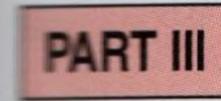


PART II

THE RECOGNITION OF ANTIGEN

Chapter 4 Antigen Recognition by B-cell and T-cell Receptors
 Chapter 5 The Generation of Lymphocyte Antigen Receptors
 Chapter 6 Antigen Presentation to T Lymphocytes



THE DEVELOPMENT OF MATURE LYMPHOCYTE RECEPTOR REPERTOIRES

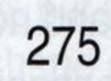
Chapter 7 Signaling Through Immune-System ReceptorsChapter 8 The Development and Survival of Lymphocytes



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PART IV THE ADAPTIVE IMMUNE RESPONSE

Chapter 9 T Cell-Mediated Immunity
Chapter 10 The Humoral Immune Response
Chapter 11 Dynamics of Adaptive Immunity
Chapter 12 The Mucosal Immune System

PART VTHE IMMUNE SYSTEM IN HEALTH AND DISEASEChapter 13Failures of Host Defense MechanismsChapter 14Allergy and Allergic DiseasesChapter 15Autoimmunity and TransplantationChapter 16Manipulation of the Immune Response

Appendix I Immunologist's Toolbox with Immunological Constants





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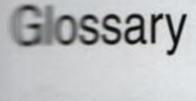
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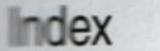
Appendix II CD Antigens

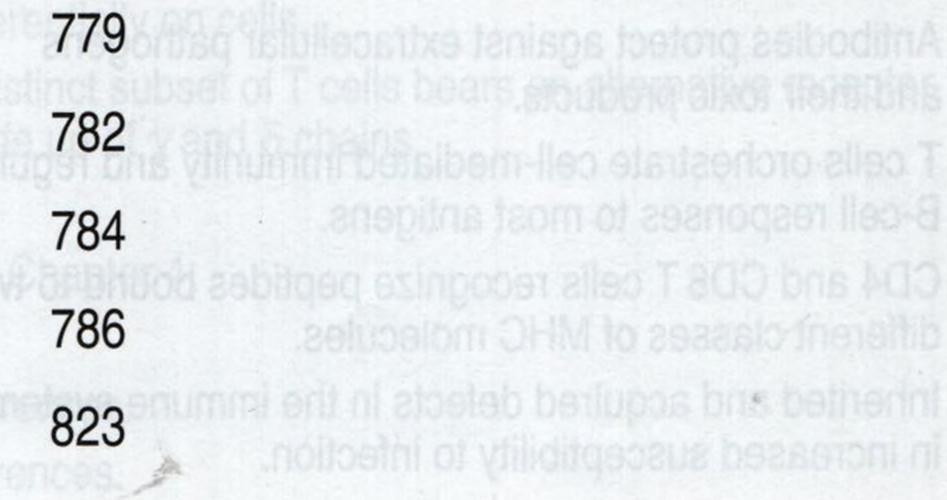
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Appendix IV Chemokines and Their Receptors

Biographies







Detailed Contents

Part I

X

AN INTRODUCTION TO IMMUNO-BIOLOGY AND INNATE IMMUNITY

Basic Concepts in Immunology Chapter 1

Principles of innate and adaptive immunity.

- The immune system recognizes infection and induces 1-1 protective responses.
- Understanding adaptive immune responses is important for 1-22 the control of allergies, autoimmune disease, and the rejection of transplanted organs. Vaccination is the most effective means of controlling 1-23 infectious diseases. Summary. ed Responses of Inna Summary to Chapter 1.
- General references.

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Summary.

Questions.

Section references.

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- The cells of the immune system derive from precursors in 1-2 the bone marrow.
- The myeloid lineage comprises most of the cells of the 1-3 innate immune system.
- The lymphoid lineage comprises the lymphocytes of the 1-4 adaptive immune system and the natural killer cells of innate immunity.
- Lymphocytes mature in the bone marrow or the thymus and 1-5 then congregate in lymphoid tissues throughout the body.
- Most infectious agents activate the innate immune system 1-6 and induce an inflammatory response.
- Pattern recognition receptors of the innate immune system 1-7 provide an initial discrimination between self and nonself.
- Adaptive immune responses are initiated by antigen and 1-8 antigen-presenting cells in secondary lymphoid tissues.
- Lymphocytes activated by antigen give rise to clones of 1-9 antigen-specific effector cells that mediate adaptive immunity. 12
- Clonal selection of lymphocytes is the central principle 1-10 of adaptive immunity.

Innate Immunity: The First Lines Chapter 2: of Defense

The first lines of defense.

- Infectious diseases are caused by diverse living agents that 2-1 replicate in their hosts.
- Infectious agents must overcome innate host defenses to 2-2 establish a focus of infection.
- Epithelial surfaces of the body provide the first line of 2-3 defense against infection.
- Epithelial cells and phagocytes produce several kinds of 2-4 antimicrobial proteins.

Summary.

The complement system and innate immunity.

The complement system recognizes features of microbial 2-5 surfaces and marks them for destruction by the deposition of C3b.

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- The structure of the antibody molecule illustrates the central 1-11 puzzle of adaptive immunity.
- Each developing lymphocyte generates a unique antigen 1-12 receptor by rearranging its receptor gene segments.
- Immunoglobulins bind a wide variety of chemical structures, 1-13 whereas the T-cell receptor is specialized to recognize foreign antigens as peptide fragments bound to proteins of the major histocompatibility complex.
- The development and survival of lymphocytes is determined 1-14 by signals received through their antigen receptors.
- Lymphocytes encounter and respond to antigen in the 1-15 peripheral lymphoid organs.
- Lymphocyte activation requires additional signals beyond 1-16 those relayed from the antigen receptor when antigen binds.
- Lymphocytes activated by antigen proliferate in the 1-17 peripheral lymphoid organs, generating effector cells and immunological memory.

Summary.

The effector mechanisms of adaptive immunity.

