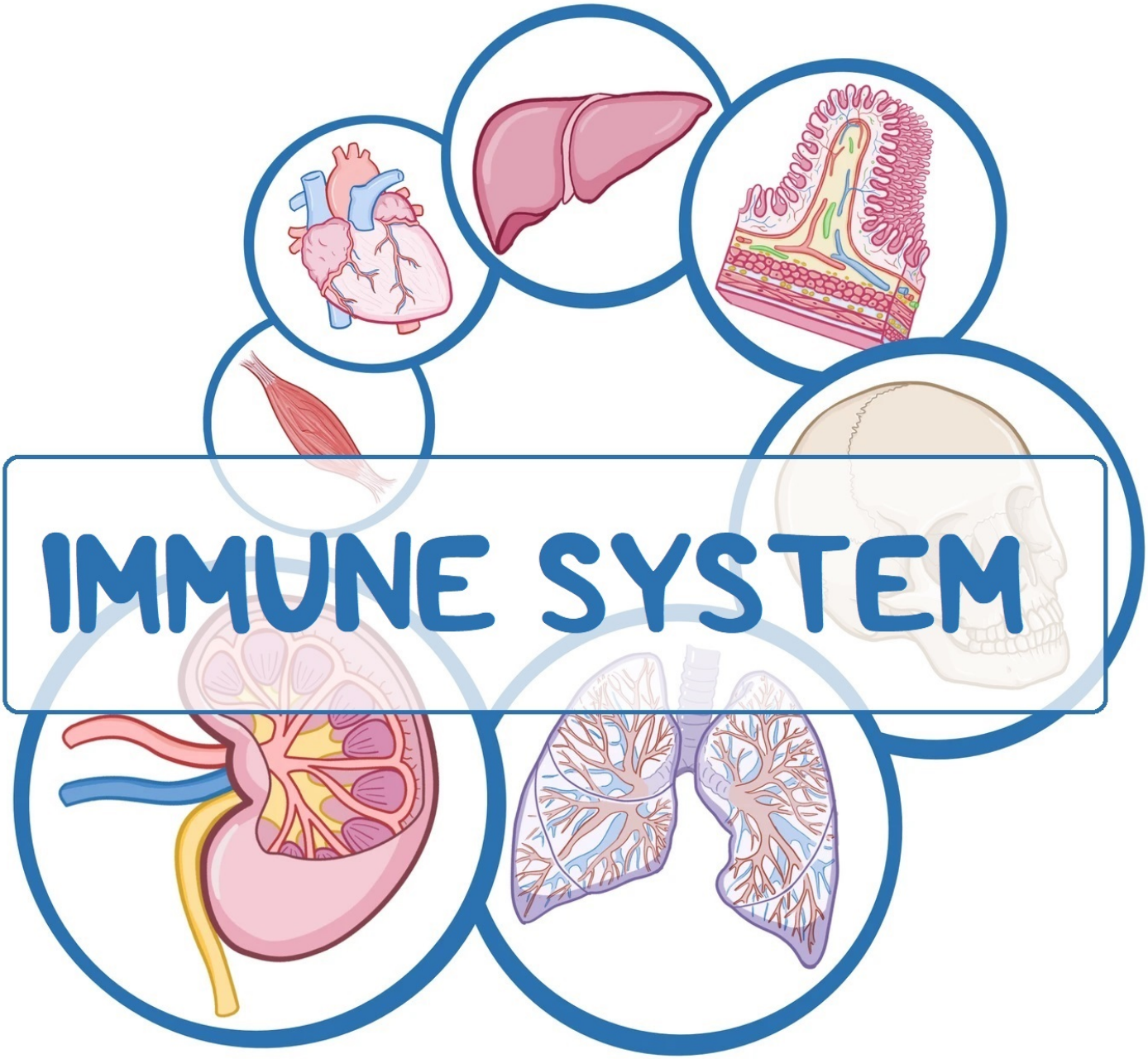
PHYSIOLOGY



IMMUNE SYSTEM

HIGH-YIELD NOTES

AfraTafreeh.com

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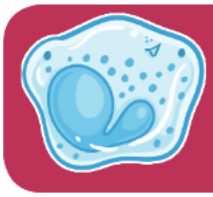


NOTES
IMMUNE SYSTEM

INTRODUCTION TO THE IMMUNE SYSTEM

osms.it/immune-system-introduction

- Includes organs, tissues, cells, molecules
- Protects from microorganisms, removes toxins, promotes inflammation, destroys tumor cells
- Two branches
  - Innate, adaptive

INNATE IMMUNE RESPONSE

- Nonspecific cells: phagocytes, natural killer (NK) cells; no immunologic memory
- "Feverishly" fast (minutes to hours)

Noncellular components

- Physical, chemical barriers (e.g. lysozymes in tears, cilia in airways)
- *Inflammation:* stops spread of infection, promotes healing
  - *Four cardinal signs:* redness, heat, swelling, pain
- Complement system: cascade of proteins; triggers inflammation, kills pathogens by cytolysis, tags cells for destruction

ADAPTIVE IMMUNE RESPONSE

- Highly specific cells; immunologic memory, need priming
- Significantly slower, esp. initially (weeks)
- *Clonal expansions:* cells replicate
- *Clonal deletion:* cells die off after immune response; some survive as memory cells

CELLS OF THE IMMUNE SYSTEM

Leukocytes (white blood cells)

- Formed by hematopoiesis in bone marrow
  - Starts with multipotent hematopoietic stem cells
  - Cells develop into myeloid/lymphoid progenitor cells
- *Myeloid cells:* contribute to innate response
  - *Neutrophils:* phagocytes, granulocytes, polymorphonuclear cells (nucleus segmented into 3–5 lobes); stain light pink/reddish-purple; most numerous leukocyte
  - *Eosinophils:* phagocytes, granulocytes, polymorphonuclear cells (nucleus usually bilobed); stain pink with eosin; larger cells fight parasites
  - *Basophils:* nonphagocytes, granulocytes, polymorphonuclear cells (nucleus bilobed/segmented); stain blue-purple with hematoxylin; aid in fighting parasites; granules contain histamine, heparin; involved in inflammatory response; least numerous leukocyte
  - *Mast cells:* nonphagocytes, granulocytes; involved in inflammatory response
  - *Monocytes:* phagocytes, antigen-presenting cells; release cytokines to recruit other cells; only circulate in blood; differentiate into macrophages/dendritic cells
  - *Dendritic cells:* phagocytes, antigen-presenting cells; release cytokines to recruit other cells; circulate in lymph,

blood, tissue; consume large proteins in interstitial fluid; break bloodborne pathogens into small amino acid chains → move to lymph node → present antigens to T cells
    - *Macrophages:* phagocytes, antigen-presenting cells; release cytokines to recruit other cells; stay in connective tissue, lymphoid organs; not in blood
- *Lymphoid cells:* contribute to the adaptive response (except NK cells)
    - *NK cells:* contribute to innate response; complete development in bone marrow; large, contain granules; primarily target infected, cancer cells; kill target cells with cytotoxic granules (punch holes in target cell membranes by binding to phospholipids → enter cell, trigger apoptosis, programmed cell death)
    - *B cells:* contribute to adaptive response; complete development in bone marrow; bind to specific antigens (antigen presentation not needed); capable of phagocytosis, antigen presentation; load antigens on major histocompatibility complex (MHC) II, display to T cells; T-cell activation → B cells mature into plasma cells; secrete lots of antibodies/immunoglobulins (B cell receptors in secreted-form, mark pathogens for destruction → "humoral immunity")
    - *T cells:* contribute to adaptive response; complete development in thymus; responsible for cell-mediated immunity; bind to specific antigens (antigen presentation needed); naive T cells primed by antigen presenting cells (usually dendritic cells); generally categorized into $CD4^+$, $CD8^+$ T cells; $CD4^+$ (helper) T cells secrete cytokines to coordinate immune response, only see antigens on MHC II; $CD8^+$ (cytotoxic) T cells kill target cells, cells with antigens on MHC I

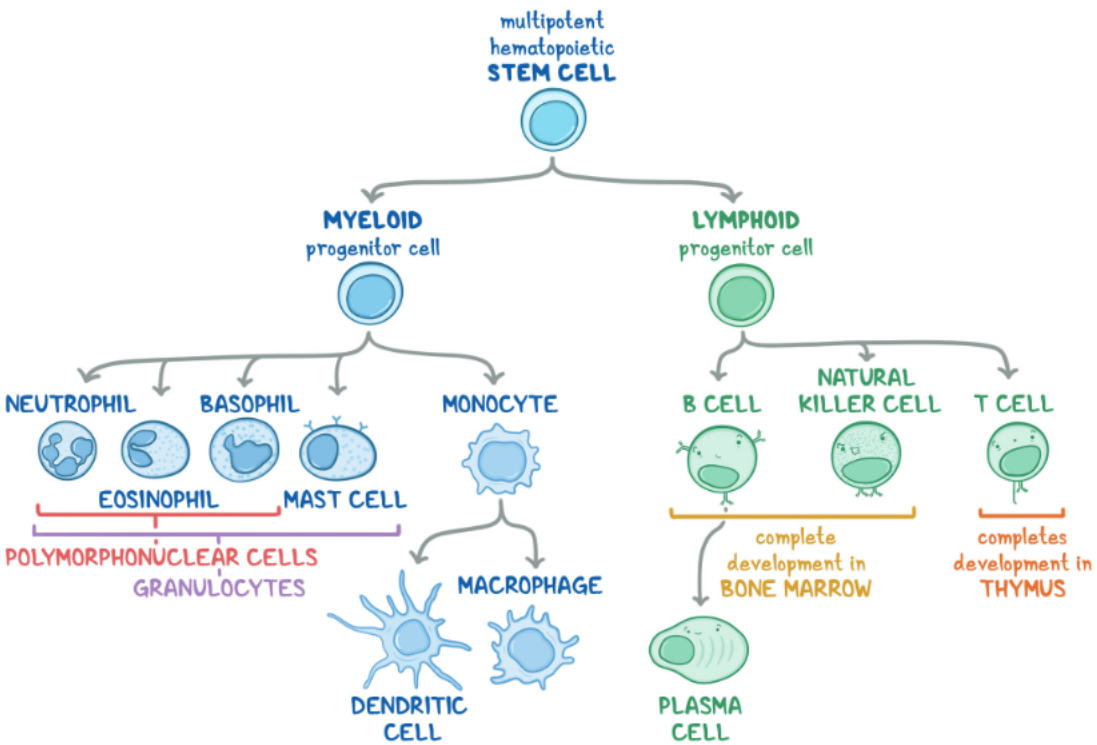


Figure 44.1 Family tree of immune system cells.

CLASSIFICATION OF IMMUNE CELLS

Phagocytes

- Reach around pathogens with cytoplasm, swallowing whole (phagosome)
- Destroy some pathogens with cytoplasmic granules (phagosomes fuse with granules → phagolysosomes; pH in vesicle drops killing pathogens)
- Continue to swallow pathogens before oxidative burst → produces highly reactive oxygen (e.g. H_2O_2; destroys proteins, nucleic acids, killing pathogens, phagocyte)

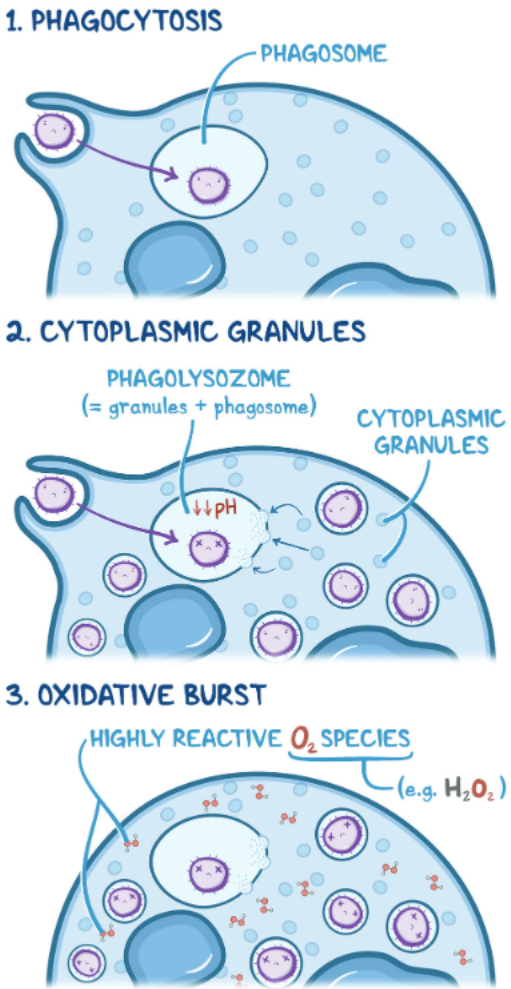


Figure 44.2 Phagocyte activities.

Granulocytes

- Contain granules in cytoplasm
- All cells (except mast cells) polymorphonuclear

Antigen-presenting cells

- Present antigens to T cells

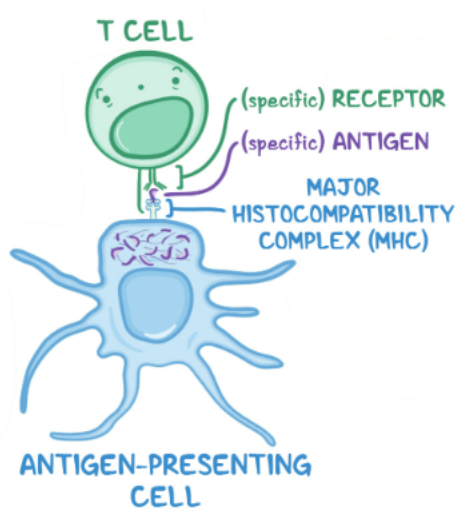


Figure 44.3 Antigen-presenting cell (depicted here as dendritic cell) presenting an antigen to a T cell.

