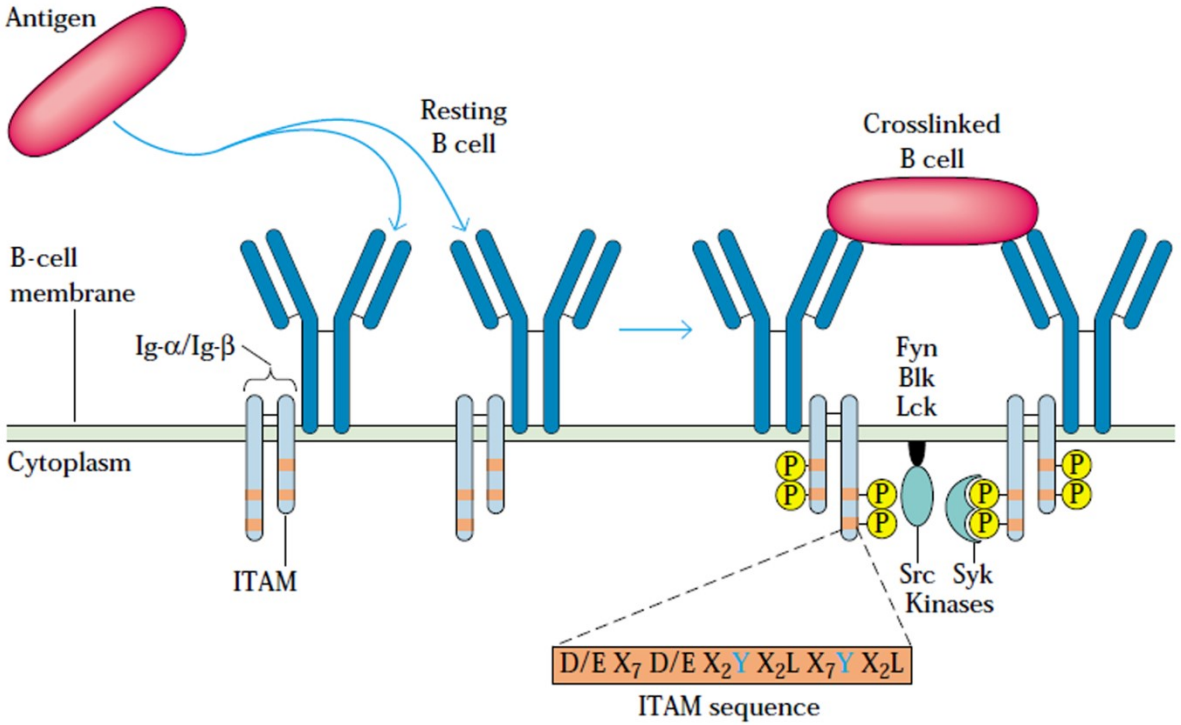
Property	TD antigens	TI ANTIGENS	
		Type 1	Type 2
Chemical nature	Soluble protein	Bacterial cell-wall components (e.g., LPS)	Polymeric protein antigens; capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No
Polyclonal activation	No	Yes (high doses)	No