- The lectin pathway uses soluble receptors that recognize 2-6 microbial surfaces to activate the complement cascade.
- The classical pathway is initiated by activation of the C1 2-7complex and is homologous to the lectin pathway.
- Complement activation is largely confined to the surface 2-8 on which it is initiated.
- The alternative pathway is an amplification loop for C3b 2-9 formation that is accelerated by recognition of pathogens by properdin.
- Membrane and plasma proteins that regulate the formation 2-10 and stability of C3 convertases determine the extent of complement activation under different circumstances.
- Complement developed early in the evolution of 2-11 multicellular organisms.
- Surface-bound C3 convertase deposits large numbers of 2-12 C3b fragments on pathogen surfaces and generates C5 convertase activity.
- Ingestion of complement-tagged pathogens by phagocytes 2-13 is mediated by receptors for the bound complement proteins. 62 The small fragments of some complement proteins initiate 2-14 a local inflammatory response. 64

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- Antibodies protect against extracellular pathogens 1-18 and their toxic products.
- 1-19 T cells orchestrate cell-mediated immunity and regulate B-cell responses to most antigens.
- CD4 and CD8 T cells recognize peptides bound to two 1-20 different classes of MHC molecules.
- Inherited and acquired defects in the immune system result 1-21 in increased susceptibility to infection.

2-15 The terminal complement proteins polymerize to form pores in membranes that can kill certain pathogens. Complement control proteins regulate all three pathways of 2-16 complement activation and protect the host from their destructive effects.

The Induced Responses of Innate Chapter 3 Immunity

Pattern recognition by cells of the innate immune system. 75

- After entering tissues, many pathogens are recognized, 3-1 ingested, and killed by phagocytes.
- G-protein-coupled receptors on phagocytes link microbe 32 recognition with increased efficiency of intracellular killing.
- Pathogen recognition and tissue damage initiate an 3-3 inflammatory response.
 - Toll-like receptors represent an ancient pathogen-recognition system.
 - Mammalian Toll-like receptors are activated by many different pathogen-associated molecular patterns. 85

Questions.
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Section references.

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THE RECOGNITION OF ANTIGEN Part II

Antigen Recognition by B-cell Chapter 4 and T-cell Receptors

The structure of a typical antibody molecule. 128 IgG antibodies consist of four polypeptide chains. 129 4-1 Immunoglobulin heavy and light chains are composed 4-2 of constant and variable regions. 130 The antibody molecule can readily be cleaved into 4-3 130 functionally distinct fragments. The immunoglobulin molecule is flexible, especially at 4-4 131 the hinge region. The domains of an immunoglobulin molecule have 4-5 132 similar structures. 133 Summary. The interaction of the antibody molecule with 134 specific antigen. Localized regions of hypervariable sequence form the 4-6 134 antigen-binding site. Antibodies bind antigens via contacts with amino acids in 4-7 CDRs, but the details of binding depend upon the size and shape of the antigen. 135 Antibodies bind to conformational shapes on the surfaces 4-8 136 of antigens. Antigen-antibody interactions involve a variety of forces. 136 4-9 138 Summary.

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- TLR-4 recognizes bacterial lipopolysaccharide in association 88 with the host accessory proteins MD-2 and CD14.
- TLRs activate the transcription factors NF_kB, AP-1, 3-7 and IRF to induce the expression of inflammatory cytokines and type I interferons.
- The NOD-like receptors act as intracellular sensors of 3-8 bacterial infection.
- The RIG-I-like helicases detect cytoplasmic viral RNAs 39 and stimulate interferon production.
- Activation of TLRs and NLRs triggers changes in gene 3-10 expression in macrophages and dendritic cells that have far-reaching effects on the immune response.
- TLR signaling shares many components with Toll signaling 3-11 in Drosophila.
- TLR and NOD genes have undergone extensive 3-12 diversification in both invertebrates and some primitive chordates.

summary.

induced innate responses to infection.

Macrophages and dendritic cells activated by pathogens

- secrete a range of cytokines that have a variety of local and distant effects.
- Chemokines released by macrophages and dendritic cells 3474 recruit effector cells to sites of infection.
- Cell-adhesion molecules control interactions between 3415 leukocytes and endothelial cells during an inflammatory response.
- Neutrophils make up the first wave of cells that cross the 3-16 blood vessel wall to enter an inflamed tissue.
 - TNF- α is an important cytokine that triggers local containment of infection but induces shock when released systemically.
- Cytokines released by macrophages and dendritic cells 1-1-1-1 activate the acute-phase response.
- Interferons induced by viral infection make several 3479 contributions to host defense.
- NK cells are activated by interferon and macrophage-derived 320 cytokines to serve as an early defense against certain intracellular infections.
- NK cells possess receptors for self molecules that prevent - And And their activation by uninfected cells.

- Antigen recognition by T cells.
- The T-cell receptor is very similar to a Fab fragment of 4-10 immunoglobulin.
- A T-cell receptor recognizes antigen in the form of a 4-11 complex of a foreign peptide bound to an MHC molecule.
- There are two classes of MHC molecules with distinct 4-12 subunit compositions but similar three-dimensional structures.
- Peptides are stably bound to MHC molecules, and also 4-13 serve to stabilize the MHC molecule on the cell surface.
- MHC class I molecules bind short peptides of 8-10 amino 4-14 acids by both ends.
- 4-15 The length of the peptides bound by MHC class II molecules is not constrained.
- The crystal structures of several peptide:MHC:T-cell 4-16 receptor complexes show a similar orientation of the T-cell receptor over the peptide:MHC complex.
- The CD4 and CD8 cell-surface proteins of T cells are 4-17 required to make an effective response to antigen.

NK cells bear receptors that activate their effector function in response to ligands expressed on infected cells or tumor cells.

The NKG2D receptor activates a different signaling pathway 3-23 from that of the other activating NK receptors.

Several lymphocyte subpopulations behave as innate-like 3000 imphocytes.

Summary to Chapter 3.

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The two classes of MHC molecules are expressed 4-18 differentially on cells.

A distinct subset of T cells bears an alternative receptor 4-19 made up of γ and δ chains.

Summary. Summary to Chapter 4.

Questions. General references.

Section references.