IMMUNE CELL CLASSIFICATIONS

	CLASSIFICATIONS		
BASOPHILS		Granulocytes	
MAST CELLS			
NEUTROPHILS	Phagocytes		
EOSINOPHILS			
MONOCYTES		Agranulocytes	Antigen-presenting cells
DENDRITIC CELLS			
MACROPHAGES			
LYMPHOCYTES			

VACCINES

osms.it/vaccines

- Generate protective adaptive immune response against microbes by exposure to nonpathogenic forms/components of microbes
  - Differs from passive immunity (body creates own antibodies)
- *Administration:* intramuscularly, intradermally, intranasally, subcutaneously, orally
- Immunoglobulin response depends on route, type of vaccine
  - Intramuscular vaccinations → IgG
  - Rotavirus vaccine (oral) → IgA
- Four main types of vaccines
  - Live attenuated, inactivated (whole cell vaccines)
  - Subunit, toxoid (fractionated vaccines)

LIVE ATTENUATED VACCINES

- Attenuated → pathogen weakened (but still replicates)
- Measles, mumps, rubella, varicella (MMRV); rotavirus; smallpox; yellow fever

INACTIVATED VACCINES

- Pathogen killed using heat/formalin
- Response humoral/antibody-mediated; no cellular immunity → ↓ response
- Hepatitis A; polio; rabies; influenza

SUBUNIT VACCINES

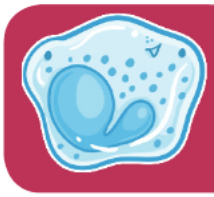
- Contain immunogenic portions of pathogens (polysaccharides/proteins)
- Combination of proteins from different pathogens → conjugate subunit vaccines
- Polysaccharide vaccines
  - T cell independent (only respond to protein antigens)
  - Not effective in children < two years old
  - Memory B cells never formed → repeated doses needed
  - *Haemophilus influenzae* type B; hepatitis B; HPV; *Bordetella pertussis* (pertussis); *Streptococcus pneumoniae*; *Neisseria meningitidis*; *Varicella zoster*

TOXOID VACCINES

- Against specific toxins (main cause of illness)
- Toxoid fixed/inactivated using formalin
- Often combined with subunit vaccines
- Tetanus, diphtheria, and pertussis (TDaP), diphtheria, tetanus, and pertussis (DTap) vaccine

CONTRAINDICATIONS

- Moderate/severe infection
- Allergy to eggs/previous vaccines
- Guillain–Barré syndrome (vaccines against influenza, DTaP)
- Weakened immune system
  - Pregnant (live attenuated vaccines)



NOTES
B & T CELLS

ANTIBODY CLASSES

osms.it/antibody-classes

- B cell receptor, major component of humoral immunity
- Heavy, light chain; fragment antigen-binding region; constant region (Fc)
- B cell develops into plasma cell → B cell receptor secreted as antibody
- *Antibodies:* monomers, polymers
  - *Valence:* number of antigen-binding fragments

FIVE TYPES

- Coded by heavy chain genes

Immunoglobulin M (IgM)

- 1st antibody response
- Monomer as B cell receptor (valence: 2)
- Pentamer as antibody held together by joining (J) chain (valence: 10)
- Works against carbohydrate, lipid antigens
- Most effective at activating complement pathway

Immunoglobulin G (IgG)

- Monomer (valence: 2)
- Four subclasses
  - IgG1, IgG2, IgG3, IgG4 (differ in constant regions)
- Serves as opsonin
- Activates classical complement pathway

Immunoglobulin A (IgA)

- Monomer (valence: 2)
- Serves as opsonin (eosinophils, neutrophils, some macrophages)
- Main immunoglobulin in mucosal sites; sometimes occurs as dimer (valence: 4)
- Two forms
  - IgA1, IgA2 (differ in constant regions)

Immunoglobulin E (IgE)

- Monomer (valence: 2)
- Production primarily induced by interleukin 4 (IL-4)
- Triggers granule release from mast cells, eosinophils, basophils
- Responds to nonpathogenic targets (e.g. peanuts) → allergies

Immunoglobulin D (IgD)

- Monomer (valence: 2)
- Found alongside IgM antibodies, signals maturation of B cells

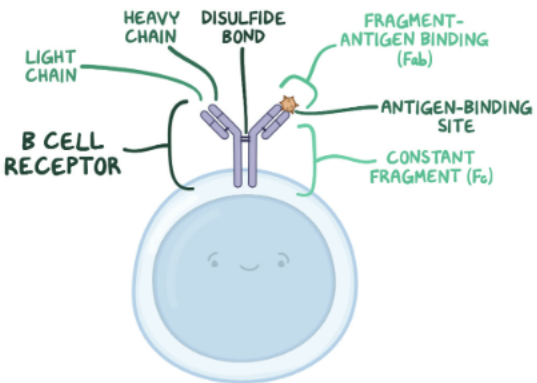


Figure 45.1 B cell receptor components.

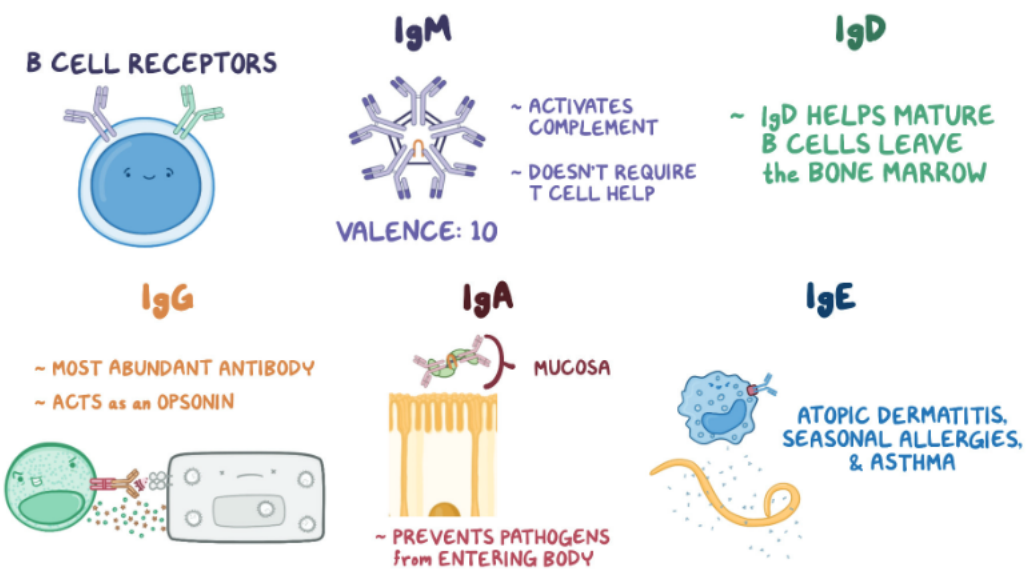


Figure 45.2 Summary of the five classes of antibodies. IgM and IgD can act as B cell receptors.

B CELL ACTIVATION & DIFFERENTIATION

osms.it/b-cell-activation-and-differentiation

- Developing B cell receptor expresses μ heavy chain → B cell receptors IgM
- Alternative splicing → IgM, IgD expressed on surface → mature, naive B cell explores lymphatic system → B cells enter paracortical region of lymph nodes, migrate to cortical region → form primary follicle

ACTIVATION

- On activation (antigen-binding), B cell forms germinal center → secondary lymphoid follicle
- Cross-linkage of two B cell receptors → Ig-alpha, Ig-beta, CD19 cluster
  - Blk, Fyn, Lyn phosphorylate tyrosine residues on immunoreceptor tyrosine based activation motif (ITAM) units → transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), nuclear factor of activated T cells (NFAT) → gene expression of cytokines, upregulation of antiapoptotic cell surface markers

DIFFERENTIATION

- B cells stimulated by cluster of differentiation 21 (CD21)/complement receptor Type II (CR2) (receptor for C3d complement fragment)
- Activated B cells differentiate into plasma cells, secrete antibodies
  - Plasma cells initially secrete IgM, remain mainly in bone marrow, safeguard against future encounters with same antigen

Activated $CD4^+$ T cell → class switching

- *B cells*: antigen-presenting cells; present antigens on major histocompatibility complex (MHC) class II to helper T cells
- CD40 ligand on T cell binds to CD40 on B cell → cytokines instruct B cell on type of antibody to produce (by activation-induced cytidine deaminase)
  - IL-4, IL-5 → IgE
  - Interferon (IFN) gamma → IgG

- Activation-induced deaminase removes constant regions during differentiation to leave desired antibody region

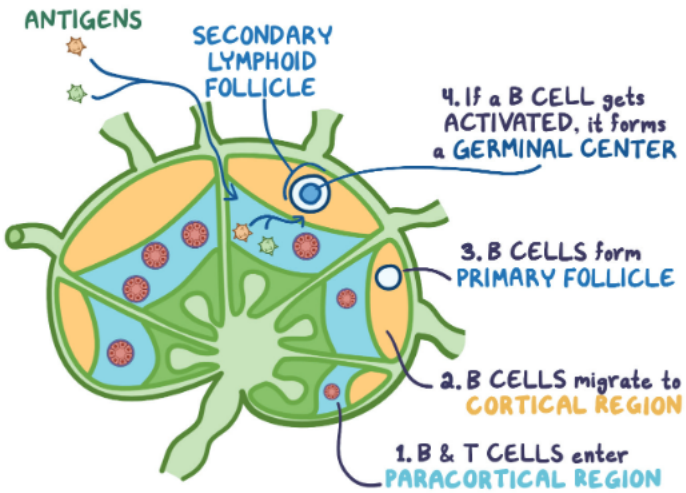


Figure 45.3 Mature, naive B cells form a primary follicle in the cortical region of a lymph node. When the B cell binds an antigen, it activates and forms a germinal center. The follicle is now called a secondary lymphoid follicle.

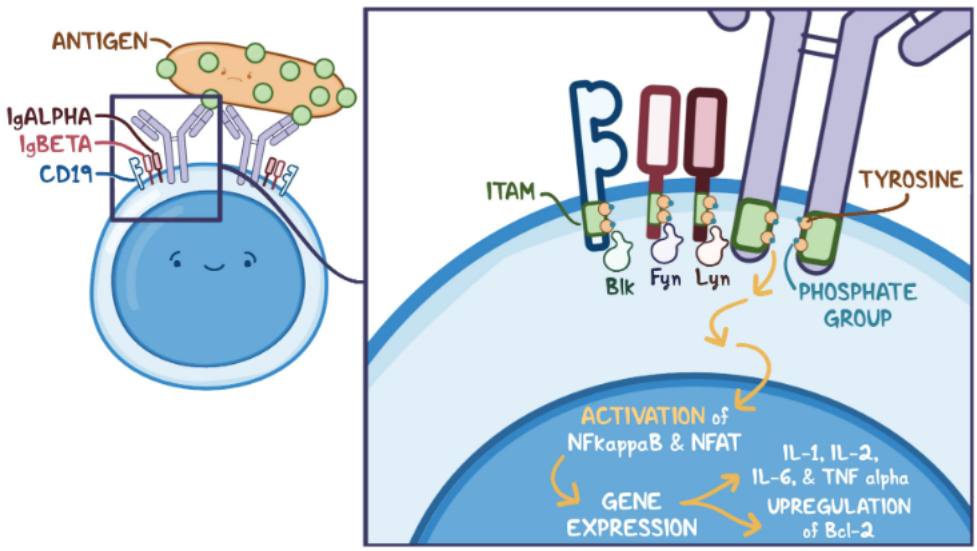


Figure 45.4 Series of events following antigen binding that lead to B cell activation. Ig-alpha, Ig-beta, and CD19 are intracellular side chains of the B cell receptors that cluster when two B cell receptors are cross-linked by an antigen.

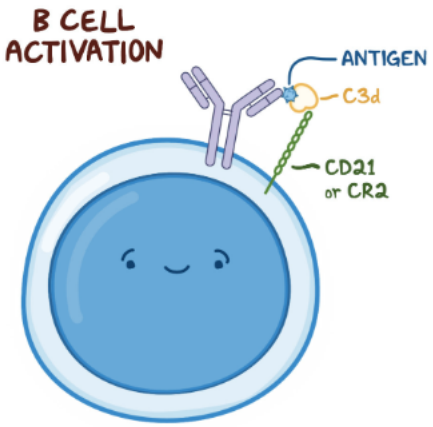


Figure 45.5 Complement fragment C3d can bind an antigen and then be bound by molecule CD21/CR2 on a B cell. B cells can also be activated when they have a B cell receptor that is bound to an antigen, and a CD21 that's bound to an antigen.

