

HIGH-YIELD PRINCIPLES IN

Immunology

“I hate to disappoint you, but my rubber lips are immune to your charms.”

—Batman & Robin

“Imagine the action of a vaccine not just in terms of how it affects a single body, but also in terms of how it affects the collective body of a community.”

—Eula Biss

“Some people are immune to good advice.”

—Saul Goodman, *Breaking Bad*

Learning the components of the immune system and their roles in host defense at the cellular level is essential for both the understanding of disease pathophysiology and clinical practice. Know the immune mechanisms of responses to vaccines. Both congenital and acquired immunodeficiencies are very testable. Cell surface markers are high yield for understanding immune cell interactions and for laboratory diagnosis. Know the roles and functions of major cytokines and chemokines.

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► IMMUNOLOGY—LYMPHOID STRUCTURES

Immune system organs

1° organs:

- Bone marrow—immune cell production, **B** cell maturation
- Thymus—**T** cell maturation

2° organs:

- Spleen, lymph nodes, tonsils, adenoids, appendix, Peyer patches
- Allow immune cells to interact with antigen

Lymph nodeA 2° lymphoid organ that has many afferents, 1 or more efferents. Encapsulated, with trabeculae **A**.

Functions are nonspecific filtration by macrophages, circulation of B and T cells, and immune response activation.

Follicle

Located in outer cortex; site of B-cell localization and proliferation. 1° follicles are dense and quiescent. 2° follicles have pale central germinal centers and are active.

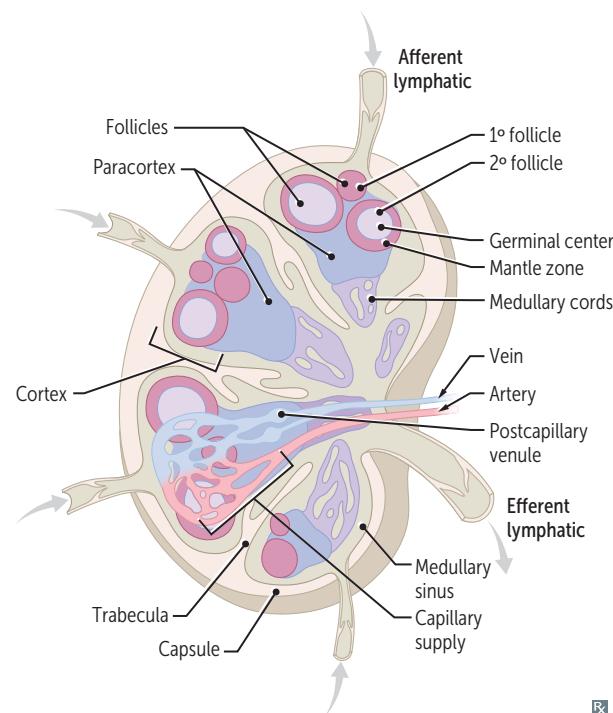
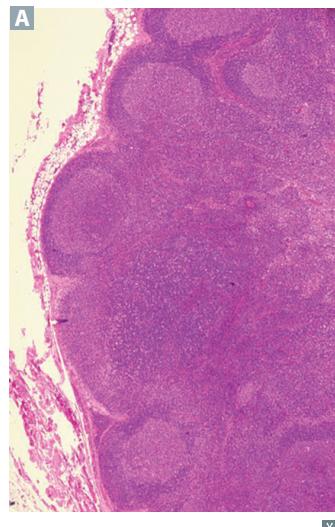
Medulla

Consists of medullary cords (closely packed lymphocytes and plasma cells) and medullary sinuses (contain reticular cells and macrophages). Medullary sinuses communicate with efferent lymphatics.

Paracortex

Contains T cells. Region of cortex between follicles and medulla. Contains high endothelial venules through which T and B cells enter from blood. Underdeveloped in patients with DiGeorge syndrome.

Paracortex enlarges in an extreme cellular immune response (eg, EBV and other viral infections → paracortical hyperplasia → lymphadenopathy).

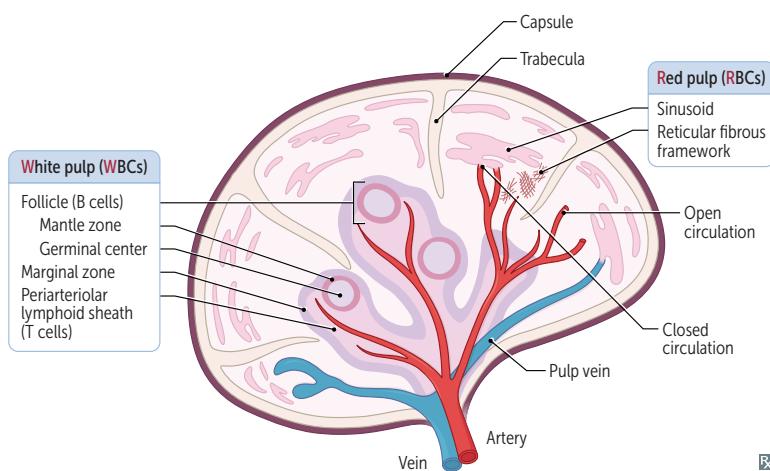


Lymphatic drainage associations

Lymph node cluster	Area of body drained	Associated pathology
Submandibular, submental	Oral cavity, anterior tongue, lower lip	Malignancy of and metastasis to the oral cavity
Deep cervical	Head, neck, oropharynx	Upper respiratory tract infection Infectious mononucleosis Kawasaki disease Malignancy of head, neck, oropharynx
Supraclavicular	Right: right hemithorax Left (Virchow node): left hemithorax, abdomen, pelvis	Malignancies of thorax, abdomen, pelvis
Mediastinal	Trachea, esophagus	Pulmonary TB (unilateral hilar) Sarcoidosis (bilateral hilar)
Hilar	Lungs	Lung cancer Granulomatous disease
Axillary	Upper limb, breast, skin above umbilicus	Mastitis Metastasis (especially breast cancer)
Epitrochlear	Hand, forearm	Secondary syphilis
Celiac	Liver, stomach, spleen, pancreas, upper duodenum	
Superior mesenteric	Lower duodenum, jejunum, ileum, colon to splenic flexure	Mesenteric lymphadenitis Inflammatory bowel disease Celiac disease
Inferior mesenteric	Colon from splenic flexure to upper rectum	
Perumbilical (Sister Mary Joseph node)	Abdomen, pelvis	Gastric cancer
Para-aortic	Pair of testes, ovaries, kidneys, fallopian tubes, fundus of uterus	Metastasis
External iliac	Body of uterus, cervix, superior bladder	
Internal iliac	Cervix, proximal vagina, corpus cavernosum, prostate, inferior bladder, lower rectum to anal canal (above pectinate line)	Sexually transmitted infections Medial foot/leg cellulitis (superficial inguinal)
Superficial inguinal	Distal vagina, vulva, scrotum, urethra, anal canal (below pectinate line), skin below umbilicus (except popliteal area)	
Popliteal ("pop-lateral")	Dorsolateral foot, posterior calf	Lateral foot/leg cellulitis

■ Right lymphatic duct drains right side of body above diaphragm into junction of the right subclavian and internal jugular vein

■ Thoracic duct drains below the diaphragm and left thorax and upper limb into junction of left subclavian and internal jugular veins (rupture of thoracic duct can cause chylothorax)

Spleen

Located in LUQ of abdomen, anterolateral to left kidney, protected by 9th-11th ribs. Splenic dysfunction (eg, postsplenectomy, sickle cell disease autosplenectomy)
→ ↓ IgM → ↓ complement activation → ↓ C3b opsonization → ↑ susceptibility to encapsulated organisms, against which patients should be vaccinated (from most to least common: pneumococci, meningococci, *Haemophilus influenzae* type b [Hib]).

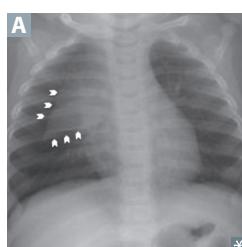
Postsplenectomy findings:

- Howell-Jolly bodies (nuclear remnants)
- Target cells
- Thrombocytosis (loss of sequestration and removal)
- Lymphocytosis (loss of sequestration)

Periarteriolar lymphatic sheath Contains T cells. Located within white pulp.

Follicle Contains B cells. Located within white pulp.

Marginal zone Contains macrophages and specialized B cells. Site where antigen-presenting cells (APCs) capture blood-borne antigens for recognition by lymphocytes. Located between red pulp and white pulp.