Chap	oter 5 The Generation of Lymphocyte Antigen Receptors	157	5-22 RAG-dependent adaptive immunity based on a diversified repertoire of immunoglobulin-like genes appeared abruptly in the cartilaginous fishes.	190
Prima	ary immunoglobulin gene rearrangement.	158	5-23 Different species generate immunoglobulin diversity in	192
5-1	Immunoglobulin genes are rearranged in antibody- producing cells.	158	different ways. 5-24 Both α : β and γ : δ T-cell receptors are present in cartilaginous fish.	192
5-2	Complete genes that encode a variable region are generated by the somatic recombination of separate gene segments.	159	5-25 MHC class I and class II molecules are also first found in the cartilaginous fishes.	195
5-3	Multiple contiguous V gene segments are present at		Summary.	195
	each immunoglobulin locus.	160	Summary to Chapter 5.	196
5-4	Rearrangement of V, D, and J gene segments is guided	The s	Questions.	197
	by flanking DNA sequences.	161	General references.	198
5-5	The reaction that recombines V, D, and J gene segments		Section references.	198

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- involves both lymphocyte-specific and ubiquitous **DNA-modifying enzymes.**
- The diversity of the immunoglobulin repertoire is 5-6 generated by four main processes.
- The multiple inherited gene segments are used in different 5-7 combinations.
- Variable addition and subtraction of nucleotides at the 5-8 junctions between gene segments contributes to the diversity of the third hypervariable region.

Summary.

T-cell receptor gene rearrangment.

- The T-cell receptor gene segments are arranged in a 5-9 similar pattern to immunoglobulin gene segments and are rearranged by the same enzymes.
- T-cell receptors concentrate diversity in the third 5-10 hypervariable region.
- $\gamma: \delta$ T-cell receptors are also generated by gene 5-11 rearrangement.

Summary.

Chapter 6

Antigen Presentation to T Lymphocytes

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The generation of T-cell receptor ligands.

- The MHC class I and class II molecules deliver peptides 6-1 to the cell surface from two intracellular compartments.
- Peptides that bind to MHC class I molecules are 6-2 actively transported from the cytosol to the endoplasmic reticulum.
- Peptides for transport into the endoplasmic reticulum 6-3 are generated in the cytosol.
- Newly synthesized MHC class I molecules are retained 6-4 in the endoplasmic reticulum until they bind a peptide.
- Many viruses produce immunoevasins that interfere with 6-5 antigen presentation by MHC class I molecules. Peptides presented by MHC class II molecules are 6-6
 - generated in acidified endocytic vesicles.
 - The invariant chain directs newly synthesized MHC

Structural variation in immunoglobulin constant regions.

- Different classes of immunoglobulins are distinguished by 5-12 the structure of their heavy-chain constant regions.
- The constant region confers functional specialization 5-13 on the antibody.
- Mature naive B cells express both IgM and IgD at their 5-14 surface.
- Transmembrane and secreted forms of immunoglobulin 5-15 are generated from alternative heavy-chain transcripts.
- IgM and IgA can form polymers. 5-16 Summary.

Secondary diversification of the antibody repertoire.

- Activation-induced cytidine deaminase (AID) introduces 5-17 mutations into genes transcribed in B cells.
- Somatic hypermutation further diversifies the rearranged V 5-18 regions of immunoglobulin genes.
- Class switching enables the same assembled V_H exon 5-19

- class II molecules to acidified intracellular vesicles.
- A specialized MHC class II-like molecule catalyzes 6-8 loading of MHC class II molecules with peptides.
- Cross-presentation allows exogenous proteins to be 6-9 presented on MHC class I molecules by a restricted set of antigen-presenting cells.
- 6-10 Stable binding of peptides by MHC molecules provides effective antigen presentation at the cell surface. Summary.

The major histocompatibility complex and its function.

- Many proteins involved in antigen processing and 6-11 presentation are encoded by genes within the MHC. The protein products of MHC class I and class II genes 6-12 are highly polymorphic.
- MHC polymorphism affects antigen recognition by T cells 6-13 by influencing both peptide binding and the contacts between T-cell receptor and MHC molecule.
- Alloreactive T cells recognizing nonself MHC molecules 6-14 are very abundant.

to be associated with different C_H genes in the course of an immune response.

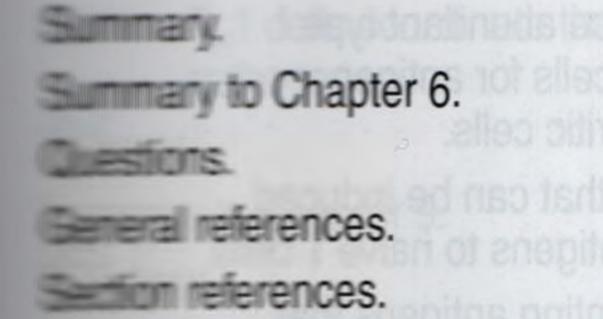
Summary.

Evolution of the adaptive immune response.

- Some invertebrates generate extensive diversity in a 5-20 repertoire of immunoglobulin-like genes.
- Agnathans possess an adaptive immune system that 5-21 uses somatic gene rearrangement to diversify receptors built from LRR domains.

- Many T cells respond to superantigens. 6-15
- MHC polymorphism extends the range of antigens to 6-16 which the immune system can respond.
- A variety of genes with specialized functions in immunity 6-17 are also encoded in the MHC.
- Specialized MHC class I molecules act as ligands for 6-18 the activation and inhibition of NK cells.
- The CD1 family of MHC class I-like molecules is encoded 6-19 outside the MHC and presents microbial lipids to CD1-restricted T cells.

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Part III

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THE DEVELOPMENT OF MATURE LYMPHOCYTE **RECEPTOR REPERTOIRES**

bind to their sturtage immunoglobutin.