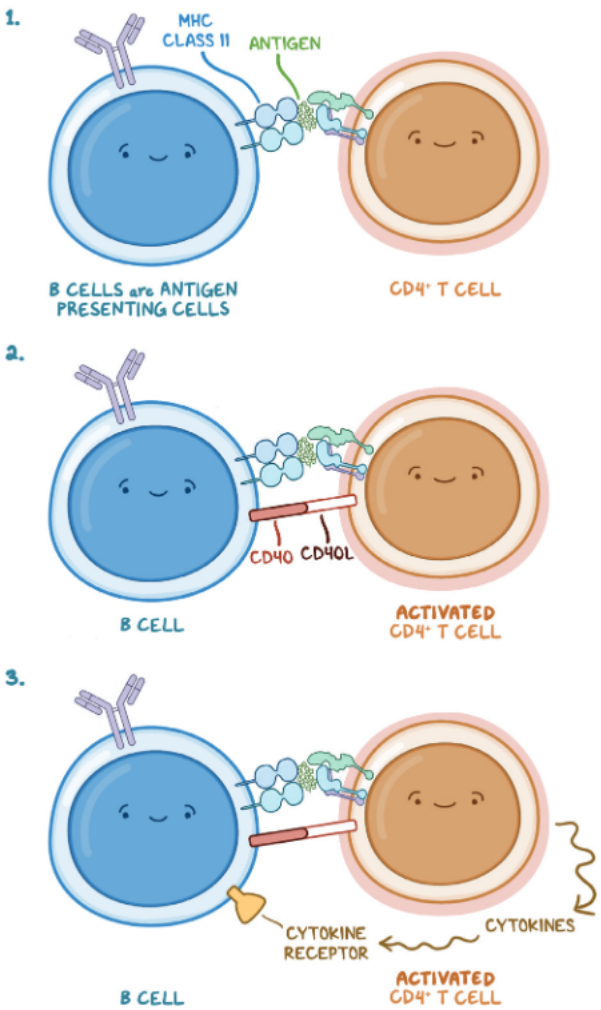


Figure 45.6 B cell differentiation. **1:** B cell presents an antigen to a CD4+ T cell. **2:** If the T cell activates, it expresses CD40L on its surface, which binds to CD40 on the B cell. **3:** CD40L and CD40 binding causes the B cell to express a cytokine receptor and the T cell to release cytokines. The type of cytokine determines what type of antibody the B cell will produce.

B CELL DEVELOPMENT

osms.it/b-cell-development

- *Lymphopoiesis:* development of diverse set of lymphocytes with unique antigen receptors

CREATION OF SUITABLE RECEPTOR

- B cell receptor contains two chains
  - Heavy, light
- Antigen-binding site made of variable (V), diversity (D), joining (J) protein segments coded by genes of same name
  - *Heavy chain:* all three segments
  - *Light chain:* V, J segments

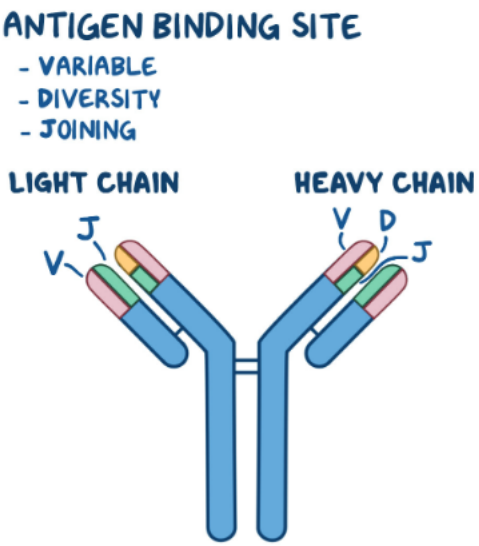


Figure 45.7 Antigen binding site on heavy chain is composed of V, D, and J segments, while antigen binding site on light chain has only V and J segments.

STAGES OF DEVELOPMENT

- *Six stages:* common lymphoid progenitor cell → early pro-B cell → late pro-B cell → large pre-B cell → small pre-B cell → immature B cell

Early pro-B cell

- Common lymphoid progenitor cell expresses recombination activating gene (RAG) 1, RAG2 → early pro-B cell

Late pro-B cell

- Heavy chain D, J gene segments spliced together (*allelic exclusion*: 1st chromosome to complete splicing suppresses 2nd) → late pro-B cell

Large pre-B cell

- Late pro-B-cell attaches D-J gene segment to V gene segment via V(D)J recombinase → binding site (heavy chain) recombined with mu gene → large pre-B cell
  - Mu gene codes for IgM constant region protein

Small pre-B cell

- Functionality of heavy chain tested by binding to surrogate light chain (VpreB, lambda 5) → if successful, cells proliferate → small pre-B cell

Immature B cell

- Light chain rearranged → functionality of light chain tested by autoimmune regulator (AIRE), identifies self-reactive cells by expressing bodily antigens in lymphoid organs → immature B cell
- *Central tolerance/negative selection:* elimination of self-reactive cells
  - Strong binding to self-antigen → cell undergoes apoptosis
  - Intermediate binding to self-antigen → light chain repeatedly rearranged with kappa gene on 1st, 2nd chromosomes, lambda gene 1st, 2nd chromosomes
  - Failure to eliminate self-reactive cells → autoimmunity
- Immature B cells finally undergo alternative splicing on constant region → IgD constant region replaces IgM constant region → cells released into blood

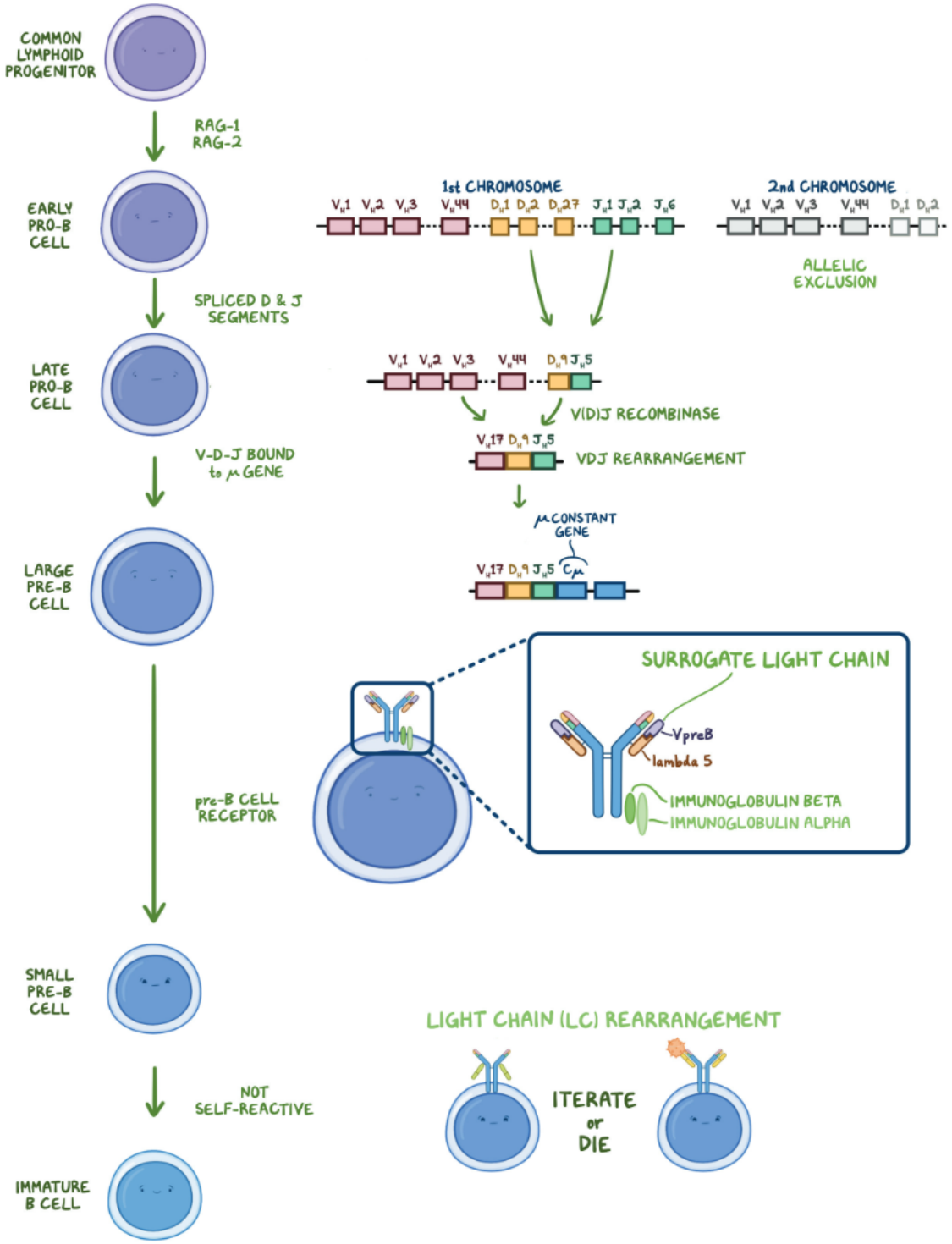


Figure 45.8 B cell development stages and the changes that move them to the next stage.

CELL MEDIATED IMMUNITY OF CD4 CELLS

osms.it/cell-mediated-immunity-CD4-cells

- CD4 cells = T helper cells (support other immune cells)
- T cells initially naive
- In response to antigen, T cell primed → effector T cell
  - *Two signals:* antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Activated T helper cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion

FOUR TYPES OF T HELPER CELL

- Depends on cytokines in environment

T helper Type I (Th1)

- Fights intracellular infections
- Macrophages → IL-12, natural killer (NK) cells → IFN-γ, infected cells → IFNα, IFNβ → transcription factors signal transducer and activator of transcription 1 (STAT1), STAT2

T helper Type II

- Fights parasites
- Eosinophils, basophils, mast cells → IL-4, IL-4, IL-10 → transcription factors STAT6, GATA-binding protein 3 (GATA3)

T helper Type XVII

- Fights fungal, bacterial infections
- Fungi, bacteria → IL1, IL6, IL23, transforming growth factor (TGF)β → transcription factors ROR-γ, STAT3

T follicular helper (Tfh)

- Establishes memory B cells
- Antigen-presenting cells → IL6, IL21, IL27 → transcription factors B cell lymphoma protein 5 (BCL-5), cMaf

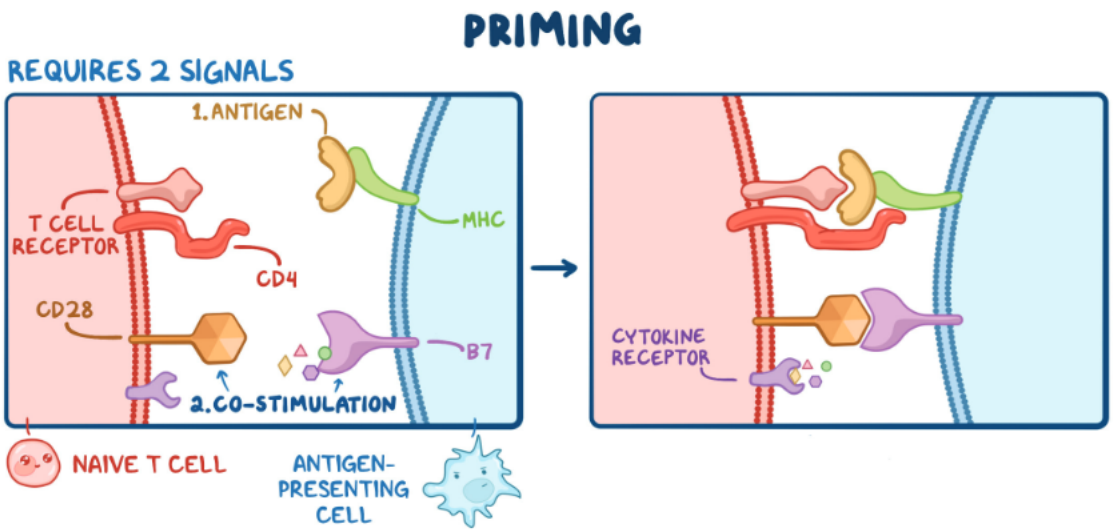


Figure 45.9 T helper cells require two signals to be primed and become effector T cells: presentation of an antigen and binding of CD28 on T cell to B7 on antigen-presenting cell.

CELL MEDIATED IMMUNITY OF NATURAL KILLER & CD8 CELLS

osms.it/cell-mediated-immunity-NK-CD8-cells

NATURAL KILLER (NK) CELLS

- Identify target cells; deliver perforin, granzymes
- Part of innate response → no need for specific antigen
- Activation receptors recognize surface molecules on infected cells; inhibitory receptors recognize molecules (e.g. native MHC class I molecules)
- Also activated by antibody-dependent cell-mediated cytotoxicity
  - IgG binds to virally-infected cell → CD16 on NK binds to antibody

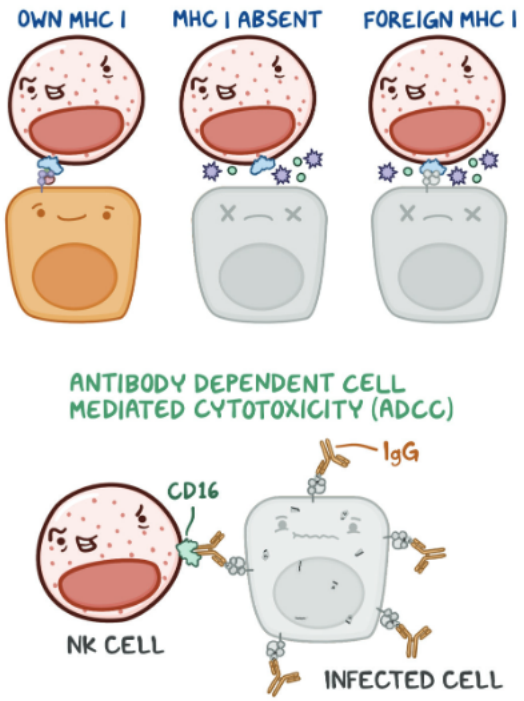


Figure 45.10 NK cells recognize cell surface molecules like MHC I to determine whether or not to kill a cell. They can also kill via ADCC. In this process, the NK cell is stimulated by binding to the constant chain of an IgG antibody attached to a virally infected cell.