Thymus

Located in the anterosuperior mediastinum. Site of T-cell differentiation and maturation. Encapsulated. Thymus epithelium is derived from third pharyngeal pouch (endoderm), whereas thymic lymphocytes are of mesodermal origin. Cortex is dense with immature T cells; medulla is pale with mature T cells and Hassall corpuscles containing epithelial reticular cells. Normal neonatal thymus “sail-shaped” on CXR (arrows in A), involutes by age 3 years.

T cells = Thymus

B cells = Bone marrow

Absent thymic shadow or hypoplastic thymus seen in some immunodeficiencies (eg, SCID, DiGeorge syndrome).

Thymoma—neoplasm of thymus. Associated with myasthenia gravis, superior vena cava syndrome, pure red cell aplasia, Good syndrome.

► IMMUNOLOGY—CELLULAR COMPONENTS

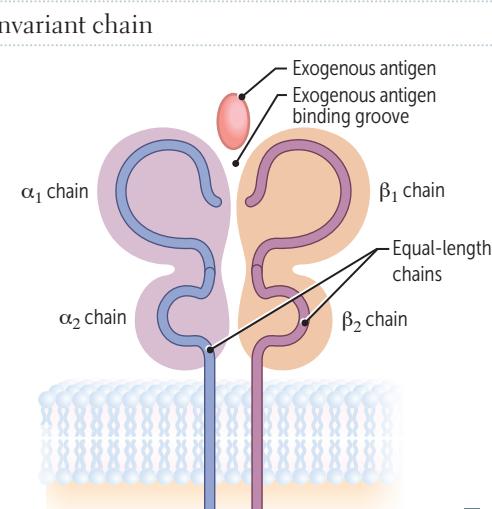
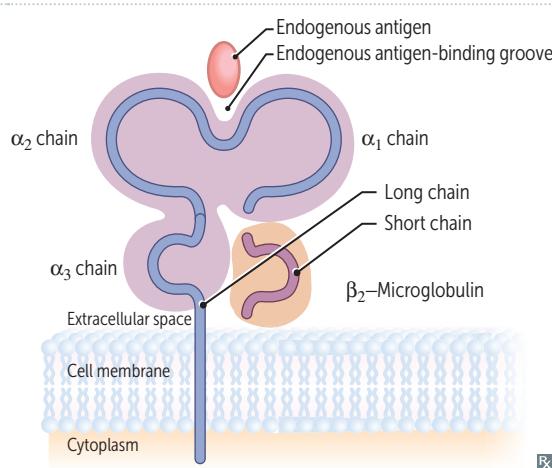
Innate vs adaptive immunity

	Innate immunity	Adaptive immunity
COMPONENTS	Neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells (lymphoid origin), complement, physical epithelial barriers, secreted enzymes.	T cells, B cells, circulating antibodies.
MECHANISM	Germline encoded.	Variation through V(D)J recombination during lymphocyte development.
RESPONSE TO PATHOGENS	Nonspecific. Occurs rapidly (minutes to hours). No memory response.	Highly specific, refined over time. Develops over long periods; memory response is faster and more robust.
SECRETED PROTEINS	Lysozyme, complement, C-reactive protein (CRP), defensins, cytokines.	Immunoglobulins, cytokines.
KEY FEATURES IN PATHOGEN RECOGNITION	Toll-like receptors (TLRs): pattern recognition receptors that recognize pathogen- and damage-associated molecular patterns (PAMPs and DAMPs) → activation of NF-κB → release of pro-inflammatory cytokines. Examples of PAMPs: LPS (gram ⊖ bacteria), flagellin (bacteria), nucleic acids (viruses). Examples of DAMPs: mitochondrial DNA, histones, heat shock proteins.	Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen → stronger, quicker immune response. Adaptive immune responses decrease with age (immunosenescence).
Immune privilege	Organs (eg, eye, brain, placenta, testes) and tissues where chemical or physical mechanisms limit immune responses to foreign antigens to avoid damage that would occur from inflammatory sequelae. Allograft rejection at these sites is less likely.	

Major histocompatibility complex I and II

MHC encoded by HLA genes. Present antigen fragments to T cells and bind T-cell receptors (TCRs).

	MHC I	MHC II
LOCI	HLA-A, HLA-B, HLA-C MHC I loci have 1 letter	HLA-DP, HLA-DQ, HLA-DR MHC II loci have 2 letters
BINDING	TCR and CD8 ($CD8 \times MHC\ 1 = 8$)	TCR and CD4 ($CD4 \times MHC\ 2 = 8$)
STRUCTURE	1 long chain, 1 short chain ($3\ \alpha, 1\ \beta$)	2 equal-length chains ($2\ \alpha, 2\ \beta$)
EXPRESSION	All nucleated cells, APCs, platelets (except RBCs)	APCs
FUNCTION	Present endogenous antigens (eg, viral or cytosolic proteins) to CD8+ cytotoxic T cells	Present exogenous antigens (eg, bacterial proteins) to CD4+ helper T cells
ANTIGEN LOADING	Antigen peptides loaded onto MHC I in RER after delivery via TAP (transporter associated with antigen processing)	Antigen loaded following release of invariant chain in an acidified endosome
ASSOCIATED PROTEINS	β_2 -microglobulin	Invariant chain

STRUCTURE**HLA subtypes associated with diseases**

HLA SUBTYPE	DISEASE	MNEMONIC
B27	Psoriatic arthritis, Ankylosing spondylitis, IBD-associated arthritis, Reactive arthritis	PAIR
DR3	DM type 1, SLE, Graves disease, Hashimoto thyroiditis, Addison disease	DM type 1 : HLA- 3 and - 4 ($1 + 3 = 4$) SL3 (SLE)
DR4	Rheumatoid arthritis, DM type 1 , Addison disease	There are 4 walls in 1 “rheum” (room)

Major functions of natural killer cells

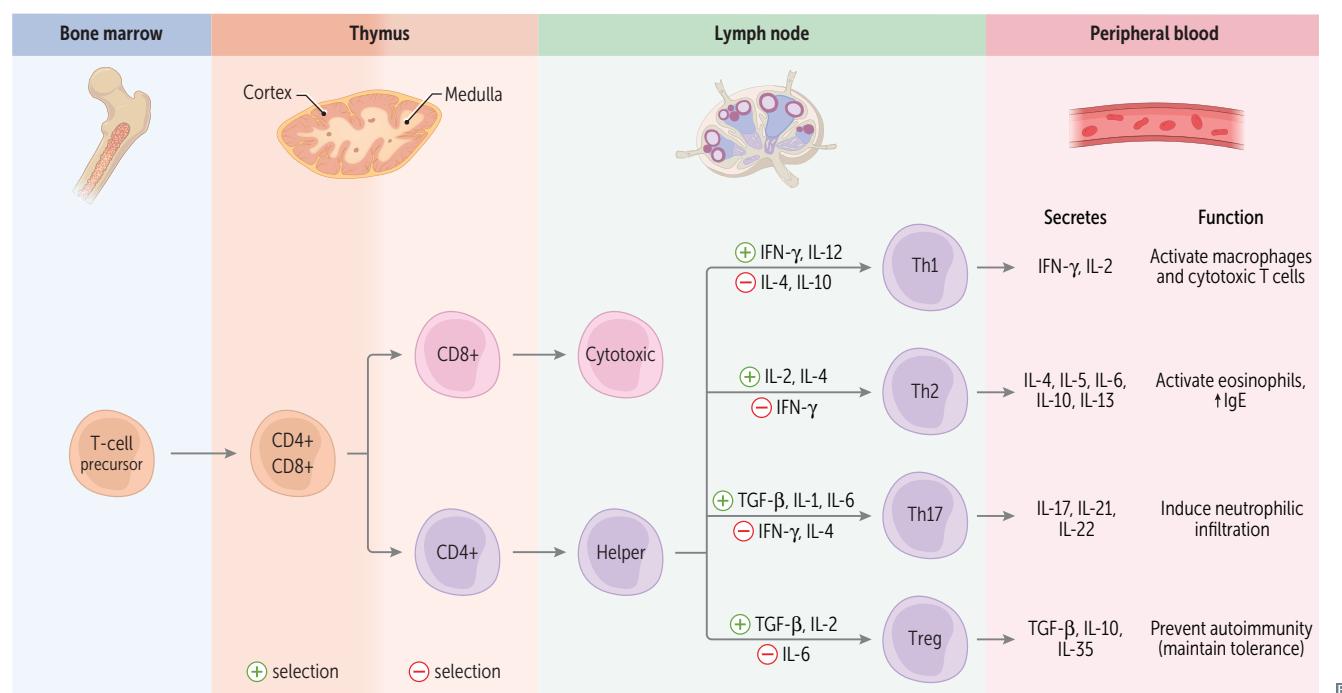
Lymphocyte member of innate immune system.
Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.
Activity enhanced by IL-2, IL-12, IFN- α , and IFN- β . Produce IFN- γ → macrophage activation.
Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of an inhibitory signal such as MHC I on target cell surface.
Also kills via antibody-dependent cell-mediated cytotoxicity (CD16 binds Fc region of bound IgG, activating the NK cell).