Signaling Through Immune-System nacter / Receptors

7-20	Cytokine receptors of the hematopoietin family are associated with the JAK family of tyrosine kinases,	
- no ma	which activate STAT transcription factors.	266
7-21	Cytokine signaling is terminated by a negative feedback mechanism.	267
7-22	The receptors that induce apoptosis activate specialized intracellular proteases called caspases.	267
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2	Intracellular signal propagation is mediated by large multiprotein signaling complexes.	242	8-1	Lympho	ocytes derive from hematopoietic stem cells in e marrow.	276
8	Small G proteins act as molecular switches in many different signaling pathways.	243	8-2	B-cell d	evelopment begins by rearrangement of the	
2	Signaling proteins are recruited to the membrane by a variety of mechanisms.	244	8-3		-B-cell receptor tests for successful production	278
5	Ubiquitin conjugation of proteins can both activate and inhibit signaling responses.	245		of a cor	nplete heavy chain and signals for the transition e pro-B cell to pre-B cell stage.	282
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	small-molecule second messengers.	246	8-5		ells rearrange the light-chain locus and express	200
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nig	en receptor signaling and lymphocyte activation.	247	8-6		re B cells are tested for autoreactivity before they e bone marrow.	285
	Arrigen receptors consist of variable antigen-binding chains associated with invariant chains that carry out	247	Summa		T. cells are guided to snes of intection by nes and newly expressed adhesion molecules.	290
	The signaling function of the receptor.		The d	evelopm	ent of T lymphocytes in the thymus.	290
	leads to phosphorylation of ITAMs by Src-family kinases.	249	8-7	Philit chat	ogenitors originate in the bone marrow, but all	
	Prosphorylated ITAMs recruit and activate the tyrosine mase ZAP-70, which phosphorylates scaffold proteins		1858		ortant events in their development occur in	291
	that recruit the phospholipase PLC-γ.	251	8-8	T-cell pr	ecursors proliferate extensively in the thymus,	
	The activation of PLC- γ requires a co-stimulatory signal.	251			t die there.	294
	Activated PLC-γ generates the second messengers dacylglycerol and inositol trisphosphate.	252	8-9		sive stages in the development of thymocytes are by changes in cell-surface molecules.	294
2	Care entry activates the transcription factor NFAT.	253	8-10		ytes at different developmental stages are found	
	Fast activation stimulates the mitogen-activated protein kinase (MAPK) relay and induces expression of the	Snut	8-11		ct parts of the thymus. with $\alpha:\beta$ or $\gamma:\delta$ receptors arise from a common	297
	manscription factor AP-1.	253		progenit		298
	Protein kinase C activates the transcription factors NF _K B and AP-1.	256	8-12		expressing particular γ - and δ -chain V regions arise dered sequence early in life.	299
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	components are specific to B cells.	258	8-14	T-cell α-	chain genes undergo successive rearrangements	004
	-Ms are also found in other receptors on leukocytes	000		until pos	sitive selection or cell death intervenes.	304

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- ale also louriu in other receptors on reunocytes that signal for cell activation. incitory receptors on lymphocytes help regulate Teres The mmune responses.
- receptors and signaling pathways. Containes and their receptors fall into distinct families of structurally related proteins.
- unui positive selection of cell death intervenes. Summary.
- Positive and negative selection of T cells.

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- The MHC type of the thymic stroma selects a repertoire of 8-15 mature T cells that can recognize foreign antigens presented by the same MHC type.
- Only thymocytes whose receptors interact with self-peptide: 8-16 self-MHC complexes can survive and mature.

- Positive selection acts on a repertoire of T-cell receptors 8-17 with inherent specificity for MHC molecules.
- Positive selection coordinates the expression of CD4 8-18 or CD8 with the specificity of the T-cell receptor and the potential effector functions of the T cell.
- Thymic cortical epithelial cells mediate positive selection 8-19 of developing thymocytes.
- T cells that react strongly with ubiquitous self antigens 8-20 are deleted in the thymus.
- Negative selection is driven most efficiently by bone 8-21 marrow derived antigen-presenting cells.
- The specificity and/or the strength of signals for negative 8-22 and positive selection must differ.

Summary.

808	9-7	Plasmacytoid dendritic cells produce abundant type I interferons and may act as helper cells for antigen presentation by conventional dendritic cells.	
	234		
808	9-8	Macrophages are scavenger cells that can be induced by pathogens to present foreign antigens to naive T cells.	
10	9-9	B cells are highly efficient at presenting antigens that bind to their surface immunoglobulin.	
	Summ	carilladinolic fich	
11	Currin	MHC class that data & ref to hat y sa chief her found in	
		ip the cardinance lighter	
	Primi	ng of naive T cells by pathogen-activated	
13	dend	ritic cells.	
	9-10	Cell-adhesion molecules mediate the initial interaction	
14	010	of naive T cells with antigen-presenting cells.	
15	9-11	Antigen-presenting cells deliver three kinds of signals for	

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Survival and maturation of lymphocytes in peripheral lymphoid tissues.

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- Different lymphocyte subsets are found in particular 8-23 locations in peripheral lymphoid tissues.
- The development of peripheral lymphoid tissues is 8-24 controlled by lymphoid tissue inducer cells and proteins of the tumor necrosis factor family.
- The homing of lymphocytes to specific regions of 8-25 peripheral lymphoid tissues is mediated by chemokines.
- Lymphocytes that encounter sufficient quantities of self 8-26 antigens for the first time in the periphery are eliminated or inactivated.
- 8-27 Immature B cells arriving in the spleen turn over rapidly and require cytokines and positive signals through the B-cell receptor for maturation and survival.
- B-1 cells and marginal zone B cells are distinct B-cell 8-28 subtypes with unique antigen receptor specificity.
- T-cell homeostasis in the periphery is regulated by 8-29 cytokines and self-MHC interactions.
- Summary.

354 the cional expansion and differentiation of naive 1 cells. CD28-dependent co-stimulation of activated T cells 9-12 induces expression of the T-cell growth factor interleukin-2 and the high-affinity IL-2 receptor. 355 Signal 2 can be modified by additional co-stimulatory 9-13 356 pathways. Antigen recognition in the absence of co-stimulation 9-14 leads to functional inactivation or clonal deletion of peripheral T cells. 357 Proliferating T cells differentiate into effector T cells that 9-15 do not require co-stimulation to act. 358 CD8 T cells can be activated in different ways to become 9-16 cytotoxic effector cells. 359 CD4 T cells differentiate into several subsets of functionally 9-17 different effector cells. 360 Various forms of signal 3 induce the differentiation of 9-18 naive CD4 T cells down distinct effector pathways. 362 Regulatory CD4 T cells are involved in controlling 9-19 364 adaptive immune responses. Summary. 365

Summary to Chapter 8. Questions. General references. Section references. THE ADAPTIVE IMMUNE Part IV RESPONSE

Chapter 9 **T Cell-Mediated Immunity**

Entry of naive T cells and antigen-presenting cells into peripheral lymphoid organs.