CD8 CELLS

- CD8 cells = cytotoxic T cells
- T cells initially naive
- In response to antigen, T cell primed → effector T cell
  - *Two signals:* antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Activated T helper cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion
- Needs to see antigen in context of MHC I to kill cell (doesn't need CD28)
- Binds nonspecifically to multiple cells with adhesion molecules → fails to bind to MHC I → disengages
- If antigen binds, cytoskeletal rearrangement → forms supramolecular activation cluster (SMAC)
  - Includes central SMAC (cSMAC) for antigen recognition, peripheral SMAC (pSMAC)
- Cytotoxic cell releases granules with perforin, granzymes (caspases → apoptosis)

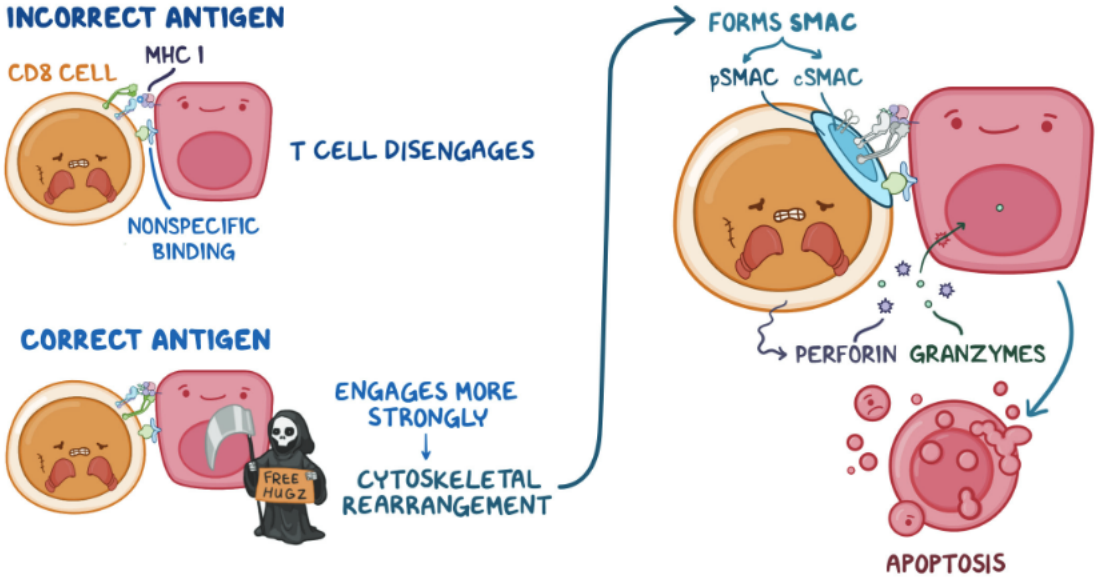


Figure 45.11 CD8 cells weakly bind a variety of cells with adhesion molecules. However, they only destroy cells with antigens on their MHC I molecules that allow the CD8 cells to bind tightly.

CYTOKINES

osms.it/cytokines

- Proteins secreted by all types of cells to communicate (bind to receptors, trigger response)

FIVE TYPES

Interleukins (ILs)

- Act as communication between leukocytes, nonleukocytes
- Promote development, differentiation of T, B cells
- Mostly synthesized by helper T cells

Tumor necrosis factors (TNFs)

- Bind to cell receptors, cause cells to die (induce apoptosis)
- Heavily involved in inflammatory response (up-regulate expression of adhesion molecules, increase vascular permeability, induce fever)

Interferons (IFNs)

- Type I
  - Produced by virally infected cells → affect surrounding cells: degrade messenger RNA (mRNA), inhibit protein synthesis, express MHC
- Type II
  - Interferon-gamma → promotes anti-viral state, activates macrophages, $CD4^+$ helper T-cells

Colony stimulating factors (CSFs)

- Bind to surface receptors on hematopoietic stem cells → proliferation, differentiation

Transforming growth factors (TGFs)

- Control proliferation, differentiation of cells

MAIN FUNCTIONAL RESPONSES

Pro-inflammatory

- Enhance innate, adaptive immune responses
- IL-1, IL-12, IL-18, TNF, IFN-γ

Parasite/allergy

- Help immune system handle large parasites, induce allergic responses
- IL-4, IL-5, IL-10, IL13

Regulatory

- Immunosuppressive
- IL-10, TGF-β

Growth and differentiation

- Replenish immune cells
- Granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), IL-7

Chemotactic

- Help cells move towards site of inflammation
- IL-17, IL-8

MHC CLASS I & MHC CLASS II MOLECULES

osms.it/MHC-class-I-MHC-class-II

- Major histocompatibility complex (MHC), AKA "human leukocyte antigen"
  - Cell surface proteins, present antigens to T cells

MHC CLASS I

- Found on all nucleated cells, presents antigens from inside
- Bound by CD8 molecules on cytotoxic T cells
- Includes HLA-A, HLA-B, HLA-C

Structure

- Contains alpha, beta-2-microglobulin chains
- *Alpha chain:* peptide binding groove, transmembrane region
  - Binding groove binds peptides 8–10 amino acids long; hydrophobic peptide residues ↔ hydrophilic groove amino acids
- *Three extracellular domains:* alpha-1, alpha-2, alpha-3

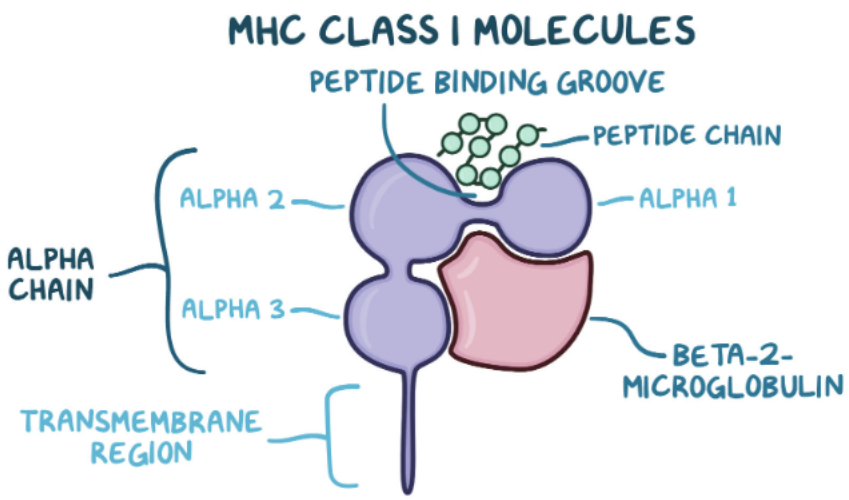


Figure 45.12 Structure of an MHC class I molecule.

Function

- Allows immune cells to sample cellular proteins (via endogenous pathway of antigen presentation)
  - Marked protein sent to proteasome
  - Proteasome degrades protein → short peptide chains
  - Transporters of antigenic peptides (TAP) move peptide chains to endoplasmic reticulum
  - TAP loads peptide onto MHC class I using tapasin
  - MHC class I loaded into exocytic vesicle, sent to cell surface
  - Cytotoxic T cells, NK cells interact with peptide (if necessary)

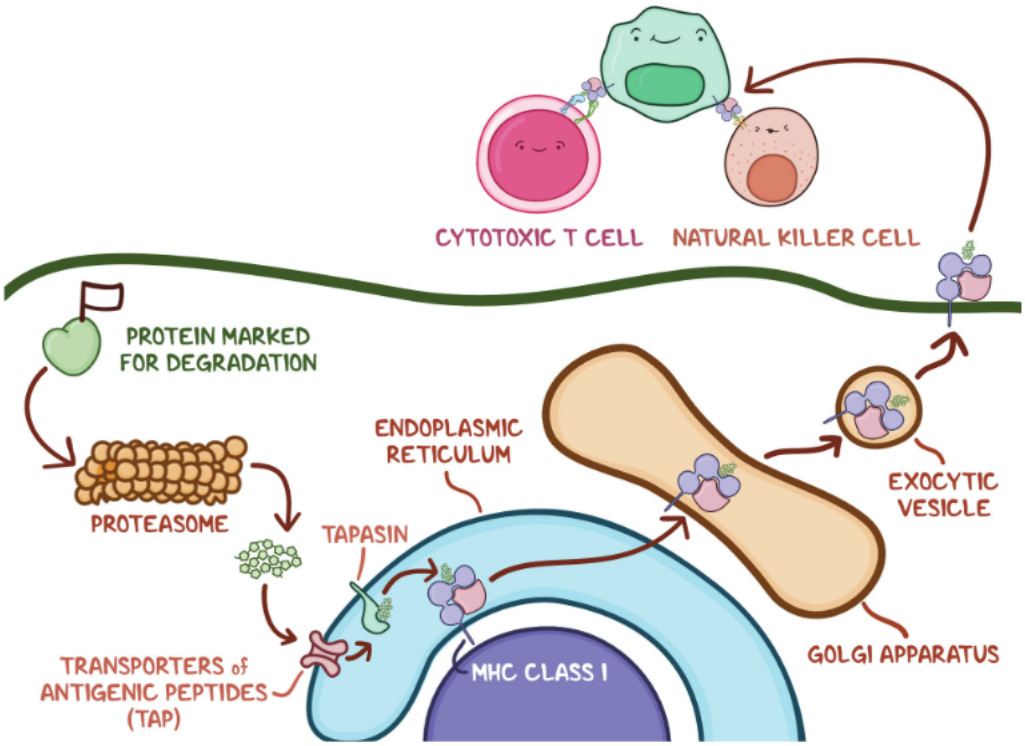


Figure 45.13 Endogenous pathway of antigen presentation.

MHC CLASS II

- Found on antigen-presenting cells, presents antigens from outside
- Bound by CD4 molecules on helper T cells
- Includes HLA-DP, HLA-DQ, HLA-DR

Structure

- Contains alpha, beta chains
  - Both penetrate cell membrane
  - Binding groove binds peptides 14–20 amino acids long

Function

- Engulfs, destroys pathogens; presents antigens to $CD4^+$ T helper cells (via exogenous pathway of antigen presentation)
  - Antigen-presenting cell ingests antigen → endosome
  - Lysosome + endosome → phagolysosome; degrades protein → short peptide chains
  - MHC class II binding groove filled temporarily with invariant chain (degrades during vesicular transportation)
  - Vesicle fuses with phagolysosome
  - MHC class II binds peptide, sent to cell surface
  - $CD4^+$ helper T cells interact with peptide (if necessary)

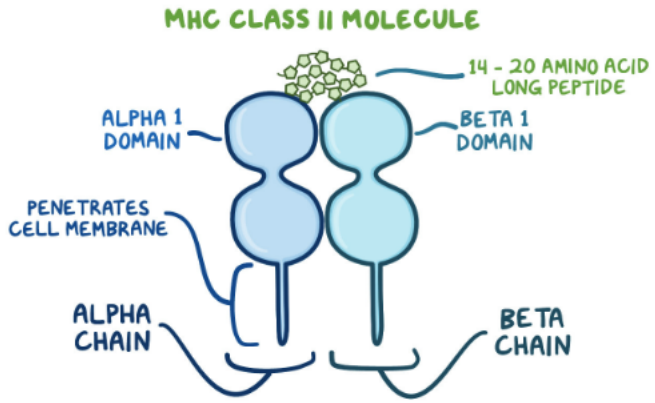


Figure 45.14 MHC class II molecule structure.

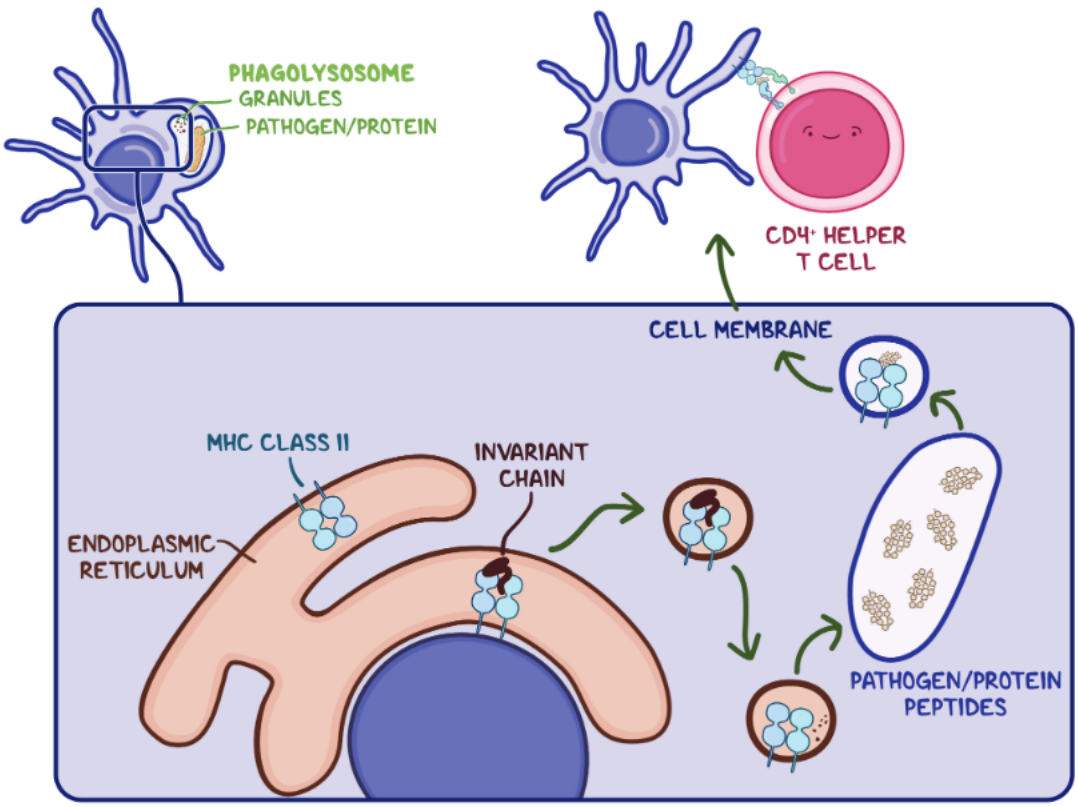


Figure 45.15 Exogenous pathway of antigen presentation.