Major functions of B and T cells**B cells**

Humoral immunity.
Recognize and present antigen—undergo somatic hypermutation to optimize antigen specificity.
Produce antibody—differentiate into plasma cells to secrete specific immunoglobulins.
Maintain immunologic memory—memory B cells persist and accelerate future response to antigen.

T cells

Cell-mediated immunity.
CD4+ T cells help B cells make antibodies and produce cytokines to recruit phagocytes and activate other leukocytes.
CD8+ T cells directly kill virus-infected and tumor cells via perforin and granzymes (similar to NK cells).
Type IV hypersensitivity reaction.
Acute and chronic cellular organ rejection.

Differentiation of T cells**Positive selection**

Thymic cortex. Keeps T cells that recognize self-peptides to allow for cooperation in immune responses. Double positive thymocytes expressing TCRs that recognize self-peptide MHC complexes receive a survival signal.

Negative selection

Thymic medulla. Removes T cells that bind too strongly to self-peptides. Thymocytes expressing TCRs with high affinity for self antigens undergo apoptosis or become regulatory T cells. The autoimmune regulator (AIRE) protein drives negative selection, and deficiency leads to autoimmune polyendocrine syndrome (Chronic mucocutaneous candidiasis, Hypoparathyroidism, Adrenal insufficiency, Recurrent *Candida* infections). “Without AIRE, your body will CHAR”.

Macrophage-lymphocyte interaction

Th1 cells secrete IFN- γ , which enhances the ability of monocytes and macrophages to kill microbes they ingest. This function is also enhanced by interaction of T cell CD40L with CD40 on macrophages. Macrophages also activate lymphocytes via antigen presentation.

Cytotoxic T cells

Kill virus-infected, neoplastic, and donor graft cells by inducing apoptosis. Release cytotoxic granules containing preformed proteins (eg, perforin, granzyme B). Cytotoxic T cells have CD8, which binds to MHC I on virus-infected cells.

Regulatory T cells

Help maintain specific immune tolerance by suppressing CD4+ and CD8+ T-cell effector functions. Identified by expression of CD3, CD4, CD25, and FOXP3. Activated regulatory T cells (Tregs) produce anti-inflammatory cytokines (eg, IL-10, TGF- β).

IPEX (Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked) syndrome—genetic deficiency of FOXP3 → autoimmunity. Characterized by enteropathy, endocrinopathy, nail dystrophy, dermatitis, and/or other autoimmune dermatologic conditions. Associated with diabetes in male infants.

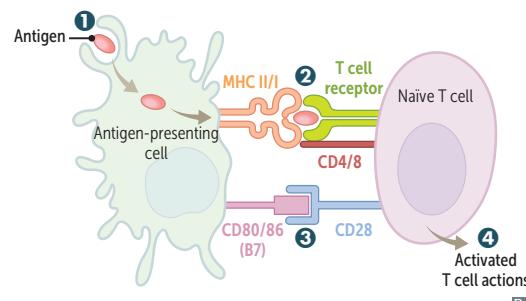
T- and B-cell activation

APCs: B cells, dendritic cells, Langerhans cells, macrophages.

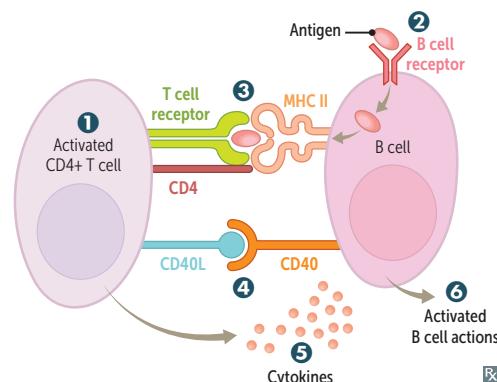
Two signals are required for T-cell activation, B-cell activation, and class switching.

T-cell activation

- ① APC ingests and processes antigen, then migrates to the draining lymph node.
- ② T-cell activation (signal 1): exogenous antigen is presented on MHC II and recognized by TCR on Th (CD4+) cell. Endogenous or cross-presented antigen is presented on MHC I to Tc (CD8+) cell.
- ③ Proliferation and survival (signal 2): costimulatory signal via interaction of B7 protein (CD80/86) on dendritic cell and CD28 on naïve T cell.
- ④ Activated Th cell produces cytokines. Tc cell able to recognize and kill virus-infected cell.

**B-cell activation and class switching**

- ① Th-cell activation as above.
- ② B-cell receptor-mediated endocytosis.
- ③ Exogenous antigen is presented on MHC II and recognized by TCR on Th cell.
- ④ CD40 receptor on B cell binds CD40 ligand (CD40L) on Th cell.
- ⑤ Th cells secrete cytokines that determine Ig class switching of B cells.
- ⑥ B cells are activated and produce IgM. They undergo class switching and affinity maturation.

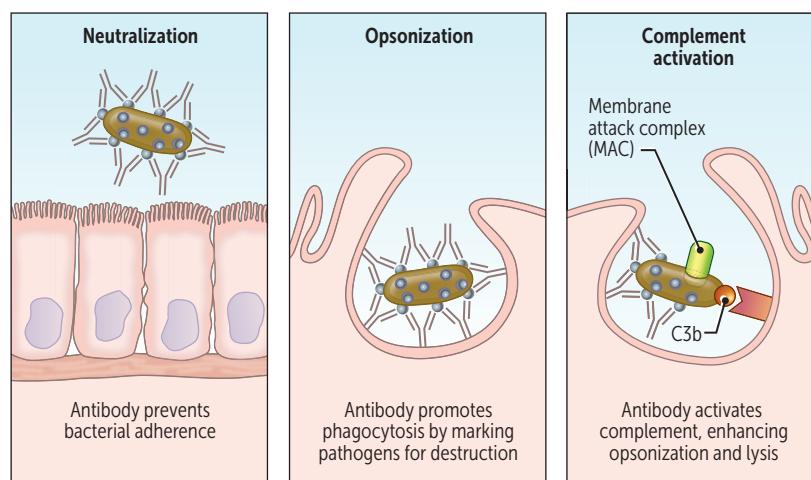
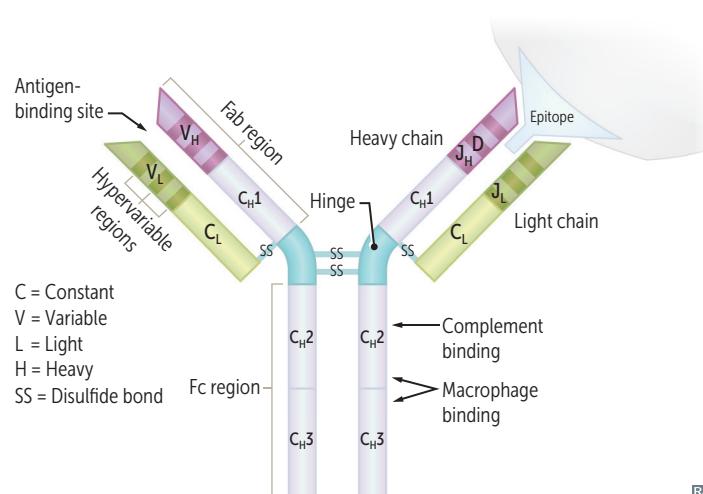
**Anergy**

State during which a cell cannot become activated by exposure to its antigen. T and B cells become anergic when exposed to their antigen without costimulatory signal (signal 2). Another example of peripheral tolerance mechanism.

► IMMUNOLOGY—IMMUNE RESPONSES

Antibody structure and function

Fab fragment consisting of light (L) and heavy (H) chains recognizes antigens. Fc region of IgM and IgG fixes complement. Heavy chain contributes to Fc and Fab regions. Light chain contributes only to Fab region.