- Naive T cells migrate through peripheral lymphoid tissues, 9-1 sampling the peptide:MHC complexes on dendritic cell surfaces.
- 9-2 Lymphocyte entry into lymphoid tissues depends on chemokines and adhesion molecules.

Gene	ral properties of effector T cells and their cytokines.	366
9-20	Effector T-cell interactions with target cells are initiated by antigen-nonspecific cell-adhesion molecules.	366
9-21	An immunological synapse forms between effector T cells and their targets to regulate signaling and to direct the	6-1
	release of effector molecules.	367
9-22	The effector functions of T cells are determined by the array of effector molecules that they produce.	369
9-23	Cytokines can act locally or at a distance.	370
9-24	T cells express several TNF-family cytokines as trimeric proteins that are usually associated with the cell surface.	371
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T cell	-mediated cytotoxicity.	372
9-25	Cytotoxic T cells can induce target cells to undergo programmed cell death.	373
9-26	Cytotoxic effector proteins that trigger apoptosis are contained in the granules of CD8 cytotoxic T cells.	374
9-27	Cytotoxic T cells are selective and serial killers of targets expressing a specific antigen.	376

- Activation of integrins by chemokines is responsible for 9-3 the entry of naive T cells into lymph nodes.
- T-cell responses are initiated in peripheral lymphoid 9-4 organs by activated dendritic cells.
- Dendritic cells process antigens from a wide array 9-5 of pathogens.
- 9-6 Pathogen-induced TLR signaling in immature dendritic cells induces their migration to lymphoid organs and enhances antigen processing.

Cytotoxic T cells also act by releasing cytokines. 9-28 Summary.

expressing a specific antigen.

Macrophage activation by T_H1 cells. $T_{H}1$ cells have a central role in macrophage activation. 9-29 Activation of macrophages by T_H1 cells promotes 9-30 microbial killing and must be tightly regulated to avoid tissue damage.

T_1 cells coordinate the host response to intracellular	
pathogens. Cause uncontrolled lymphoptoligration of viso	379
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E-cell activation by helper T cells.	388
The humoral immune response is initiated when B cells that bind antigen are signaled by helper T cells or by certain microbial antigens alone.	389

	estruction of antibody-coated pathogens via ceptors.	417
10-21	The Fc receptors of accessory cells are signaling receptors specific for immunoglobulins of different classes.	418
10-22	Fc receptors on phagocytes are activated by antibodies bound to the surface of pathogens and enable the phagocytes to ingest and destroy pathogens.	419
10-23	Fc receptors activate NK cells to destroy antibody-coated targets.	420
10-24	Mast cells and basophils bind IgE antibody via the high-affinity Fcc receptor.	421
10-25	IgE-mediated activation of accessory cells has an important role in resistance to parasite infection.	422
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Summa	ary to Chapter 10.	424

- E-cell responses are enhanced by co-ligation of the B-cell receptor and B-cell co-receptor by antigen and complement regments on microbial surfaces.
- Helper T cells activate B cells that recognize the same artigen.
 - T cells make membrane-bound and secreted molecules that activate B cells.
- E cells that encounter their antigens migrate toward the coundaries between B-cell and T-cell areas in secondary mphoid tissues.
- Articody-secreting plasma cells differentiate from activated B cells.
- The second phase of a primary B-cell immune response occurs when activated B cells migrate into follicles and proliferate to form germinal centers.
- Germinal center B cells undergo V-region somatic incommutation, and cells with mutations that improve affinity for antigen are selected. 398
- Cass switching in thymus-dependent antibody responses requires expression of CD40 ligand by helper T cells and
- 425 Questions. General references. 426 426 Section references. **Dynamics of Adaptive Immunity** 429 Chapter 11 The course of the immune response to infection. 430 The course of an infection can be divided into several 11-1 430 distinct phases. The nonspecific responses of innate immunity are 11-2 necessary for an adaptive immune response to be initiated. 432 Cytokines made during infection can direct differentiation 11-3 of CD4 T cells toward the T_H17 subset. 434 T_H1 and T_H2 cells are induced by cytokines generated 11-4 in response to different pathogens. 435 CD4 T-cell subsets can cross-regulate each other's 11-5 437 differentiation. Effector T cells are guided to sites of infection by 11-6 chemokines and newly expressed adhesion molecules. 439 Differentiated effector T cells are not a static population 11-7 but continue to respond to signals as they carry out their effector functions. 441 Primary CD8 T-cell responses to pathogens can occur 11-8 in the absence of CD4 T-cell help. 442 Antibody responses develop in lymphoid tissues under 11-9 the direction of T_{FH} cells. 444 Antibody responses are sustained in medullary cords 11-10 445 and bone marrow. The effector mechanisms used to clear an infection 11-11 depend on the infectious agent. 445 Resolution of an infection is accompanied by the death 11-12 of most of the effector cells and the generation of 447 memory cells. 448 Summary. Immunological memory. 448 Immunological memory is long-lived after infection 11-13 449 or vaccination. Memory B-cell responses differ in several ways from 11-14

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- Ligation of CD40 and prolonged contact with T follicular below cells is required to sustain germinal center B cells.
- Sumining germinal center B cells differentiate into either plasma cells or memory cells.
- Some bacterial antigens do not require T-cell help to induce B-cell responses.
- B-cell responses to bacterial polysaccharides do not require peptide-specific T-cell help.

development result in severe immunodeliclencies.

The distributions and functions of immunoglobulin

- Artibodies of different classes operate in distinct places and have distinct effector functions.
- Transport proteins that bind to the Fc regions of antibodies carry particular isotypes across epithelial barriers.
 - High-affinity IgG and IgA antibodies can neutralize bacterial toxins.
 - High-affinity IgG and IgA antibodies can inhibit the

infectivity of viruses.