SOMATIC HYPERMUTATION & AFFINITY MATURATION

osms.it/somatic-hypermutation-affinity-maturation

SOMATIC HYPERMUTATION

- Intentional mutation of antibody genes to create new antigen specificities → stronger, more specific response to antigen
- Occurs in activated B cells (germinal centers, spleen)
- CD40L on T cell binds to CD40 on B cell → cytokines instruct B cell to produce specific type of antibody
- Activation-induced cytidine deaminase (AID) turns cytidine into uridine (not usually found in DNA) → mismatch/base excision repair to remove uridine
  - Mismatch repair proteins MSH2, MSH6 use nucleases to remove uridine; DNA polymerase replaces nucleotides → mutations
  - *Base excision:* uracil-DNA glycosylase removes uracil from uridine → next round of replication, random nucleotide inserted → mutations
- Only some mutations increase affinity
  - Low affinity B cells die naturally with time
  - High affinity B cells live on (affinity maturation)

AFFINITY MATURATION

- Process by which B cells increase affinity for antigen during an immune response
- Somatic hypermutation, clonal selection (only high affinity cells activated → only high affinity cells replicate)

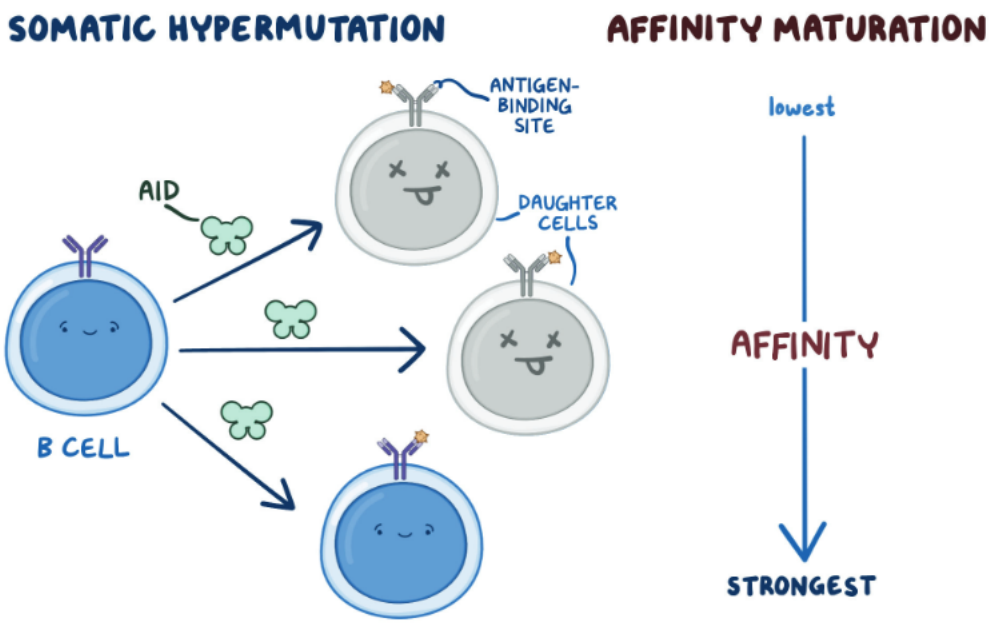


Figure 45.16 Somatic hypermutation only occurs in B cells which express enzyme AID. AID makes small mutations directly in antigen binding site of B cell receptor, which get expressed in daughter cells of a rapidly proliferating cell. These changes in the variable region change affinity (strength) that B cell receptor has for its antigen. As antigen becomes limited, B cells with lowest affinity will die off first, so only B cells with strongest affinity for their antigen remain.

T CELL ACTIVATION

osms.it/t-cell-activation

- *Priming:* T cell begins differentiation when exposed to antigen
  - *Two signals:* antigen (MHC molecule on antigen-presenting cell), costimulation (CD28 binds to B7 on antigen-presenting cells)
- Signal sent to nucleus by CD3 peptide chains
  - Lymphocyte-specific protein tyrosine kinase (LCK) phosphorylates tyrosine residues on immunoreceptor tyrosine based activation motif (ITAM) units
  - Zeta-chain-associated protein kinase 70 (ZAP-70) phosphorylates LAT, SLP-76 → activation of transcription factors NF-kB, NFAT → gene expression of cytokines, upregulation of antiapoptotic cell surface markers
- Activated T cell → IL-2 → up-regulates IL-2 alpha receptor
- T helper cell binds to IL-2 (autocrine stimulation) → clonal expansion

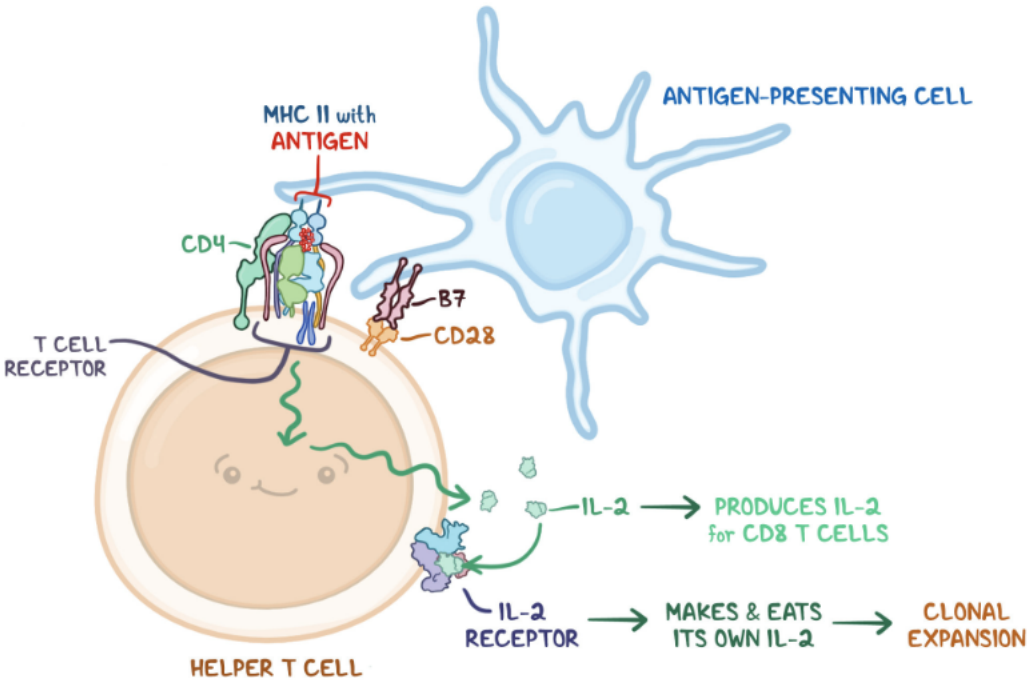


Figure 45.17 Summary of T cell activation. T cells need two signals to activate: first, presentation of its antigen by MHC class I (cytotoxic C cells) or class II (helper T cells), and costimulation, which is when CD28 and B7 bind. In helper T cells, this triggers a series of steps that lead to upregulation of the IL-2 alpha receptor and production of IL-2 for itself, causing clonal expansion, and CD8 T cells.

T CELL DEVELOPMENT

osms.it/t-cell-development

- *Lymphopoiesis:* hematopoietic stem cell → common lymphoid progenitor cell → immature B cell (bone marrow)

CREATION OF SUITABLE RECEPTOR

- T cell receptor contains two chains: alpha, beta
  - *Alpha:* comparable to B cell's light chain
  - *Beta:* comparable to B cell's heavy chain
- *Antigen-binding site:* V, D, J protein segments coded by genes of same name
  - *Beta chain:* all three segments
  - *Alpha chain:* V, J segments

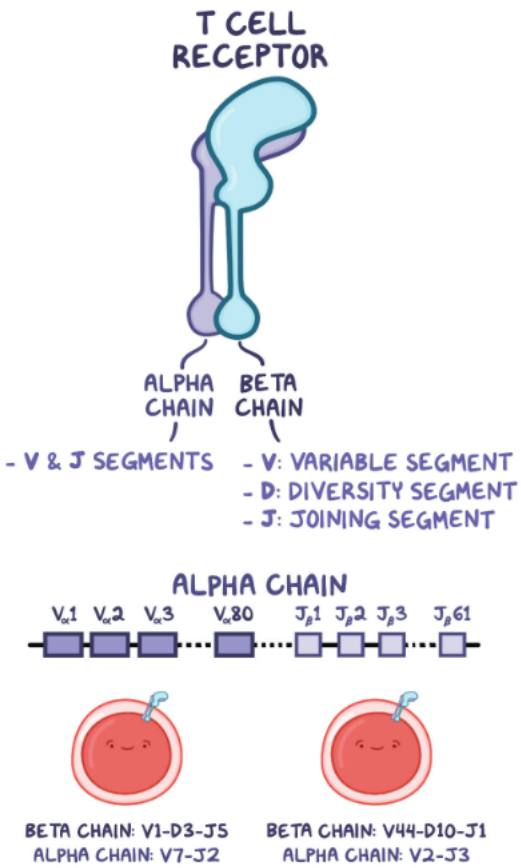


Figure 45.18 Structure of T cell receptor. Different combinations of V, D, and J segments provide T cell receptors with a wide variety of antigen specificities.

STAGES OF REARRANGEMENT

- Tracked by CD3, CD4, CD8 cell surface markers

Double negative/DN stage

- Common lymphoid progenitor initially $CD3^-$, $CD4^-$, $CD8^-$ (double negative/DN stage; broken down into DN1, DN2, DN3, DN4)
  - DN1 cell expresses RAG1, RAG2 → DN2 cell
  - Beta chain D, J gene segments spliced together (allelic exclusion) → DN3 cell
  - V gene segment combines with DJ gene segment by V(D)J recombinase → V-D-J gene segment bound to μ gene segment → DN4 cell
  - Functionality of beta chain tested by binding to invariant pre-T alpha chain → if successful, cells proliferate

Double positive/DP stage

- Daughter cells express CD3, CD4, CD8 (double positive/DP stage)

Single positive/SP stage

- *Central tolerance:* eliminates potentially self-reactive cells by positive, negative selection
  - Self-reactive cell elimination failure → autoimmunity
- Positive selection
  - T cells recognize/bind to self-MHC molecules
  - Binding failure → apoptosis
- Negative selection
  - *Autoimmune regulator gene (AIRE):* allows primary lymphoid organs to express antigens normally found throughout body; aids in testing self-reactivity
  - Excessively strong binding to self-antigens → apoptosis

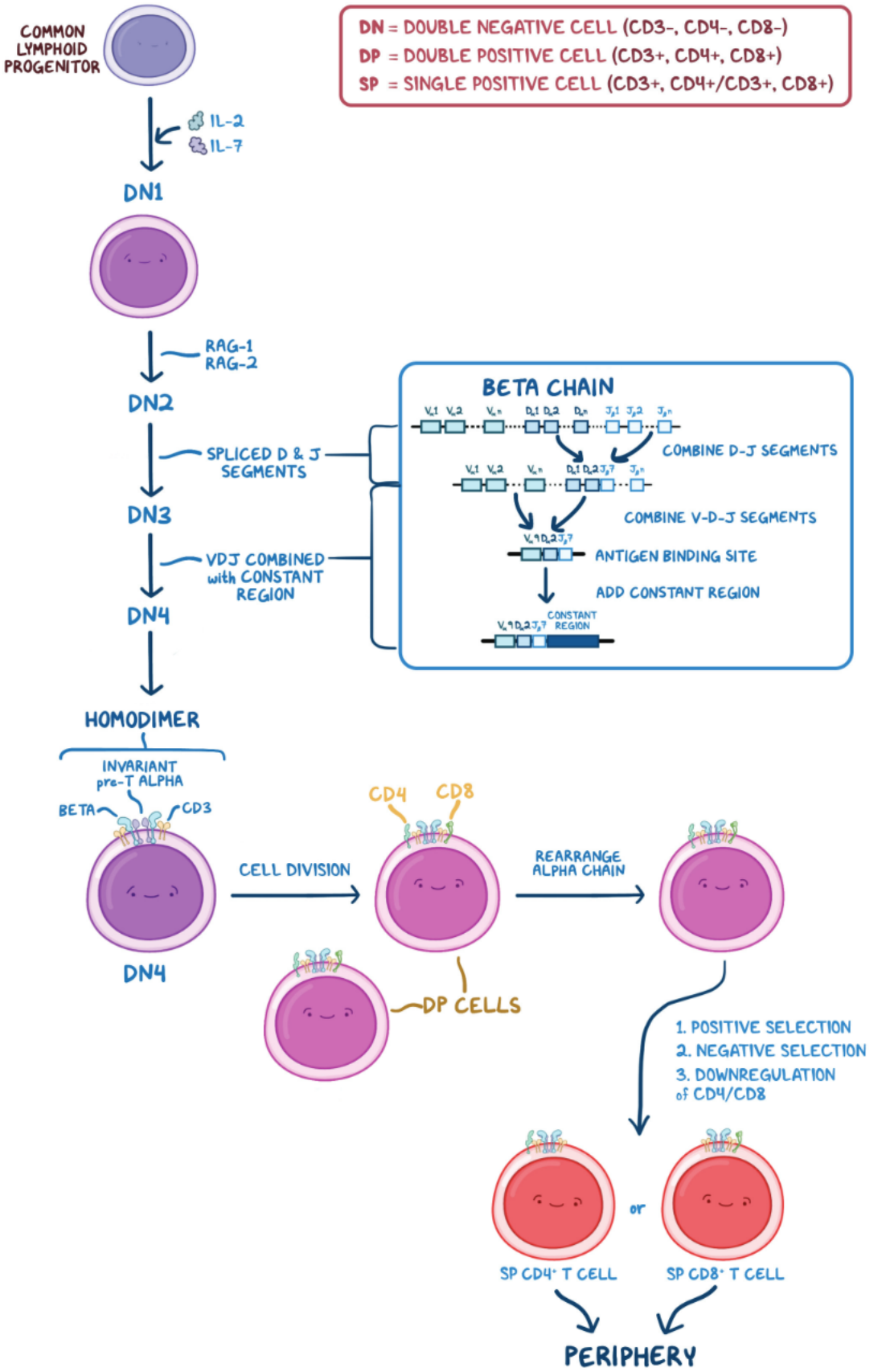


Figure 45.19 T cell development summary.