**Fab:**

- Fragment, antigen binding
- Determines idioype: unique antigen-binding pocket; only 1 antigenic specificity expressed per B cell

Fc (5 C's):

- Constant
- Carboxy terminal
- Complement binding
- Carbohydrate side chains
- Confers (determines) isotype (IgM, IgD, etc)

Generation of antibody diversity (antigen independent)

1. Random recombination of VJ (light-chain) or V(D)J (heavy-chain) genes by RAG1 and RAG2
2. Random addition of nucleotides to DNA during recombination by terminal deoxynucleotidyl transferase (TdT)
3. Random combination of heavy chains with light chains

Generation of antibody specificity (antigen dependent)

4. Somatic hypermutation and affinity maturation (variable region)
5. Isotype switching (constant region)

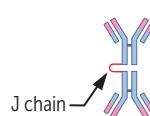
Immunoglobulin isotypes

All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgG, or IgE. “For B cells, IgM^{om} and IgD^{ad} mature to plasma cells as they AGE.”

Affinity refers to the individual antibody-antigen interaction, while avidity describes the cumulative binding strength of all antibody-antigen interactions in a multivalent molecule.

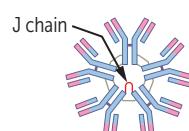
IgG

Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). “IgG Greets the Growing fetus.” Associated with warm autoimmune hemolytic anemia (“warm weather is Good!”).

IgA

Prevents attachment of bacteria and viruses to mucous membranes; does not fix complement.

Monomer (in circulation) or dimer (with J chain when secreted). Crosses epithelial cells by transcytosis. Produced in GI tract (eg, by Peyer patches) and protects against gut infections (eg, *Giardia*). Most produced antibody overall, but has lower serum concentrations. Released into secretions (tears, saliva, mucus) and breast milk. Picks up secretory component from epithelial cells, which protects the Fc portion from luminal proteases.

IgM

First antibody to be produced during an immune response. Fixes complement. Antigen receptor on the surface of B cells. Monomer on B cell, pentamer with J chain when secreted. Pentamer enables avid binding to antigen while humoral response evolves. Associated with cold autoimmune hemolytic anemia.

IgD

Expressed on the surface of mature, naïve B cells. Normally, low levels are detectable in serum.

IgE

Binds mast cells and basophils; cross-links when exposed to allergen, mediating immediate (type I) hypersensitivity through release of inflammatory mediators such as histamine. Contributes to immunity to parasites by activating Eosinophils.

Antigen type and memory**Thymus-independent antigens**

Antigens lacking a peptide component (eg, lipopolysaccharides from gram ⊖ bacteria); cannot be presented by MHC to T cells. Weakly immunogenic; vaccines often require boosters and adjuvants (eg, capsular polysaccharide subunit of *Streptococcus pneumoniae* PPSV23 vaccine).

Thymus-dependent antigens

Antigens containing a protein component (eg, diphtheria toxoid). Class switching and immunologic memory occur as a result of direct contact of B cells with Th cells.

Complement

System of hepatically synthesized plasma proteins that play a role in innate immunity and inflammation. Membrane attack complex (MAC) defends against gram \ominus bacteria. The CH₅₀ test is used to screen for activation of the classical complement pathway.

ACTIVATION PATHWAYS

Classic—IgG or IgM mediated.

General Motors makes **classic** cars.

Alternative—bacterial products.

Lectin—mannose or other sugars on microbe surface.

FUNCTIONS

C3b—opsonization.

C3b binds to lipopolysaccharides on **bacteria**.

C3a, C4a, C5a—anaphylaxis.

MAC complex is important for neutralizing

Neisseria species. Deficiency results in recurrent infection.

C5a—neutrophil chemotaxis.

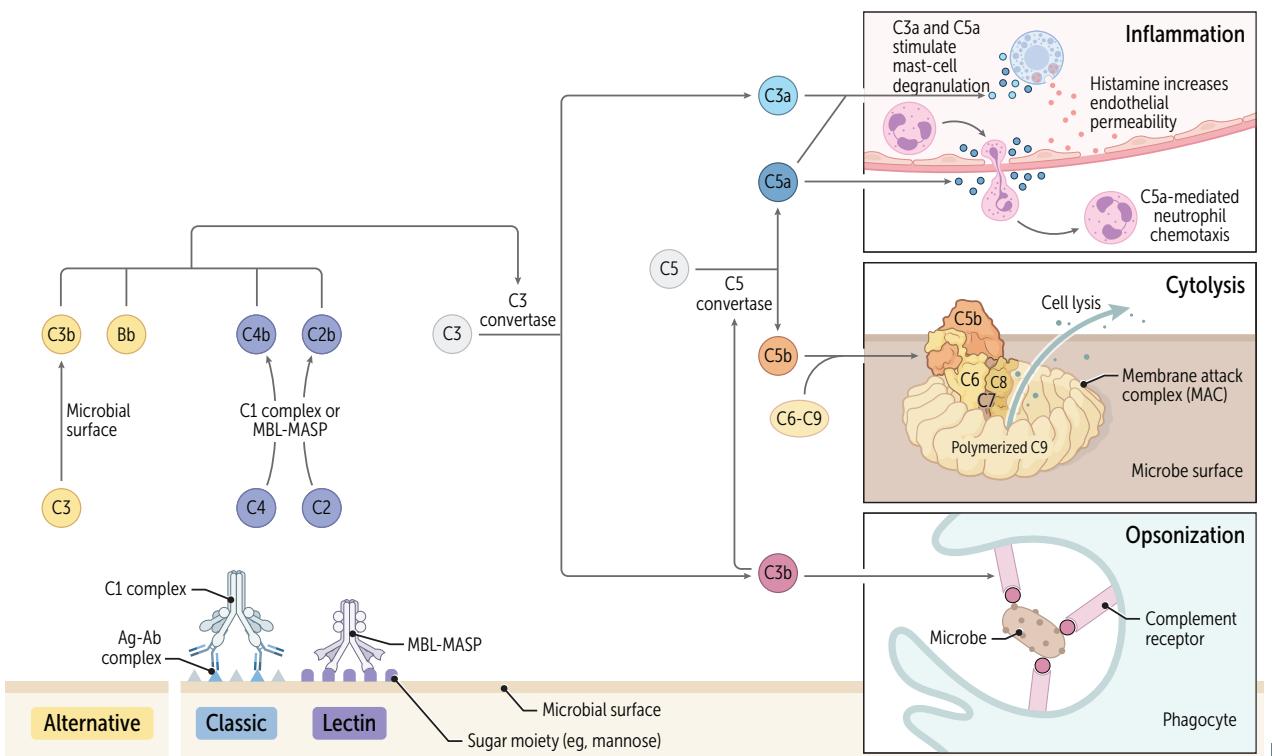
Get “**Neis**” (nice) Big **MACs** from **5-9 pm**.

C5b-9 (MAC)—cytolysis.

Opsonin (Greek) = to prepare for eating.

Opsonins—C3b and IgG are the two 1° opsonins in bacterial defense; enhance phagocytosis. C3b also helps clear immune complexes.

Inhibitors—decay-accelerating factor (DAF, also called CD55) and C1 inhibitor (formerly called C1 esterase inhibitor) help prevent complement activation on self cells (eg, RBCs).



Complement disorders

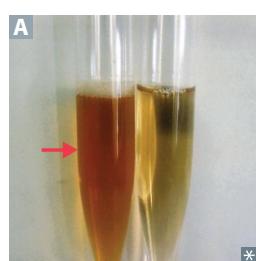
Complement protein deficiencies

- Early complement deficiencies (C1–C4)** ↑ risk of severe, recurrent pyogenic sinus and respiratory tract infections. C3b used in clearance of antigen-antibody complexes → ↑ risk of **SLE** (think **SLEarly**).
- Terminal complement deficiencies (C5–C9)** ↑ susceptibility to recurrent *Neisseria* bacteremia.

Complement regulatory protein deficiencies

- C1 inhibitor deficiency** Causes hereditary angioedema due to unregulated activation of kallikrein → ↑ bradykinin. Characterized by ↓ C4 levels. ACE inhibitors are contraindicated (also ↑ bradykinin).

- Paroxysmal nocturnal hemoglobinuria** A defect in the *PIGA* gene prevents the formation of glycosylphosphatidylinositol (GPI) anchors for complement inhibitors, such as decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). Causes complement-mediated intravascular hemolysis → ↓ haptoglobin, dark urine **A**.