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Antibodies can block the adherence of bacteria to host cells. 413 Antibody:antigen complexes activate the classical pathway of complement by binding to C1q. 414 Complement receptors are important in the removal

of immune complexes from the circulation.

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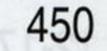
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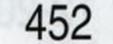
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those of naive B cells.



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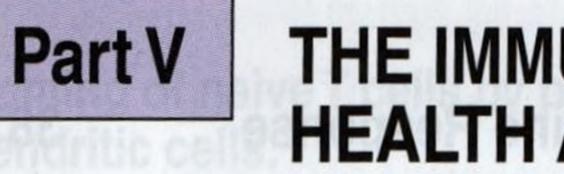
- 11-15 Repeated immunization leads to increasing affinity of antibody due to somatic hypermutation and selection by antigen in germinal centers.
- 11-16 Memory T cells are increased in frequency compared with naive T cells specific for the same antigen, and have distinct activation requirements and cell-surface proteins that distinguish them from effector T cells.



- Memory T cells are heterogeneous and include central 11-17 memory and effector memory subsets.
- CD4 T-cell help is required for CD8 T-cell memory and 11-18 involves CD40 and IL-2 signaling.
- In immune individuals, secondary and subsequent 11-19 responses are mainly attributable to memory lymphocytes. Summary. Summary to Chapter 11. Questions. Section references.

The Mucosal Immune System Chapter 12 The organization of the mucosal system

Summary. Summary to Chapter 12. Questions. General references. Section references.



inherited gene defects.

THE IMMUNE SYSTEM IN **HEALTH AND DISEASE**

Failures of Host Defense Mechanisms 509 Chapter 13 Evasion and aubuaraian of immuna defenses 509

organization of the mucosal system.	465	Evasion and subversion of immune defenses.	
The mucosal immune system protects the internal surfaces of the body.	465	13-1 Antigenic variation allows pathogens to escape from immunity.	
The mucosal immune system may be the original vertebrate immune system.	468	13-2 Some viruses persist <i>in vivo</i> by ceasing to replicate u immunity wanes.	Intil
Cells of the mucosal immune system are located both in anatomically defined compartments and scattered	400	13-3 Some pathogens resist destruction by host defense mechanisms or exploit them for their own purposes.	
throughout mucosal tissues. The intestine has distinctive routes and mechanisms of	468	13-4 Immunosuppression or inappropriate immune respon can contribute to persistent disease.	ises
antigen uptake. The mucosal immune system contains large numbers of	472	13-5 Immune responses can contribute directly to pathogenesis.	
effector lymphocytes even in the absence of disease. The circulation of lymphocytes within the mucosal immune	473	13-6 Regulatory T cells can affect the outcome of infectiou disease.	IS
system is controlled by tissue-specific adhesion molecules and chemokine receptors.	474	Summary.	
Priming of lymphocytes in one mucosal tissue can induce protective immunity at other mucosal surfaces.	475	Immunodeficiency diseases.	
Unique populations of dendritic cells control mucosal immune responses.	476	13-7 A history of repeated infections suggests a diagnosis immunodeficiency.	of
The intestinal lamina propria contains antigen-experienced	324	13-8 Primary immunodeficiency diseases are caused by	

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The intestinal epithelium is a unique compartment of the 12-10 immune system.

T cells and populations of unusual innate-type lymphocytes.

- Secretory IgA is the class of antibody associated with the 12-11 mucosal immune system.
- IgA deficiency is common in humans but may be 12-12 compensated for by secretory IgM.

Summary.

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The mucosal response to infection and regulation of mucosal immune responses.

- Enteric pathogens cause a local inflammatory response 12-13 and the development of protective immunity.
- The outcome of infection by intestinal pathogens is 12-14 determined by a complex interplay between the microorganism and the host immune response.
- The mucosal immune system must maintain a balance 12-15 between protective immunity and homeostasis to a large number of different foreign antigens.
- The healthy intestine contains large quantities of bacteria 12-16 but does not generate potentially harmful immune
- Defects in T-cell development can result in severe 13-9 combined immunodeficiencies. 522 SCID can also be due to defects in the purine salvage 13-10 523 pathway. Defects in antigen receptor gene rearrangement can 13-11 result in SCID. 524 Defects in signaling from T-cell antigen receptors can 13-12 cause severe immunodeficiency. 524 Genetic defects in thymic function that block T-cell 13-13 development result in severe immunodeficiencies. 525 Defects in B-cell development result in deficiencies in 13-14 antibody production that cause an inability to clear extracellular bacteria. 527 Immune deficiencies can be caused by defects in B-cell 13-15 or T-cell activation and function. 528 Defects in complement components and complement-13-16 regulatory proteins cause defective humoral immune function and tissue damage. 532 Defects in phagocytic cells permit widespread bacterial 13-17 533 infections.

responses against them.

- Full immune responses to commensal bacteria provoke 12-17 intestinal disease.
- Intestinal helminths provoke strong T_H2-mediated immune 12-18 responses.
- Other eukaryotic parasites provoke protective immunity 12-19 and pathology in the gut.
- The mucosal immune system has to compromise between 12-20 suppression and activation of an immune response.
- Mutation in the molecular regulators of inflammation can 13-18 cause uncontrolled inflammatory responses that result in 'autoinflammatory disease.'
- The normal pathways for host defense against intracellular 13-19 bacteria are pinpointed by genetic deficiencies of IFN-y and IL-12 and their receptors.
- X-linked lymphoproliferative syndrome is associated with 13-20 fatal infection by Epstein-Barr virus and with the development of lymphomas.