B-Cell Activation and Proliferation



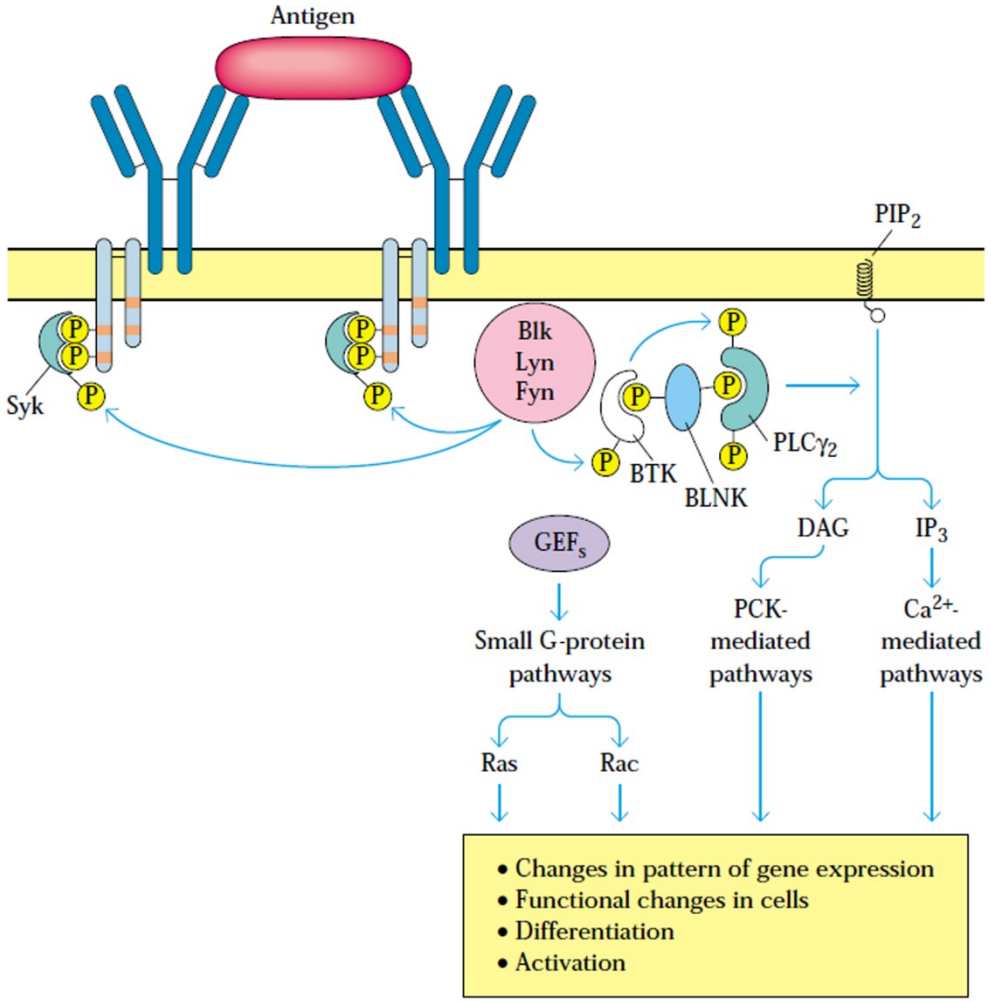
An effective signal for B-cell activation involves two distinct signals induced by membrane events. Binding of a type 1 thymus-independent (TI-1) antigen to a B cell provides both signals. A thymus-dependent (TD) antigen provides signal 1 by crosslinking mIg, but a separate interaction between CD40 on the B cell and CD40L on an activated TH cell is required to generate signal 2.

B-Cell Activation and Proliferation



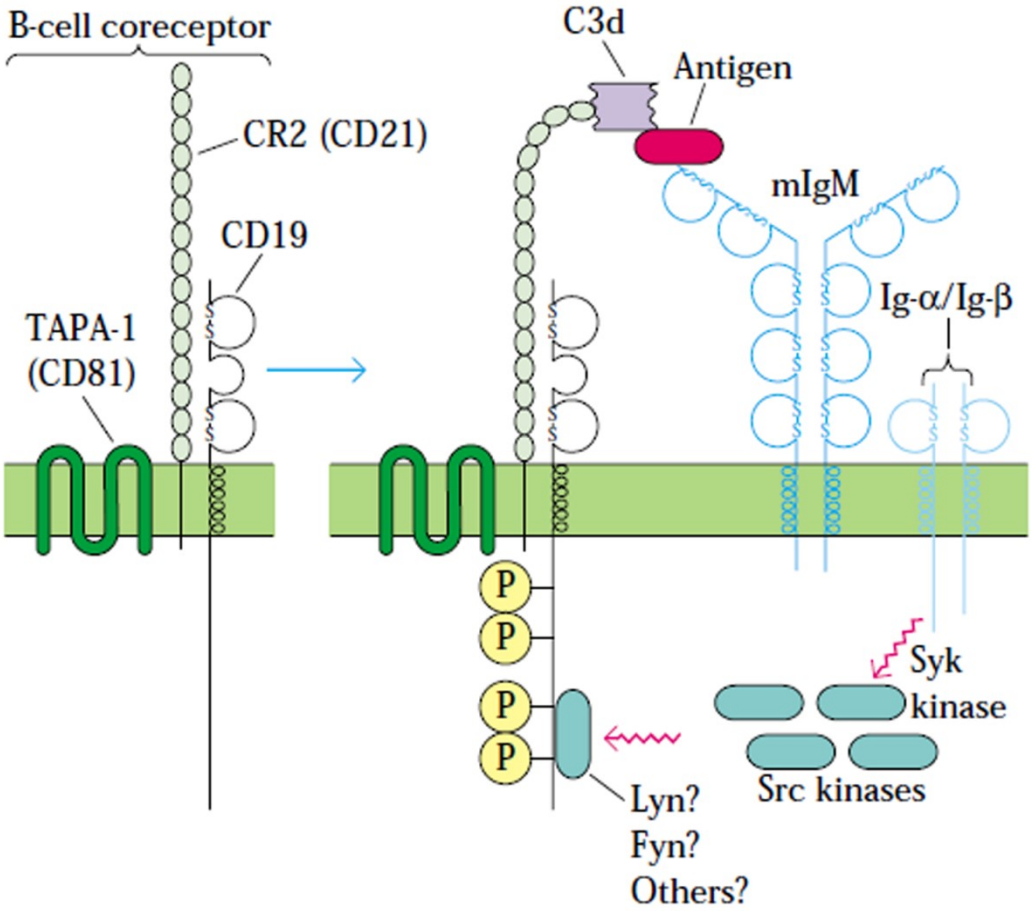
The initial stages of signal transduction by an activated B-cell receptor (BCR). The BCR comprises an antigen-binding mIg and one signal-transducing Ig-α/Ig-β heterodimer. Following antigen crosslinkage of the BCR, the immunoreceptor tyrosine-based activation motifs (ITAMs) interact with several members of the Src family of tyrosine kinases (Fyn, Blk, and Lck), activating the kinases. The activated enzymes phosphorylate tyrosine residues on the cytoplasmic tails of the Ig-α/Ig-β heterodimer, creating docking sites for Syk kinase, which is then also activated. The highly conserved sequence motif of ITAMs is shown with the tyrosines (Y) in blue. D/E indicates that an aspartate or a glutamate can appear at the indicated position, and X indicates that the position can be occupied by any amino