Can cause atypical venous thrombosis (eg, Budd-Chiari syndrome; portal vein, cerebral, or dermal thrombosis).

Treatment: eculizumab (anti-C5 antibody; inhibits terminal complement system and MAC formation).

Important cytokines Acute (IL-1, IL-6, TNF- α), then recruit (IL-8, IL-12).

Secreted by macrophages

Interleukin-1

Causes fever, acute inflammation. Activates endothelium to express adhesion molecules. Induces chemokine secretion to recruit WBCs. Also called osteoclast-activating factor.

"Hot T-bone stEAK":

IL-1: fever (**hot**).
 IL-2: stimulates **T** cells.
 IL-3: stimulates **bone** marrow.
 IL-4: stimulates Ig**E** production.
 IL-5: stimulates Ig**A** production.
 IL-6: stimulates a**K**ute-phase protein production.

Interleukin-6

Causes fever and stimulates production of acute-phase proteins.

Causes cachexia in malignancy.
 Maintains granulomas in TB.
 IL-1, IL-6, TNF- α can mediate fever and sepsis.

Tumor necrosis factor- α

Activates endothelium. Causes WBC recruitment, vascular leak.

"Clean up on aisle 8." Neutrophils are recruited by **IL-8** to **clear** infections.

Interleukin-8

Major chemotactic factor for neutrophils.

Interleukin-12

Induces differentiation of T cells into Th1 cells. Activates NK cells.

Facilitates granuloma formation in TB.

Secreted by T cells

Interleukin-2

Stimulates growth of helper, cytotoxic, and regulatory T cells, and NK cells.

Stimulates proliferation of eosinophils, basophils, neutrophils, monocytes.

From Th1 cells

Interferon-gamma

Secreted by NK cells and T cells in response to antigen or IL-12 from macrophages; stimulates macrophages to kill phagocytosed pathogens. Inhibits differentiation of Th2 cells. Induces Ig**G** isotype switching in B cells.

Increases MHC expression and antigen presentation by all cells.
 Activates macrophages to induce granuloma formation.

From Th2 cells

Interleukin-4

Induces differentiation of T cells into Th (**helper**) **2** cells. Promotes growth of **B** cells. Enhances class switching to Ig**E** and Ig**G**.

Ain't too proud **2 BEG 4 help**.

Interleukin-5

Promotes growth and differentiation of **B** cells. Enhances class switching to Ig**A**. Stimulates growth and differentiation of Eosinophils.

I have **5 BAEs**.

Interleukin-10

Attenuates inflammatory response. Decreases expression of MHC class II and Th1 cytokines. Inhibits activated macrophages and dendritic cells. Also secreted by regulatory T cells.

TGF- β and IL-10 both **attenuate** the immune response.

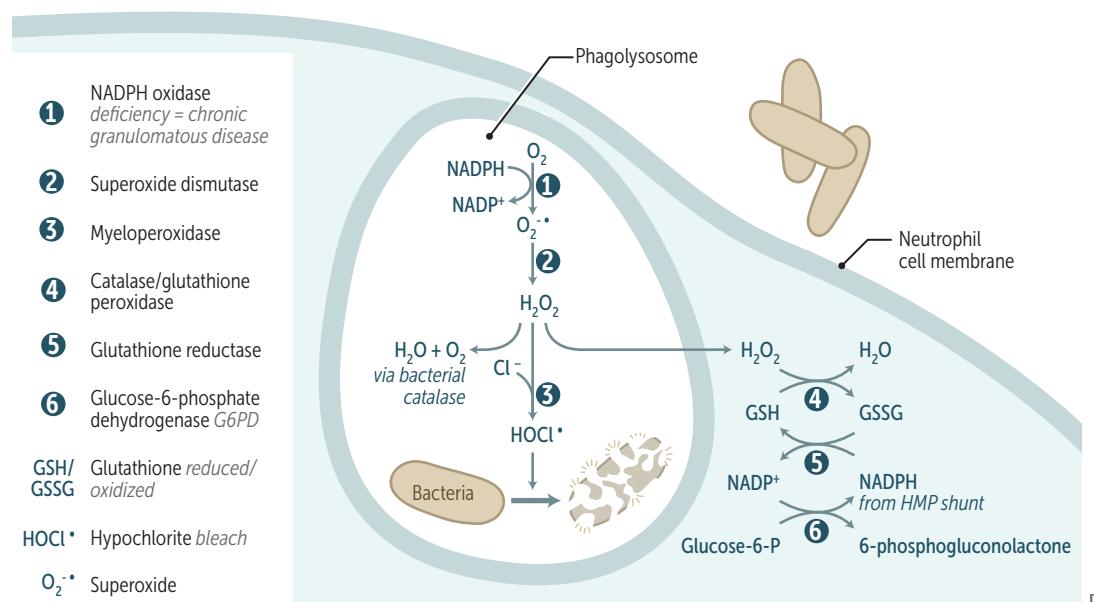
Interleukin-13

Promotes Ig**E** production by B cells. Induces alternative macrophage activation.

Interleukin thirteEN promotes Ig**E**.

Respiratory burst

Also called oxidative burst. Involves the activation of the phagocyte NADPH oxidase complex (eg, in neutrophils, monocytes), which utilizes O₂ as a substrate. Plays an important role in the immune response → rapid release of reactive oxygen species (ROS). NADPH plays a role in both the creation and neutralization of ROS. Myeloperoxidase contains a blue-green, heme-containing pigment that gives sputum its color. **NO Safe Microbe (NADPH Oxidase → Superoxide dismutase → Myeloperoxidase).**



Phagocytes of patients with CGD can utilize H₂O₂ generated by invading organisms and convert it to ROS. Patients are at ↑ risk for infection by catalase + species (eg, *S aureus*, *Aspergillus*) capable of neutralizing their own H₂O₂, leaving phagocytes without ROS for fighting infections. Pyocyanin of *P aeruginosa* generates ROS to kill competing pathogens. Oxidative burst leads to release of lysosomal enzymes.

Type I interferonsIFN- α , IFN- β .

MECHANISM

A part of innate host defense, **interferons interfere** with both RNA and DNA viruses. Cells infected with a virus synthesize these glycoproteins, which act on local cells, priming them for viral defense by downregulating protein synthesis to resist potential viral replication and by upregulating MHC expression to facilitate recognition of infected cells. Also play a major role in activating antitumor immunity.

CLINICAL USE

Chronic HBV, Kaposi sarcoma, hairy cell leukemia, condyloma acuminatum, renal cell carcinoma, malignant melanoma, multiple sclerosis.

ADVERSE EFFECTS

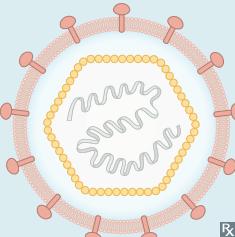
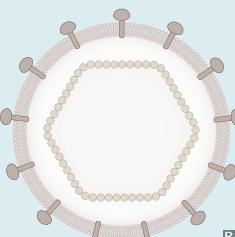
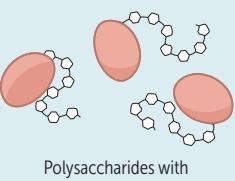
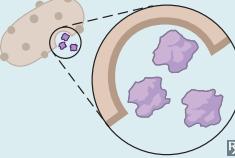
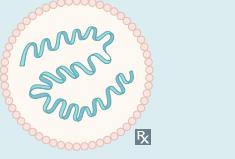
Flulike symptoms, depression, neutropenia, myopathy, interferon-induced autoimmunity.