- DP cells recognize self-MHC but do not recognize self-antigen presented in MHC molecule → downregulate either CD4/CD8 receptor → further development into single positive (SP) cell
  - Strong binding to MHC → CD4 downregulated → SP $CD8^+$ T cell
  - Weak binding to MHC → CD8 downregulated → SP $CD4^+$ T cell

VDJ REARRANGEMENT

osms.it/VDJ-rearrangement

- Mechanism used to generate range of B, T cell receptors
- *Antigen-binding sites:* V, D, J protein segments coded by genes of same name
  - Each cell inherits multiple V, D, J segments → randomly recombine → recombinational inaccuracy, random assortment of two chains (heavy/beta chain rearranged first) → new specificities
- V(D)J rearrangement only affects V region (creates variability in hypervariable regions)

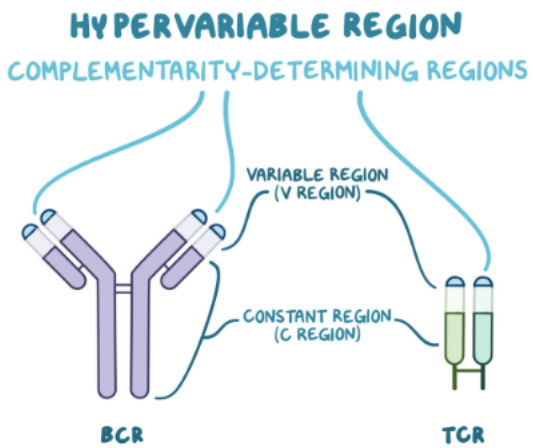


Figure 45.20 Locations of hypervariable regions on BCRs and TCRs affected by V(D)J rearrangement.

HEAVY/BETA CHAIN REARRANGEMENT

- Recombination signal sequence
  - Heptamer 5'-CACAGTC-3', 12, 23 nucleotides, nonamer 5'-ACAAAAACC-3'
  - DNA loops to bring together two recombination signal sequences
  - RAG1, RAG2 cut DNA at recombination signal sequence
  - Recombinases (e.g. ku, artemis) reattach, recombine DNA
- Error-prone process
  - Cut end placed onto terminal deoxynucleotide transferase (TdT) to add random nucleotides → alters antigen specificity
- Functionality of heavy chain tested → random assortment of chain

LIGHT CHAIN REARRANGEMENT

- Rearranged into kappa/lambda light chain (kappa rearranged before lambda)

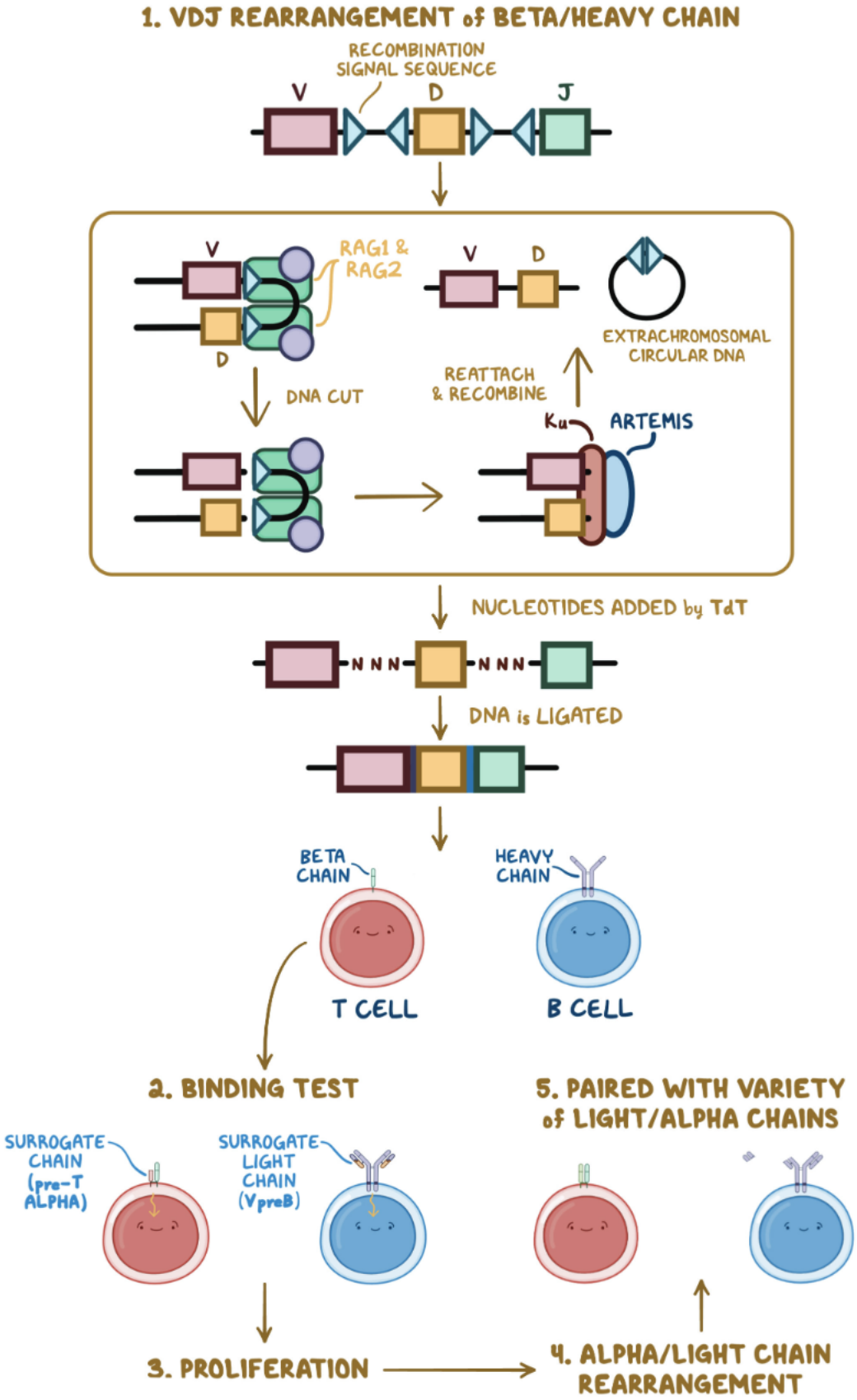


Figure 45.21 Summary of the process by which B and T cell receptors are made.

NOTES
CONTRACTION OF THE IMMUNE RESPONSE

ANERGY, EXHAUSTION, & CLONAL DELETION

osms.it/contracting-immune-response

CLONAL ANERGY

- Functional unresponsiveness to self antigens
- Lymphocytes can bind to antigens, without costimulation
- *T cells:* costimulation involves CD28 binding to B7 on antigen-presenting cells (APCs)
  - T regulatory cells reduce B7 expression on antigen presenting cells
  - Later in immune response, T cells begin to express cytotoxic T-lymphocyte associated protein 4 (CTLA-4) → binds to B7

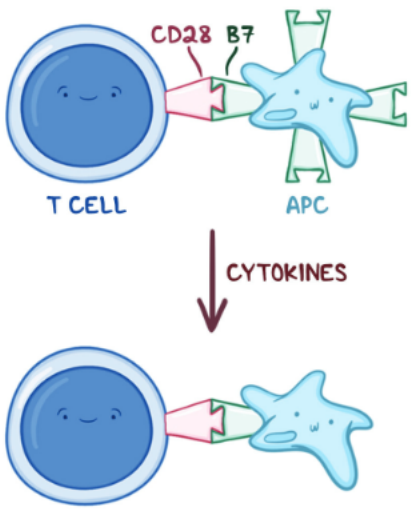


Figure 46.1 T regulatory cells reduce costimulation by releasing cytokines that reduce B7 expression on antigen-presenting cells (APCs).

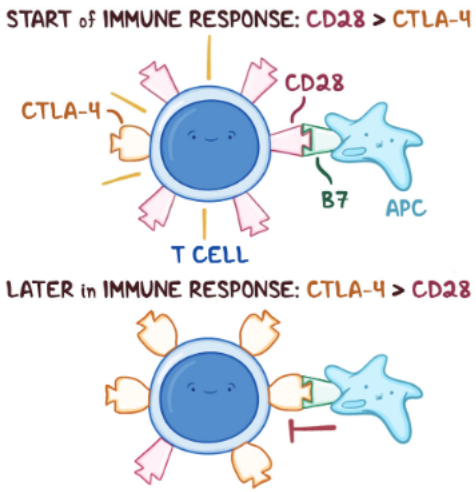


Figure 46.2 T cells express much more CTLA-4 later in immune response. B7 binds to CTLA-4 more strongly than it does to CD28 and inhibits T cell → T cell inactivation.

CLONAL EXHAUSTION

- Later in immune response, T cells begin to express program death 1 (PD-1)
- Program death ligand 1 (PD-L1) on antigen-presenting cells bind to PD-1 → T cells shut down

CLONAL DELETION

- Recognition of self antigens → T cell apoptosis (programmed cell death)
- Later in immune response, T cells express Fas
- Fas ligands on CD8+ T cells, NK cells bind to Fas → activate enzymes called caspases → apoptosis

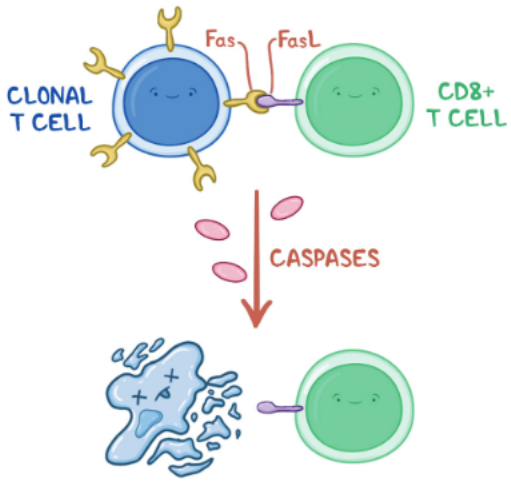


Figure 46.3 Clonal deletion. T cells express Fas → bind to Fas ligand on CD8+ T cell/NK cell → caspases activated → apoptosis.

B & T CELL MEMORY

osms.it/B-and-T-cell-memory

- Ability of B, T cells to "remember" particular antigen
  - B, T cells multiply when receptors detect particular antigen
  - After immune response mounted, excess cells undergo apoptosis
  - Memory B, T cells contain same receptors after immune response
- Immunologic memory → secondary (anamnestic) response
  - *Primary response:* naive B, T cells require activation before response to pathogen → high pathogen burden (response can take days, weeks)
  - *Secondary response:* memory B, T cells, antibodies needed to respond to pathogen already exist → low pathogen burden (response occurs right away)

MEMORY B CELLS

- Only B cells that have undergone class switching become memory B cells
  - Memory response limited to peptide antigens (not lipids/carbohydrates)—follicular T helper cells needed for class-switching only respond to peptide antigens
  - Memory B cells don't produce IgM/IgD
- Live up to 10 years in lymph nodes
- Often differentiate into IgG-producing plasma cells when reactivated
- Due to somatic hypermutation, IgG created late in immune response typically has higher affinity than IgM created early in immune response → IgG binds to Fc gamma receptor II on IgM-producing B cells, prevents differentiation into plasma cells → ↓ IgM production, ↑ IgG production