13-21	Genetic abnormalities in the secretory cytotoxic pathway of lymphocytes cause uncontrolled lymphoproliferation and inflammatory responses to viral infections.	539
13-22	Hematopoietic stem cell transplantation or gene therapy can be useful to correct genetic defects.	541
13-23	Secondary immunodeficiencies are major predisposing causes of infection and death.	542
Summa	ter 16 Manipulation of the Immune Response	543
Acqui	red immune deficiency syndrome.	543
13-24	Most individuals infected with HIV progress over time to AIDS.	545
13-25	HIV is a retrovirus that infects CD4 T cells, dendritic cells, and macrophages.	547

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14-8	Eosinophils and basophils cause inflammation and tissue damage in allergic reactions.	58
14-9	IgE-mediated allergic reactions have a rapid onset but can also lead to chronic responses.	58
14-10	Allergen introduced into the bloodstream can cause anaphylaxis.	589
14-11	Allergen inhalation is associated with the development of rhinitis and asthma.	59
14-12	A genetically determined defect in the skin's barrier function increases the risk of atopic eczema.	592
14-13	Allergy to particular foods causes systemic reactions as well as symptoms limited to the gut.	594
14-14	IgE-mediated allergic disease can be treated by inhibiting the effector pathways that lead to symptoms or by desensitization techniques that aim at restoring tolerance	74

- 13-26 Genetic variation in the host can alter the rate of progression of disease.
- A genetic deficiency of the co-receptor CCR5 confers 13-27 resistance to HIV infection in vivo.
- HIV RNA is transcribed by viral reverse transcriptase 13-28 into DNA that integrates into the host-cell genome.

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- Replication of HIV occurs only in activated T cells. 13-29
- Lymphoid tissue is the major reservoir of HIV infection. 13-30
- An immune response controls but does not eliminate HIV. 13-31
- The destruction of immune function as a result of HIV 13-32 infection leads to increased susceptibility to opportunistic infection and eventually to death.
- Drugs that block HIV replication lead to a rapid decrease 13-33 in titer of infectious virus and an increase in CD4 T cells.
- HIV accumulates many mutations in the course of infection, 13-34 and drug treatment is soon followed by the outgrowth of drug-resistant variants.
- Vaccination against HIV is an attractive solution but 13-35 poses many difficulties.
- Prevention and education are one way in which the 13-36

549		to the allergen.	595
	Summa	ary. entitication of T-cell receives the pecificity using peptide MP	597
549	Non-l	gE-mediated allergic diseases.	598
551	14-15	Innocuous antigens can cause type II hypersensitivity reactions in susceptible individuals by binding to the	
551		surfaces of circulating blood cells.	598
554	14-16	Systemic disease caused by immune-complex formation	
554		can follow the administration of large quantities of poorly catabolized antigens.	598
	14-17	Hypersensitivity reactions can be mediated by T _H 1 cells	000
556		and CD8 cytotoxic T cells.	600
	14-18	Celiac disease has features of both an allergic response	
557	644	and autoimmunity.	603
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560	Section references.		

	spread of HIV and AIDS can be controlled.	561
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Chap	ter 14 Allergy and Allergic Diseases	571
IgE a	nd IgE-mediated allergic diseases.	573
14-1	Sensitization involves class switching to IgE production on first contact with an allergen.	573
14-2	Allergens are usually delivered transmucosally at low dose, a route that favors IgE production.	575
14-3	Genetic factors contribute to the development of IgE- mediated allergic disease.	577
14-4	Environmental factors may interact with genetic susceptibility to cause allergic disease.	579

Chapter 15 Autoimmunity and Transplantation 611 The making and breaking of self-tolerance. 611 A critical function of the immune system is to discriminate 15-1 612 self from nonself. Multiple tolerance mechanisms normally prevent 15-2 613 autoimmunity. Central deletion or inactivation of newly formed 15-3 lymphocytes is the first checkpoint of self-tolerance. 614 Lymphocytes that bind self antigens with relatively low 15-4 affinity usually ignore them but in some circumstances 616 become activated. Antigens in immunologically privileged sites do not induce 15-5 617 immune attack but can serve as targets. Autoreactive T cells that express particular cytokines 15-6 may be nonpathogenic or may suppress pathogenic 619 lymphocytes. Autoimmune responses can be controlled at various 15-7 619 stages by regulatory T cells.

Regulatory T cells can control allergic responses. 14-5 Summary.

Effector mechanisms in IgE-mediated allergic reactions.

- Most IgE is cell-bound and engages effector mechanisms 14-6 of the immune system by different pathways from those of other antibody isotypes.
- Mast cells reside in tissues and orchestrate allergic 14-7 reactions.
- 621 Summary. 622 Autoimmune diseases and pathogenic mechanisms. Specific adaptive immune responses to self antigens 15-8 622 can cause autoimmune disease. Autoimmune diseases can be classified into clusters 15-9 623 that are typically either organ-specific or systemic. Multiple components of the immune system are typically 15-10 624 recruited in autoimmune disease.

- 15-11 Chronic autoimmune disease develops through positive feedback from inflammation, inability to clear the self antigen, and a broadening of the autoimmune response.
- 15-12 Both antibody and effector T cells can cause tissue damage in autoimmune disease.
- 15-13 Autoantibodies against blood cells promote their destruction.
- 15-14 The fixation of sublytic doses of complement to cells in tissues stimulates a powerful inflammatory response.
- 15-15 Autoantibodies against receptors cause disease by stimulating or blocking receptor function.
- 15-16 Autoantibodies against extracellular antigens cause inflammatory injury by mechanisms akin to type II and type III hypersensitivity reactions.
- 15-17 T cells specific for self antigens can cause direct tissue injury and sustain autoantibody responses.

15-38	The fetus is an allograft that is tolerated repeatedly.	661
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16-1	Corticosteroids are powerful anti-inflammatory drugs that alter the transcription of many genes.	670
16-2	Cytotoxic drugs cause immunosuppression by killing dividing cells and have serious side-effects.	671
16-3	Cyclosporin A, tacrolimus (FK506), and rapamycin	

Summary.

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The genetic and environmental basis of autoimmunity.

- 15-18 Autoimmune diseases have a strong genetic component.
- 15-19 Several approaches have given us insight into the genetic basis of autoimmunity.
- 15-20 Many genes that predispose to autoimmunity fall into categories that affect one or more of the mechanisms of tolerance.
- 15-21 A defect in a single gene can cause autoimmune disease.
- 15-22 MHC genes have an important role in controlling susceptibility to autoimmune disease.
- 15-23 Genetic variants that impair innate immune responses can predispose to T cell-mediated chronic inflammatory disease.
- 15-24 External events can initiate autoimmunity.
- 15-25 Infection can lead to autoimmune disease by providing an environment that promotes lymphocyte activation.
- 15-26 Cross-reactivity between foreign molecules on

(sirolimus) are powerful immunosuppressive agents that interfere with T-cell signaling.