Cell surface proteins

T cells	TCR (binds antigen-MHC complex), CD3 (associated with TCR for signal transduction), CD28 (binds B7 on APC)
Helper T cells	CD4, CD40L, CXCR4/CCR5 (coreceptors for HIV)
Cytotoxic T cells	CD8
Regulatory T cells	CD4, CD25
B cells	Ig (binds antigen), CD19, CD20, CD21 (receptor for Epstein-Barr virus), CD40, MHC II, B7 (CD80/86)
NK cells	CD16 (binds Fc of IgG), CD56 (suggestive marker for NK cells)
Macrophages	CD14 (receptor for PAMPs [eg, LPS]), CD40, CCR5, MHC II, B7, Fc and C3b receptors (enhanced phagocytosis)
Hematopoietic stem cells	CD34

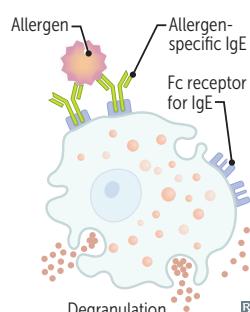
Passive vs active immunity

	Passive	Active
MEANS OF ACQUISITION	Receiving preformed antibodies	Exposure to exogenous antigens
ONSET	Rapid	Slow
DURATION	Short span of antibodies (half-life = 3 weeks)	Long-lasting protection (memory)
EXAMPLES	IgA in breast milk, maternal IgG crossing placenta, antitoxin, humanized monoclonal antibody	Natural infection, vaccines, toxoid
NOTES	IVIG and other immune globulin preparations can be administered to provide temporary but specific passive immunity to a target pathogen	Combined passive and active immunizations can be given for hepatitis B or rabies exposure

Vaccination	Induces an active immune response (humoral and/or cellular) to specific pathogens.		
VACCINE TYPE	DESCRIPTION	PROS/CONS	EXAMPLES
Live attenuated vaccine	<p>Microorganism rendered nonpathogenic but retains capacity for transient growth within inoculated host.</p> <p>Certain live vaccines (MMR, varicella) may be given to people living with HIV who have a CD4+ cell count ≥ 200 cells/mm³ in consultation with a specialist in infectious disease or immunology.</p> 	<p>Pros: induces cellular and humoral responses. Induces strong, often lifelong immunity.</p> <p>Cons: may revert to virulent form. Contraindicated in pregnancy and patients with immunodeficiency.</p>	<p>Adenovirus (nonattenuated, given to military recruits), typhoid (Ty21a, oral), polio (Sabin), varicella (chickenpox), smallpox, BCG, yellow fever, influenza (intranasal), MMR, rotavirus.</p> <p>Attention teachers! Please vaccinate small, Beautiful young infants with MMR routinely!</p>
Killed or inactivated vaccine	<p>Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response.</p> 	<p>Pros: safer than live vaccines.</p> <p>Cons: weaker cell-mediated immune response; mainly induces a humoral response. Booster shots usually needed.</p>	<p>Hepatitis A, Typhoid (Vi polysaccharide, intramuscular), Rabies, Influenza (intramuscular), Polio (Sal^K).</p> <p>A TRIP could Kill you.</p>
Subunit, recombinant, polysaccharide, and conjugate	<p>All use specific antigens that best stimulate the immune system.</p>  <p>Polysaccharides with conjugate proteins</p>	<p>Pros: targets specific epitopes of antigen; lower chance of adverse reactions.</p> <p>Cons: expensive; weaker immune response.</p>	<p>HBV (antigen = HBsAg), HPV, acellular pertussis (aP), <i>Neisseria meningitidis</i> (various strains), <i>Streptococcus pneumoniae</i> (PPSV23 polysaccharide primarily T-cell-independent response; PCV13, PCV15, and PCV20 polysaccharide produces T-cell-dependent response), Hib, herpes zoster.</p>
Toxoid	<p>Denatured bacterial toxin with an intact receptor binding site. Stimulates immune system to make antibodies without potential for causing disease.</p> 	<p>Pros: protects against the bacterial toxins.</p> <p>Cons: antitoxin levels decrease with time, thus booster shots may be needed.</p>	<p><i>Clostridium tetani</i>, <i>Corynebacterium diphtheriae</i>.</p>
mRNA	<p>A lipid nanoparticle delivers mRNA, causing cells to synthesize foreign protein (eg, spike protein of SARS-CoV-2).</p> 	<p>Pros: high efficacy; induces cellular and humoral immunity. Safe in pregnancy.</p> <p>Cons: local and transient systemic (fatigue, headache, myalgia) reactions are common. Rare myocarditis, pericarditis particularly in young males.</p>	<p>SARS-CoV-2.</p>

Hypersensitivity types

Four types: Anaphylactic and atopic (type I), antibody-mediated (type II), immune complex (type III), cell-mediated (type IV). Types I, II, and III are all antibody-mediated.

Type I hypersensitivity

Anaphylactic and atopic—two phases:

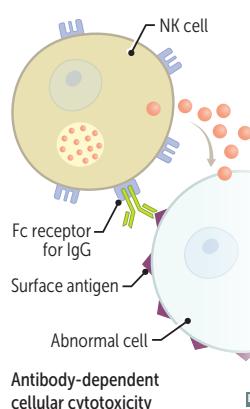
- Immediate (minutes): antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine), tryptase (marker of mast cell activation), and leukotrienes.
- Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and other mediators from mast cells → inflammation and tissue damage.

First (type) and **Fast** (anaphylaxis).

Test: skin test or blood test (ELISA) for allergen-specific IgE.

Example:

- Anaphylaxis (eg, food, drug, or bee sting allergies)
- Allergic asthma

Type II hypersensitivity

Antibodies bind to cell-surface antigens or extracellular matrix → cellular destruction, inflammation, and cellular dysfunction.

Cellular destruction—cell is opsonized (coated) by antibodies, leading to either:

- Phagocytosis and/or activation of complement system.
- NK cell killing (antibody-dependent cellular cytotoxicity).

Inflammation—binding of antibodies to cell surfaces → activation of complement system and Fc receptor-mediated inflammation.

Cellular dysfunction—antibodies bind to cell-surface receptors → abnormal blockade or activation of downstream process.

Direct Coombs test—detects antibodies attached **directly** to the RBC surface.

Indirect Coombs test—detects presence of unbound antibodies in the serum.

Examples:

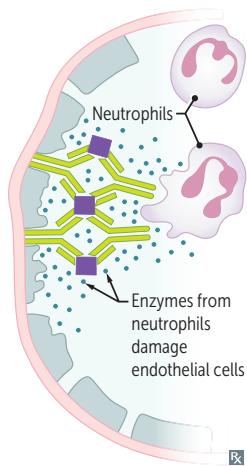
- Autoimmune hemolytic anemia (including drug-induced form)
- Immune thrombocytopenia
- Transfusion reactions
- Hemolytic disease of the newborn

Examples:

- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

Examples:

- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris

Hypersensitivity types (continued)**Type III hypersensitivity**

Immune complex—antigen-antibody (mostly IgG) complexes activate complement, which attracts neutrophils; neutrophils release lysosomal enzymes.
Can be associated with vasculitis and systemic manifestations.

In type **III** reaction, imagine an immune complex as **3** things stuck together: antigen-antibody-complement.

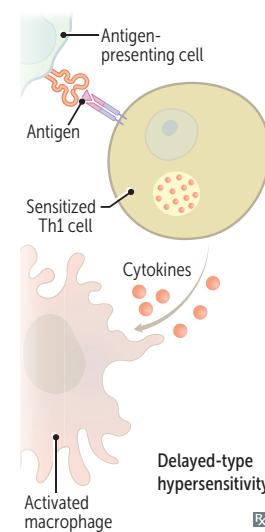
Examples:

- SLE
- Reactive arthritis
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis
- IgA vasculitis

Fever, urticaria, arthralgia, proteinuria, lymphadenopathy occur 1–2 weeks after antigen exposure. Serum sickness-like reactions are associated with some drugs (may act as haptens, eg, penicillin, monoclonal antibodies) and infections (eg, hepatitis B).

Serum sickness—the prototypic immune complex disease. Antibodies to foreign proteins are produced and 1–2 weeks later, antibody-antigen complexes form and deposit in tissues → complement activation → inflammation and tissue damage (↓ serum C3, C4).

Arthus reaction—a local subacute immune complex-mediated hypersensitivity reaction. Intradermal injection of antigen into a presensitized (has circulating IgG) individual leads to immune complex formation in the skin (eg, enhanced local reaction to a booster vaccination). Characterized by edema, fibrinoid necrosis, activation of complement.

Type IV hypersensitivity

Two mechanisms, each involving T cells:

1. Direct cell cytotoxicity: CD8+ cytotoxic T cells kill targeted cells.
2. Inflammatory reaction: effector CD4+ T cells recognize antigen and release inflammation-inducing cytokines (shown in illustration).

Response does not involve antibodies (vs types I, II, and III).

Examples:

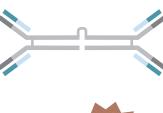
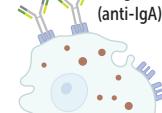
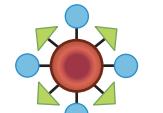
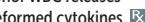
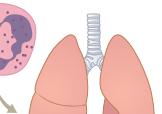
- Contact dermatitis (eg, poison ivy, nickel allergy)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Graft-versus-host disease

Tests: PPD for TB infection; patch test for contact dermatitis; *Candida* skin test for T cell immune function.