B-Cell Activation and Proliferation



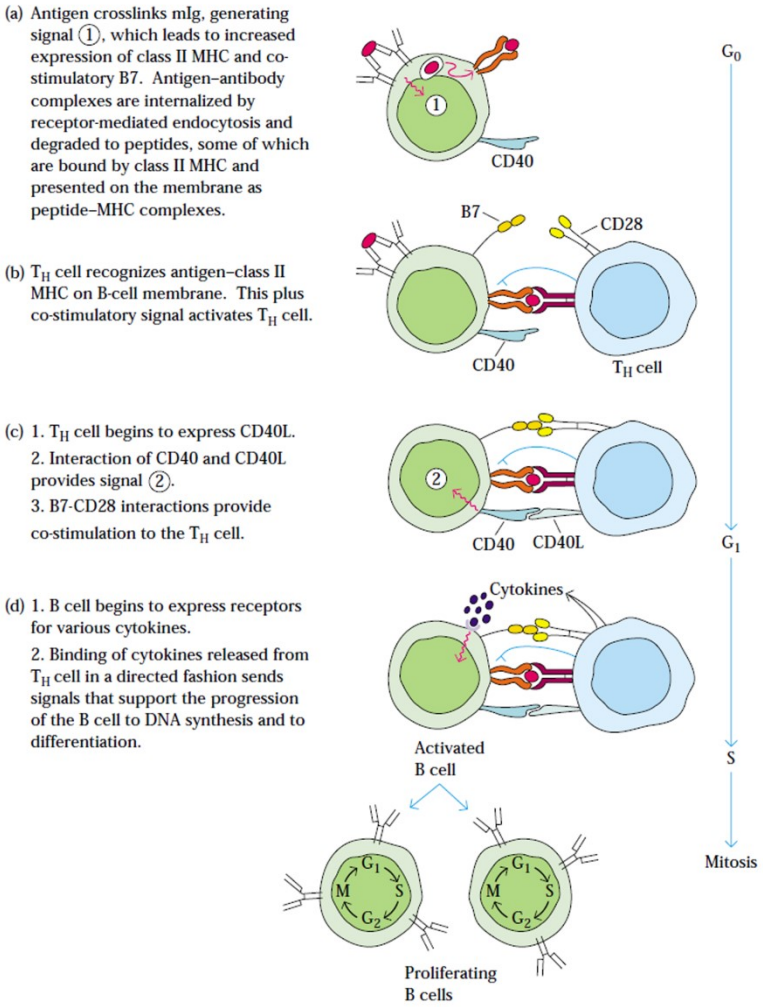
Some of the many signal-transduction pathways activated by the BCR. In one pathway, Syk activates PLC2 by tyrosine phosphorylation. PLCγ2 thenv hydrolyzes PIP2, a membrane phospholipid, to produce the second messengers DAG and IP3.
DAG and Ca2+ released by the action of IP3 collaboratively activate the PKC, which induces additional signal-transduction pathways. The activated receptor complex also generates signals that activate the Ras pathway. Activated Ras initiates a cascade of phosphorylations that culminates in the activation of transcription factors that up-regulate the expression of many genes.

B-Cell Activation and Proliferation



The B-cell coreceptor is a complex of three cell membrane molecules: TAPA-1 (CD81), CR2 (CD21), and CD19. Binding of the CR2 component to complement-derived C3d that has coated antigen captured by mIg results in the phosphorylation of CD19. The Src family tyrosine kinase Lyn binds to phosphorylated CD19. The resulting activated Lyn and Fyn can trigger the signal-transduction pathways shown in Figure 11-8 that begin with phospholipase C.

B-Cell Activation and Proliferation



Sequence of events in B-cell activation by a thymus-dependent antigen. The cell-cycle phase of the interacting B cell is indicated on the right.