- 16-4 Antibodies against cell-surface molecules can be used to eliminate lymphocyte subsets or to inhibit lymphocyte function.
- 16-5 Antibodies can be engineered to reduce their immunogenicity in humans.
- 16-6 Monoclonal antibodies can be used to prevent allograft rejection.
- 16-7 Depletion of autoreactive lymphocytes can treat autoimmune disease.
- 16-8 Biologic agents that block TNF- α or IL-1 can alleviate autoimmune diseases.
- 16-9 Biologic agents can block cell migration to sites of inflammation and reduce immune responses.
- 16-10 Blockade of co-stimulatory pathways that activate lymphocytes can be used to treat autoimmune disease.
- 16-11 Some commonly used drugs have immunomodulatory properties.
- 16-12 Controlled administration of antigen can be used to

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	pathogens and self molecules can lead to anti-self responses and autoimmune disease.	649
15-27	Drugs and toxins can cause autoimmune syndromes.	651
15-28	Random events may be required for the initiation of autoimmunity.	651
Summa	ary. Inevend villamon amainarioem eonarelof eldifuM	651
Respo	onses to alloantigens and transplant rejection.	652
15-29	Graft rejection is an immunological response mediated primarily by T cells.	652
15-30	Transplant rejection is caused primarily by the strong immune response to nonself MHC molecules.	653
15-31	In MHC-identical grafts, rejection is caused by peptides from other alloantigens bound to graft MHC molecules.	654
15-32	There are two ways of presenting alloantigens on the transplanted donor organ to the recipient's	CEE
15-33	T lymphocytes. Antibodies that react with endothelium cause hyperacute graft rejection.	655 657
15-34	Late failure of transplanted organs is caused by chronic	Sem

manipulate the nature of an antigen-specific response. Summary.

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Using the immune response to attack tumors.

- 16-13 The development of transplantable tumors in mice led to the discovery of protective immune responses to tumors.
- 16-14 Tumors are 'edited' by the immune system as they evolve and can escape rejection in many ways.
- 16-15 Tumor-specific antigens can be recognized by T cells and form the basis of immunotherapies.
- 16-16 Monoclonal antibodies against tumor antigens, alone or linked to toxins, can control tumor growth.
- 16-17 Enhancing the immune response to tumors by vaccination holds promise for cancer prevention and therapy.
- 16-18 Checkpoint blockade can augment immune responses to existing tumors.

Summary.

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Fighting infectious diseases with vaccination.

injury to the graft.

- 15-35 A variety of organs are transplanted routinely in clinical medicine.
- 15-36 The converse of graft rejection is graft-versus-host disease.
- 15-37 Regulatory T cells are involved in alloreactive immune responses.
- 16-19 Vaccines can be based on attenuated pathogens or material from killed organisms.
 16-20 Most effective vaccines generate antibodies that prevent the damage caused by toxins or that neutralize the pathogen and stop infection.
 16-21 Effective vaccines must induce long-lasting protection while being safe and inexpensive.

Principles of innate and adaptive immunity

- Live-attenuated viral vaccines are usually more potent 16-22 than 'killed' vaccines and can be made safer by the use of recombinant DNA technology.
- Live-attenuated vaccines can be developed by selecting 16-23 nonpathogenic or disabled bacteria or by creating genetically attenuated parasites (GAPs).
- The route of vaccination is an important determinant 16-24 of success.
- Bordetella pertussis vaccination illustrates the importance 16-25 of the perceived safety of a vaccine.
- Conjugate vaccines have been developed as a result of 16-26 understanding how T and B cells collaborate in an immune response.
- Peptide-based vaccines can elicit protective immunity, but 16-27 they require adjuvants and must be targeted to the appropriate cells and cell compartment to be effective

Isola	tion of lymphocytes.	739
A-20	Isolation of peripheral blood lymphocytes by Ficoll-Hypaque TM gradient.	739
A-21	Isolation of lymphocytes from tissues other than blood.	740
A-22	Flow cytometry and FACS analysis.	740
A-23	Lymphocyte isolation using antibody-coated magnetic beads.	742
A-24	Isolation of homogeneous T-cell lines.	742
	acterization of lymphocyte specificity, frequency, unction.	743
A-25	Limiting-dilution culture.	744
A-26	ELISPOT assays.	745
A-27	Identification of functional subsets of T cells by staining	746

	appropriate cells and cell compartment to be effective.	705	A-21	for cytokines.	746
16-28	Adjuvants are important for enhancing the immunogenicity of vaccines, but few are approved for use in humans.	707	A-28	Identification of T-cell receptor specificity using peptide:MHC tetramers.	746
16-29	Protective immunity can be induced by DNA-based vaccination.	708	A-29	Assessing the diversity of the T-cell repertoire by 'spectratyping.'	748
16-30	The effectiveness of a vaccine can be enhanced by targeting it to sites of antigen presentation.	708	A-30	Biosensor assays for measuring the rates of association and disassociation of antigen receptors for their ligands.	749
16-31	An important question is whether vaccination can be used therapeutically to control existing chronic infections.	709	A-31	Stimulation of lymphocyte proliferation by treatment with polyclonal mitogens or specific antigen.	750
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ATT 10. 10 Routes of immunization. A-2 Effects of antigen dose. A-3 Adjuvants. A-4

The detection, measurement, and characterization of antibodies and their use as research and diagnostic tools.

- Affinity chromatography. A-5
- Radioimmunoassay (iiiA), enzyme-linked immunosorbent A-6 assay (ELISA), and competitive inhibition assay.
- Hemagglutination and blood typing. A-7
 - Precipitin reaction.

A-8

- Equilibrium dialysis: measurement of antibody affinity 49 and avidity.
- Anti-immunoglobulin antibodies. A-10
- Coombs tests and the detection of Rhesus incompatibility. 4-11 Monoclonal antibodies. 4-12
- Phage display libraries for antibody V-region production. 4-13

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