4T's: **T** cells, **T**ransplant rejections, **T**B skin tests, **T**ouching (contact dermatitis).

Fourth (type) and **last** (delayed).

Immunologic blood transfusion reactions

TYPE	PATHOGENESIS	TIMING	CLINICAL PRESENTATION	DONOR BLOOD	HOST BLOOD
Allergic/ anaphylactic reaction	Type I hypersensitivity reaction against plasma proteins in transfused blood IgA-deficient individuals should receive blood products without IgA	Within minutes to 2–3 hr (due to release of preformed inflammatory mediators in degranulating mast cells)	Allergies: urticaria, pruritus Anaphylaxis: wheezing, hypotension, respiratory arrest, shock	 Donor plasma proteins, including IgA	 Host mast cell 
Acute hemolytic transfusion reaction	Type II hypersensitivity reaction Typically causes intravascular hemolysis (ABO blood group incompatibility)	During transfusion or within 24 hr (due to preformed antibodies)	Fever, hypotension, tachypnea, tachycardia, flank pain, hemoglobinuria (intravascular), jaundice (extravascular)	 Donor RBC with A and/or B group antigens	 Host anti-A, anti-B IgG, IgM 
Febrile nonhemolytic transfusion reaction	Cytokines created by donor WBCs accumulate during storage of blood products Reactions prevented by leukoreduction of blood products	Within 1–6 hr (due to preformed cytokines)	Fever, headaches, chills, flushing More common in children	 Donor WBC releases preformed cytokines 	
Transfusion- related acute lung injury	Two-hit mechanism: <ul style="list-style-type: none">▪ Neutrophils are sequestered and primed in pulmonary vasculature due to recipient risk factors▪ Neutrophils are activated by a product (eg, antileukocyte antibodies) in the transfused blood and release inflammatory mediators → ↑ capillary permeability → pulmonary edema	Within minutes to 6 hr	Respiratory distress, noncardiogenic pulmonary edema	 Donor antileukocyte antibody	 
Delayed hemolytic transfusion reaction	Anamnestic response to a foreign antigen on donor RBCs (Rh [D] or other minor blood group antigens) previously encountered by recipient Typically causes extravascular hemolysis	Onset over 24 hr Usually presents within 1–2 wk (due to slow destruction by reticuloendothelial system)	Generally self limited and clinically silent Mild fever, hyperbilirubinemia		

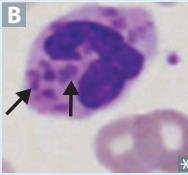
Autoantibodies

AUTOANTIBODY	ASSOCIATED DISORDER
Anti-postsynaptic ACh receptor	Myasthenia gravis
Anti-presynaptic voltage-gated Ca^{2+} channel	Lambert-Eaton myasthenic syndrome
Anti- β_2 glycoprotein I	Antiphospholipid syndrome
Antinuclear (ANA)	Nonspecific screening antibody, often associated with SLE
Anticardiolipin, lupus anticoagulant	SLE, antiphospholipid syndrome
Anti-dsDNA, anti-Smith	SLE
Antihistone	Drug-induced lupus
Anti-U1 RNP (ribonucleoprotein)	Mixed connective tissue disease
Rheumatoid factor (IgM antibody against IgG Fc region), anti-cyclic citrullinated peptide (anti-CCP, more specific)	Rheumatoid arthritis
Anti-Ro/SSA, anti-La/SSB	Sjögren syndrome
Anti-Scl-70 (anti-DNA topoisomerase I)	Scleroderma (diffuse)
Anticentromere	Limited scleroderma (CREST syndrome)
Antisynthetase (eg, anti-Jo-1), anti-SRP, anti-helicase (anti-Mi-2)	Polymyositis, dermatomyositis
Antimitochondrial	1° biliary cholangitis
Anti-smooth muscle, anti-liver/kidney microsomal-1	Autoimmune hepatitis
Myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)/perinuclear ANCA (p-ANCA)	Microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, ulcerative colitis, 1° sclerosing cholangitis
PR3-ANCA/cytoplasmic ANCA (c-ANCA)	Granulomatosis with polyangiitis
Anti-phospholipase A ₂ receptor	1° membranous nephropathy
Anti-hemidesmosome	Bullous pemphigoid
Anti-desmoglein (anti-desmosome)	Pemphigus vulgaris
Antithyroglobulin, antithyroid peroxidase (antimicrosomal)	Hashimoto thyroiditis
Anti-TSH receptor	Graves disease
IgA anti-endomysial, IgA anti-tissue transglutaminase, IgA and IgG deamidated gliadin peptide	Celiac disease
Anti-glutamic acid decarboxylase, islet cell cytoplasmic antibodies	Type 1 diabetes mellitus
Antiparietal cell, anti-intrinsic factor	Pernicious anemia
Anti-glomerular basement membrane	Goodpasture syndrome

Immunodeficiencies

DISEASE	DEFECT	PRESENTATION	FINDINGS
B-cell disorders			
X-linked (Bruton) agammaglobulinemia	Defect in BTK , a tyrosine kinase gene → no B -cell maturation; X-linked recessive (↑ in Boys)	Recurrent bacterial and enteroviral infections after 6 months (↓ maternal IgG)	Absent B cells in peripheral blood, ↓ Ig of all classes. Absent/scanty lymph nodes and tonsils (1° follicles and germinal centers absent) → live vaccines contraindicated
Selective IgA deficiency	May be familial or sporadic Most common 1° immunodeficiency May also arise 2° to certain viral infections or medications	Majority Asymptomatic Can see Airway and GI infections, Autoimmune disease , Atopy , Anaphylaxis to IgA in blood products	↓ IgA with normal IgG, IgM levels ↑ susceptibility to giardiasis Can cause false-negative celiac disease test and false-positive serum pregnancy test
Common variable immunodeficiency	Defect in B-cell differentiation. Cause unknown in most cases	May present in childhood but usually diagnosed after puberty ↑ risk of autoimmune disease, bronchiectasis, lymphoma, sinopulmonary infections	↓ plasma cells, ↓ immunoglobulins
T-cell disorders			
Thymic aplasia	22q11 microdeletion; failure to develop 3rd and 4th pharyngeal pouches → absent thymus and parathyroids DiGeorge syndrome —thymic, parathyroid, cardiac defects Velocardiofacial syndrome —palate, facial, cardiac defects	CATCH-22: Cardiac defects (conotruncal abnormalities [eg, tetralogy of Fallot, truncus arteriosus]), Abnormal facies , Thymic hypoplasia → T-cell deficiency (recurrent viral/fungal infections), Cleft palate , Hypocalcemia 2° to parathyroid aplasia → tetany	↓ T cells, ↓ PTH, ↓ Ca ²⁺ Thymic shadow absent on CXR
IL-12 receptor deficiency	↓ Th1 response; autosomal recessive	Disseminated mycobacterial and fungal infections; may present after administration of BCG vaccine	↓ IFN-γ Most common cause of Mendelian susceptibility to mycobacterial diseases (MSMD)
Autosomal dominant hyper-IgE syndrome (Job syndrome)	Deficiency of Th17 cells due to STAT3 mutation → impaired recruitment of neutrophils to sites of infection	Cold (noninflamed) staphylococcal Abscesses , retained Baby teeth , Coarse facies , Dermatologic problems (eczema), ↑ IgE, bone Fractures from minor trauma	↑ IgE ↑ eosinophils Learn the ABCDEF's to get a Job STAT!
Chronic mucocutaneous candidiasis	T-cell dysfunction Impaired cell-mediated immunity against <i>Candida</i> sp Classic form caused by defects in <i>AIRE</i>	Persistent noninvasive <i>Candida albicans</i> infections of skin and mucous membranes	Absent in vitro T-cell proliferation in response to <i>Candida</i> antigens Absent cutaneous reaction to <i>Candida</i> antigens

Immunodeficiencies (continued)