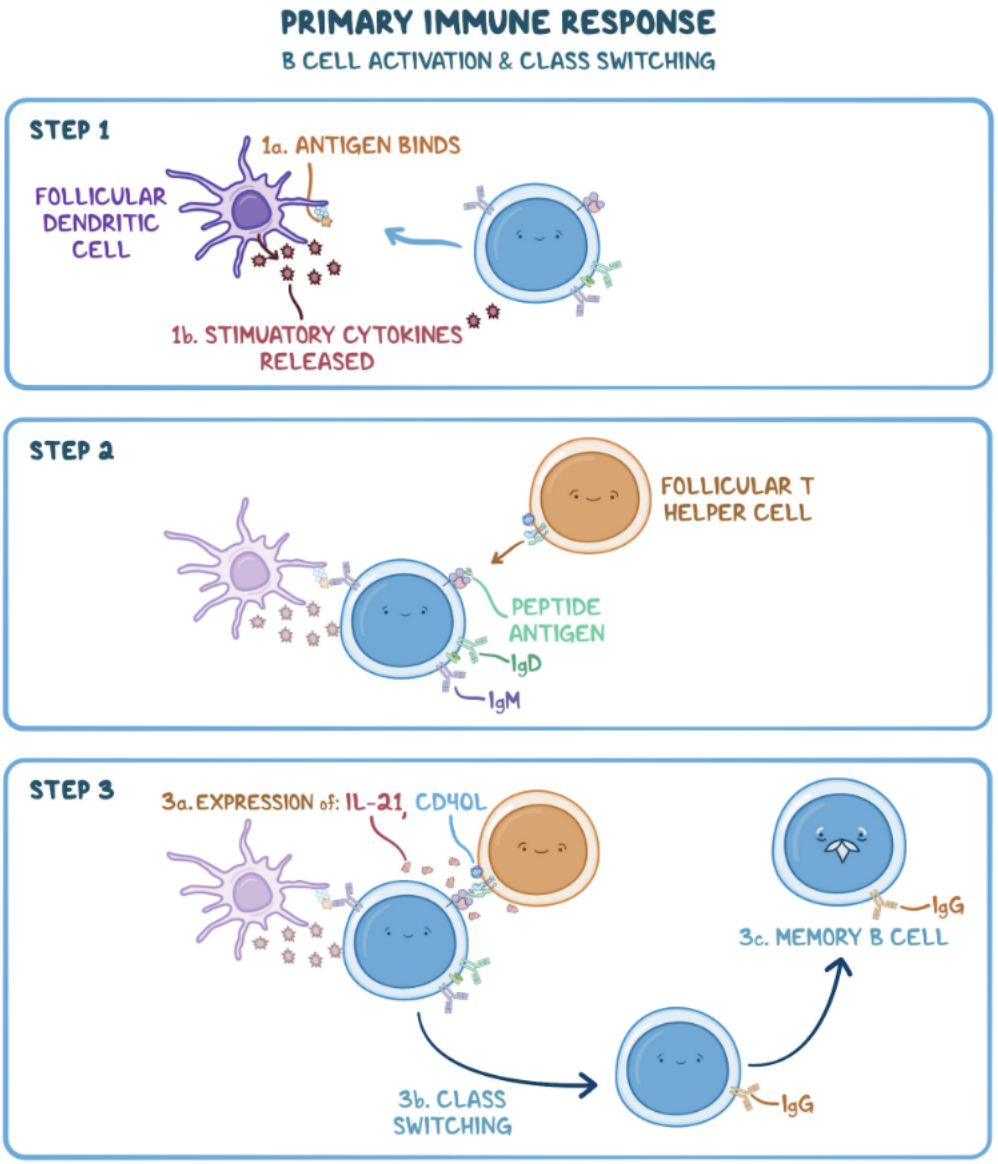


Figure 46.4 B cells are activated through interactions with other immune cells. Step 1a: follicular dendritic cell traps antigens and 1b: sends out stimulatory cytokines. Step 2: the B cell presents the antigen to a follicular T helper cell. Step 3a: the follicular T helper cell expresses CD40L on its surface and produces IL-21. 3b: together, they induce the B cell to undergo class switching (shift from expressing a B cell receptor with IgM and IgD to expressing IgG, IgE, or IgA. 3c: some of these B cells become memory B cells.

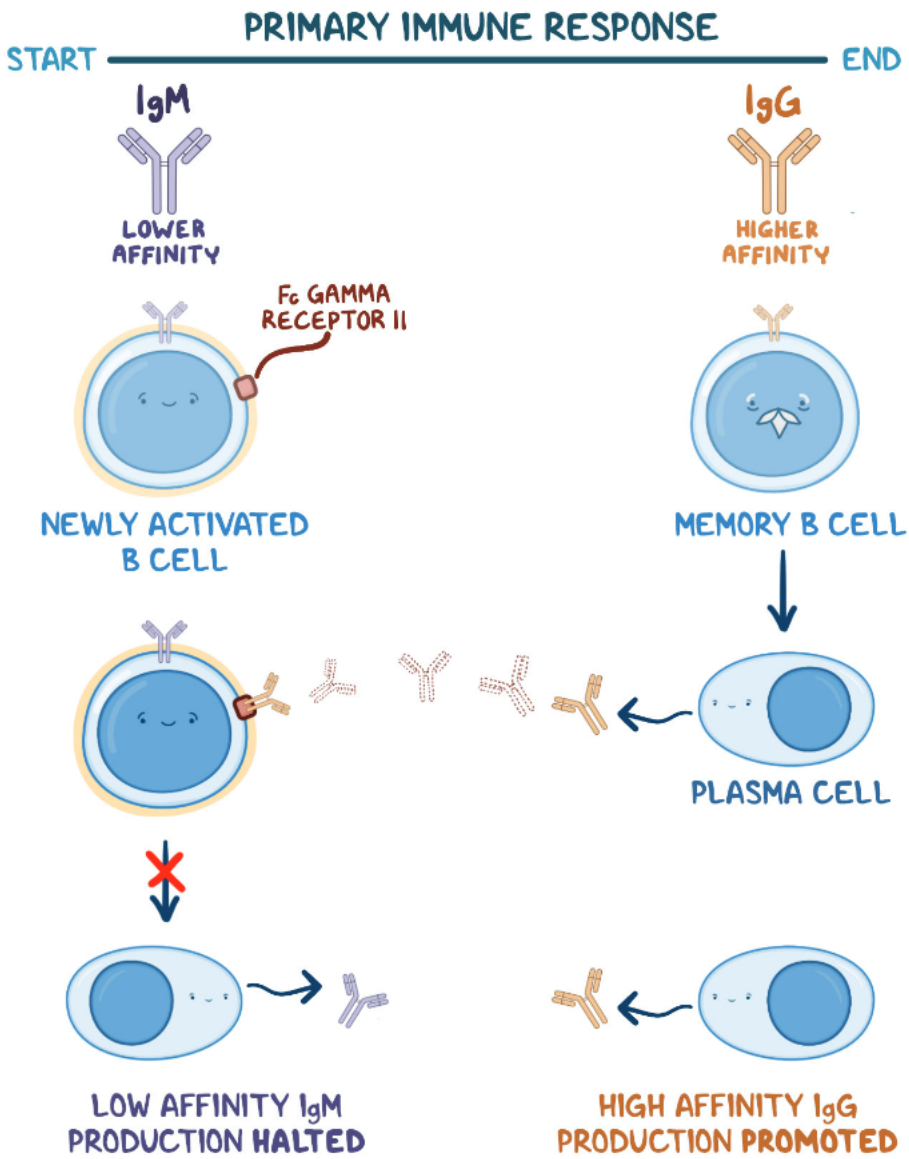


Figure 46.5 Process by which higher affinity IgG production is favored over lower affinity IgM production. Memory B cells differentiate into high affinity IgG-producing plasma cells. IgG binds to Fc gamma receptor II on newly activated B cells, which produce low affinity IgM. This prevents them from differentiating into low affinity IgM-producing plasma cells, allowing the proportion of high affinity IgG in the response to be greater.

MEMORY T CELLS

- Cell surface ligand CD45 used to identify T cells
  - Naive T cells express CD45A
  - Memory T cells express CD45O

Effector memory T cells

- Move around body looking for pathogens
- Respond as primary response (for CD4+ helper cells, secreting cytokines; for CD8+ cytotoxic cells, binding to, destroying target cells)
- IL-7 receptors replaced with IL-2 receptors during activation → cells die shortly after immune response

Central memory T cells

- Live up to 25 years
- Remain in lymphoid tissues
- High levels of IL-7 receptors maintained → cells live on after immune response

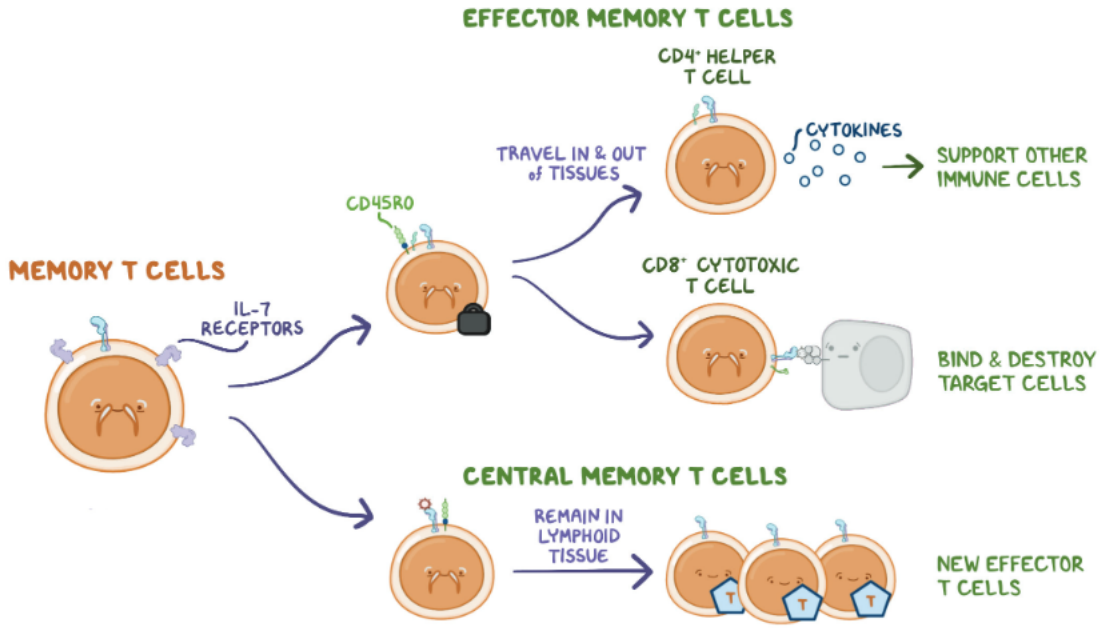


Figure 46.6 The two types of memory T cells (effector memory T cells and central memory T cells) and their functions.

CONTRACTING THE IMMUNE RESPONSE

osms.it/contracting-immune-response

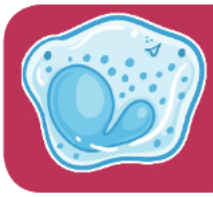
- Immune response termination
- Peripheral tolerance to self antigens limits immune response (preventing autoimmune disease)
- Mechanisms directed primarily at T cells; includes use of T regulatory cells, clonal anergy, exhaustion, deletion

T REGULATORY CELLS

- Inhibit antigen-presenting cells by releasing specific molecules (e.g. indoleamine 2,3 dioxygenase)
- Release cytokines (e.g. IL-10, TGF-beta) → antigen-presenting cells express inhibitory ligand (e.g. PD-L1)
- Express high levels of IL-2, adenosine receptors (competing with other T cells)

B CELLS

- Similar mechanisms to T cells
- Later in immune response, reduced presence of antigens, T cells prevent B cell activation → anergy
- Surplus IgG binds to Fcγr II on B cells → prevent differentiation into plasma cells



NOTES
INNATE IMMUNITY

INNATE IMMUNE SYSTEM

osms.it/innate-immune-system

- Comprises immune system along with adaptive immunity
- Includes barriers to repel pathogens
  - *Chemical barriers*: lysozyme (tears), low stomach pH
  - *Physical barriers*: epithelium (skin/gut), cilia lining airways

Key features

- Nonspecific cells do not distinguish invaders
- Response occurs within minutes–hours
- No memory
  - Always responds to pathogen in same manner

Human microbiome

- Included in innate immunity
- Bacteria, fungi, viruses in/on humans
- May affect host response in own way

RESPONSE TO PATHOGENS

Phagocyte response to pathogens

- Phagocytes eat, kill pathogens
- Phagocyte consumes pathogen
  - Phagocytic pattern recognition receptors (PRRs) on phagocyte identify pathogen-associated molecular patterns (PAMPs) on pathogens (e.g. bacterial-wall components)
  - Phagocyte swallows pathogen, traps it in phagosome
- Phagocyte kills pathogen (post-identification)
  - Phagosome binds with lysosome, forms phagolysosome
  - Specific phagolysosome granules (proteases, hydrolases) kill internal microorganisms while decreasing pH
  - Azurophilic granules (hydrolases, oxidative enzymes) activate in acidic environment → more microorganisms killed
  - Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases oxidize oxygen molecules → superoxide ion creation
  - Superoxide dismutase converts superoxide into hydrogen peroxide, killing remaining microorganisms

Signalling PRRs response to pathogens

- Large amount of pathogens enter → signalling pattern recognition receptors also activated
- Signalling PRRs → phagocytes to release cytokines
- Toll-like receptors (TLRs) especially important in signalling PRRs
  - PAMP activation → TLRs activate transcription factor NF-κB → proinflammatory cytokines (e.g. TNFα, IL-1β, IL-6) secreted → vasodilation, fever, recruiting leukocytes
  - *Intracellular pathogens*: interferon alpha, beta may be secreted (prevents pathogen multiplication)

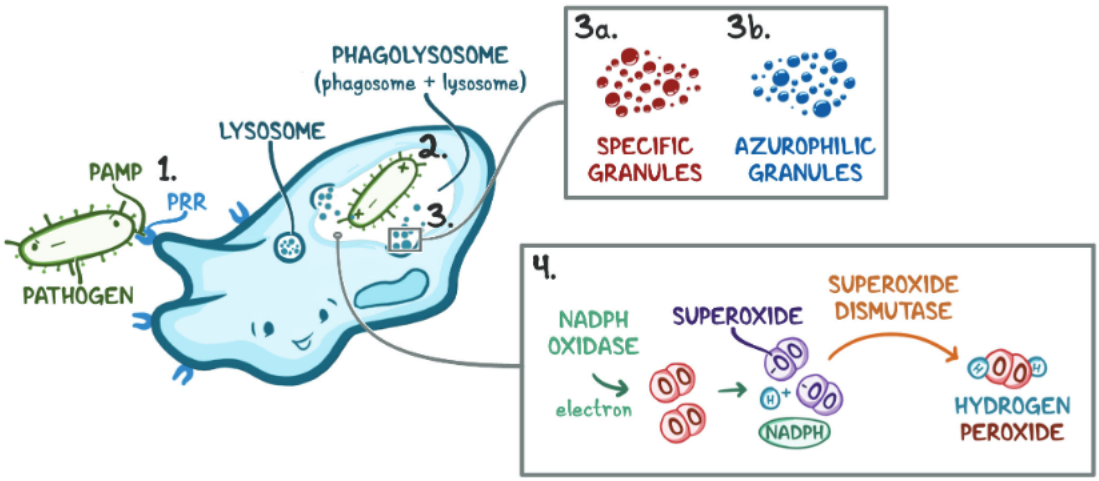


Figure 47.1 Overview of the phagocyte response to pathogens.
1. The phagocyte's pattern recognition receptors (PRRs) identify pathogen-associated molecular patterns (PAMPs) on the pathogen.
2. The pathogen is phagocytosed and trapped in a phagosome, which then
3. binds with lysosomes, forming a phagolysosome.
3a. Specific granules from the lysosomes act first to kill pathogens and decrease pH.
3b. After the pH is sufficiently lowered, azurophilic granules are activated and kill more pathogens.
4. NADPH oxidases oxidize oxygen molecules to create superoxide ions. The ions are then converted by superoxide dismutase into hydrogen peroxide, which kill the remaining pathogens.

COMPLEMENT SYSTEM

osms.it/complement-system

- Collection of plasma proteins called complement proteins
- Produced in liver, collectively destroy pathogens

COMPLEMENT SYSTEM PATHWAYS

- Acts follow one of three pathways
  - Classical, alternative, lectin

Classical pathway

- Features C1–C9 proteins
- C1
  - Component proteins C1q, C1r, C1s (latter two—serine proteases)

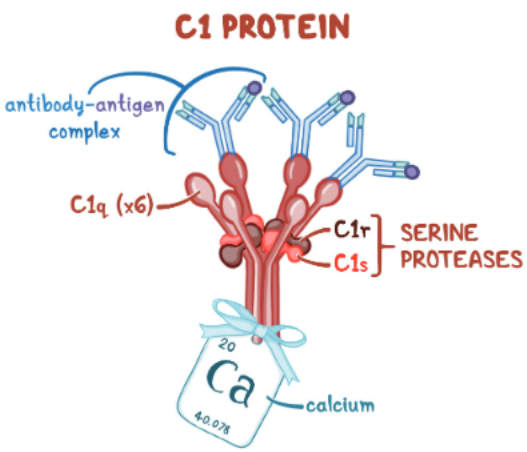


Figure 47.2 Structure of a C1 protein. Each of the six C1q proteins can bind to an antibody-antigen complex. Calcium ties the protein together.

- Proteins inactive until "cleaved" (portion of protein breaks off)
- Pathway steps
  - C1q proteins bind to Fc portion of antibody when bound to antigen
  - Two C1q proteins bind → C1 changes shapes (conformational change) exposing C1r, C1s
  - C1r cleaves C1s (activating C1 molecule) → C1 cleaves C4 into C4a, C4b → C4b binds to pathogen
  - C1 also cleaves C2 into C2a, C2b → C2a joins C4b on pathogen → C4b2a (C3 convertase) formed
  - C3 convertase cleaves C3 into C3a, C3b
  - C3b binds to pathogen near C4b2a/C3 convertase, creates C5 convertase (C4b2a3b)
  - C5 convertase cleaves C5 into C5a, C5b
  - C5b binds to C6, C7, C8, many C9s → forms membrane attack complex (MAC) → penetrates pathogen cell membrane
- C1 consists of six C1q proteins
  - Binds to six antibody-antigen complexes
- Calcium ties together C1
  - Lack of calcium → lack of C1

Alternative pathway

- Factor B, factor D proteins
- C3 cleaved spontaneously (small amounts)
- Pathway steps
  - C3b binds to pathogen → factor B binds to pathogen
  - Factor D cleaves factor B → forms Ba, Bb → C3bBb formed (C3 convertase)
  - Follows classical pathway
- Constant activation prevention
  - C1-inhibitor protein dissociates C3bBb

Lectin pathway

- Features mannose-binding lectin protein (binds to bacterial mannose)
- Pathway steps
  - Mannose-binding lectin protein acts similar to C1 → cleaves C4, C2 to eventually establish C4b2a (C3 convertase)
  - Follows classical pathway

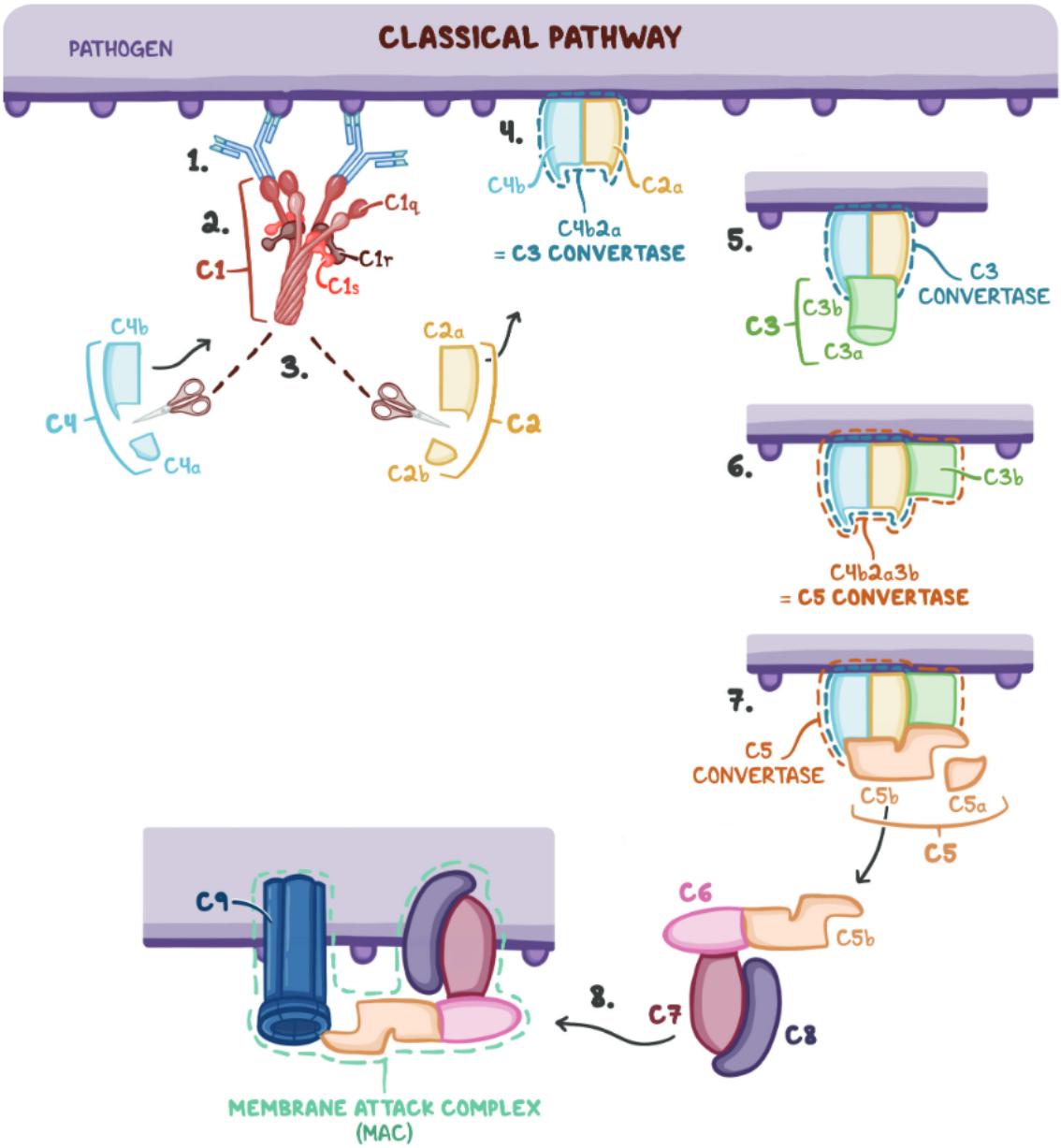


Figure 47.3 Overview of the classical complement pathway.
1. C1q binds to an antibody-antigen complex.
2. When two C1q proteins are bound, C1 undergoes a conformational change, exposing C1r and C1s. C1r then cleaves C1s to activate C1.
3. C1 cleaves C4 and C2.
4. C4 and C2 bind to the surface of the pathogen, forming C3 convertase.
5. C3 convertase cleaves C3.
6. C3b binds to the pathogen near the C3 convertase, forming C5 convertase.
7. C5 convertase cleaves C5.
8. C5b joins C6, C7, C8, and then multiple C9s to form the membrane attack complex, penetrating the pathogen cell membrane.

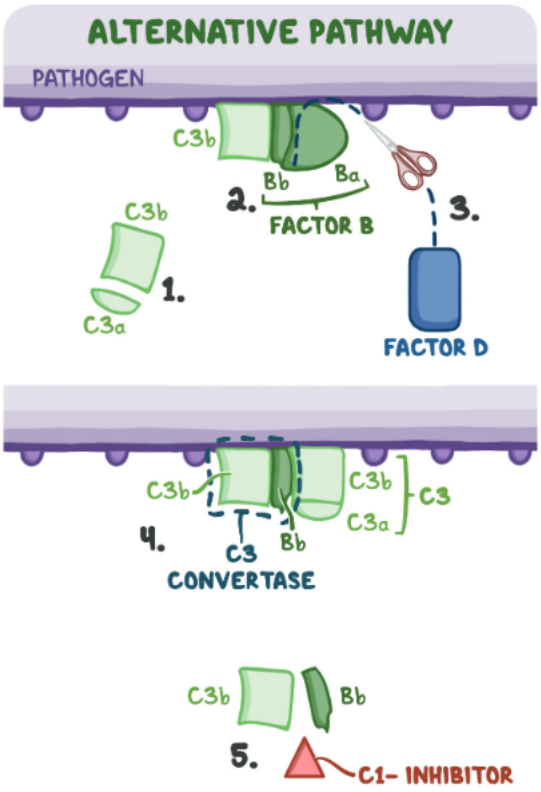


Figure 47.4 Overview of the alternative complement pathway. **1.** Small amounts of C3 are cleaved spontaneously. **2.** C3b and factor B bind to the pathogen. **3.** Factor D cleaves factor B. **4.** C3b and Bb form a C3 convertase and cleave more C3 proteins. The rest follows the classical pathway (from step 6 in previous figure). **5.** C1-inhibitor constantly prevents activation of this pathway by dissociating C3bBb.

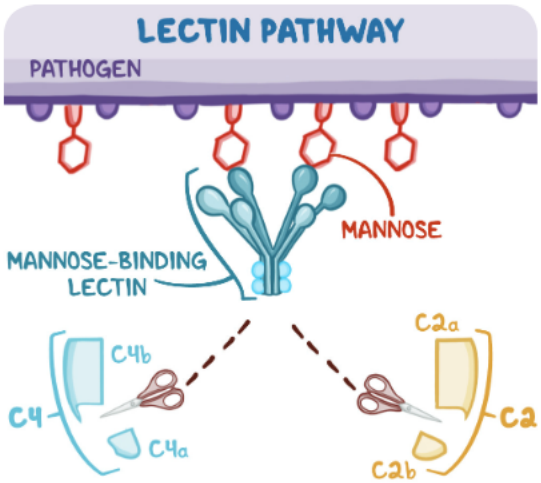


Figure 47.5 Overview of the lectin pathway. Mannose-binding lectin protein binds to mannose on the pathogen, then cleaves C4 and C2. The rest follows the classical pathway (from step 4 in earlier figure).

OTHER COMPLEMENT PROTEIN ROLES

- In addition to MAC-formation
  - C3b: opsonin → opsonizes pathogens, coats them with molecules, encourages phagocytosis
  - C5a, C3a: chemotaxins → recruit neutrophils, eosinophils, monocytes, macrophages
  - C5a, C3a: anaphylatoxins → cause basophil, mast cell degranulation, releases proinflammatory molecules

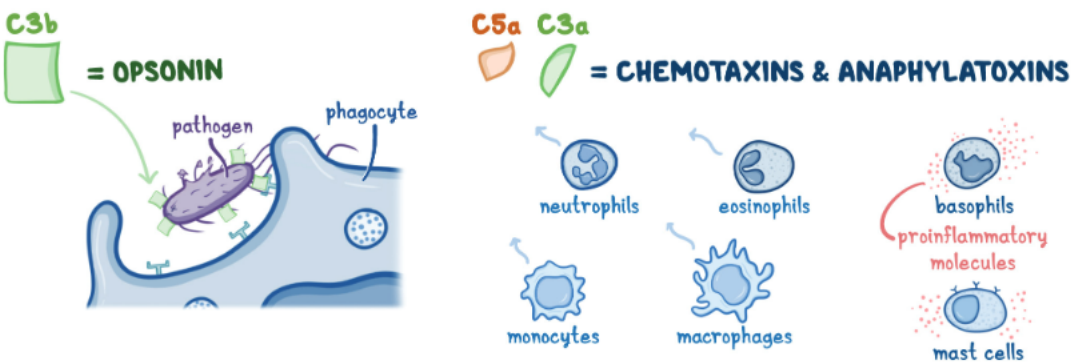


Figure 47.6 Other roles of complement proteins. C3b acts as an opsonin; it coats pathogens to facilitate phagocytosis. C5a and C3a act as chemotaxins; they recruit neutrophils, eosinophils, monocytes, and macrophages. C5a and C3a also act as anaphylatoxins; they cause basophils and mast cells to degranulate.