DISEASE	DEFECT	PRESENTATION	FINDINGS
B- and T-cell disorders			
Severe combined immunodeficiency	Several types including defective IL-2R gamma chain (most common, X-linked recessive); adenosine deaminase deficiency (autosomal recessive); RAG mutation → VDJ recombination defect	Failure to thrive, chronic diarrhea, thrush Recurrent viral, bacterial, fungal, and protozoal infections	↓ T-cell receptor excision circles (TRECs) Part of newborn screening for SCID Absence of thymic shadow (CXR), germinal centers (lymph node biopsy), and T cells (flow cytometry)
Ataxia-telangiectasia 	Defects in ATM gene → failure to detect DNA damage → failure to halt progression of cell cycle → mutations accumulate; autosomal recessive	Triad: cerebellar defects (Ataxia), spider Angiomas (telangiectasia A), IgA deficiency ↑ sensitivity to radiation (limit x-ray exposure)	↑ AFP ↓ IgA, IgG, and IgE Lymphopenia, cerebellar atrophy ↑ risk of lymphoma and leukemia
Hyper-IgM syndrome	Most commonly due to defective CD40L on Th cells → class switching defect; X-linked recessive	Severe pyogenic infections early in life; opportunistic infection with <i>Pneumocystis</i> , <i>Cryptosporidium</i> , CMV	Normal or ↑ IgM ↓ IgG, IgA, IgE Failure to make germinal centers
Wiskott-Aldrich syndrome	WAS mutation; leukocytes and platelets unable to reorganize actin cytoskeleton → defective antigen presentation; X-linked recessive	WATER: Wiskott-Aldrich: Thrombocytopenia, Eczema, Recurrent (pyogenic) infections ↑ risk of autoimmune disease and malignancy	↓ to normal IgG, IgM ↑ IgE, IgA Fewer and smaller platelets
Phagocyte dysfunction			
Leukocyte adhesion deficiency (type 1)	Autosomal recessive defect in LFA-1 integrin (CD18) protein on phagocytes leads to impaired migration and chemotaxis by C5a, IL-8, and leukotriene B4	Late separation (>30 days) of umbilical cord, absent pus, dysfunctional neutrophils → recurrent skin and mucosal bacterial infections	↑ neutrophils in blood Absence of neutrophils at infection sites → impaired wound healing
Chédiak-Higashi syndrome 	Defect in lysosomal trafficking regulator gene (LYST) Microtubule dysfunction in phagosome-lysosome fusion; autosomal recessive	PLAIN: Progressive neurodegeneration, Lymphohistiocytosis, Albinism (partial), recurrent pyogenic Infections, peripheral Neuropathy	Giant granules (B, arrows) in granulocytes and platelets Pancytopenia Mild coagulation defects
Chronic granulomatous disease	Defect of NADPH oxidase → ↓ reactive oxygen species (eg, superoxide) and ↓ respiratory burst in neutrophils; X-linked form most common	↑ susceptibility to catalase + organisms (granby's cats keep her positive) Recurrent infections and granulomas	Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence) Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue

Infections in immunodeficiency

PATHOGEN	↓ T CELLS	↓ B CELLS	↓ GRANULOCYTES	↓ COMPLEMENT
Bacteria	Sepsis	Encapsulated (Please SHINE my SKiS): <i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type b, <i>Neisseria meningitidis</i> , <i>Escherichia coli</i> , <i>Salmonella</i> , <i>Klebsiella pneumoniae</i> , group B <i>Streptococcus</i>	Some Bacteria Produce No Serious granules: <i>Staphylococcus</i> , <i>Burkholderia cepacia</i> , <i>Pseudomonas aeruginosa</i> , <i>Nocardia</i> , <i>Serratia</i>	Encapsulated species with early complement deficiencies <i>Neisseria</i> with late complement (C5–C9) deficiencies
Viruses	CMV, EBV, JC virus, VZV, chronic infection with respiratory/GI viruses	Enteroviral encephalitis, poliovirus (live vaccine contraindicated)	N/A	N/A
Fungi/parasites	<i>Candida</i> (local), PCP, <i>Cryptococcus</i>	GI giardiasis (no IgA)	<i>Candida</i> (systemic), <i>Aspergillus</i> , <i>Mucor</i>	N/A

Note: B-cell deficiencies tend to produce recurrent bacterial infections, whereas T-cell deficiencies produce more fungal and viral infections.

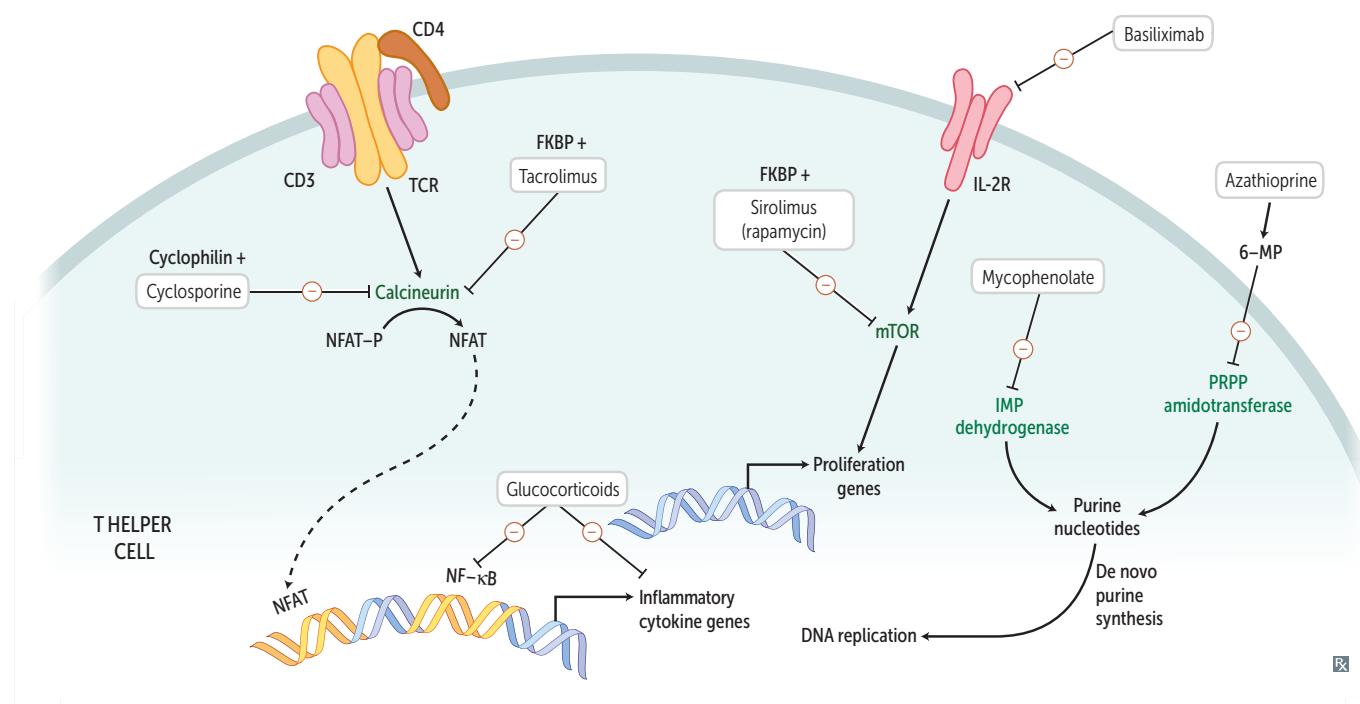
Transplant rejection

TYPE OF REJECTION	ONSET	PATHOGENESIS	FEATURES
Hyperacute	Within minutes	Pre-existing recipient antibodies react to donor antigen (type II hypersensitivity reaction), activate complement	Widespread thrombosis of graft vessels (arrows within glomerulus A) → ischemia and fibrinoid necrosis Graft must be removed
Acute	Weeks to months	Cellular: CD8+ T cells and/or CD4+ T cells activated against donor MHCs (type IV hypersensitivity reaction) Humoral: similar to hyperacute, except antibodies develop after transplant (associated with C4d deposition)	Vasculitis of graft vessels with dense interstitial lymphocytic infiltrate B Prevent/reverse with immunosuppressants
Chronic	Months to years	CD4+ T cells respond to recipient APCs presenting donor peptides, including allogeneic MHC Both cellular and humoral components (type II and IV hypersensitivity reactions)	Dominated by arteriosclerosis C Recipient T cells react and secrete cytokines → proliferation of vascular smooth muscle, parenchymal atrophy, interstitial fibrosis Organ-specific examples: <ul style="list-style-type: none">▪ Chronic allograft nephropathy▪ Bronchiolitis obliterans▪ Accelerated atherosclerosis (heart)▪ Vanishing bile duct syndrome
Graft-versus-host disease	Varies	Grafted immunocompetent T cells proliferate in the immunocompromised host and reject host cells with “foreign” proteins → severe organ dysfunction HLA mismatches ↑ the risk for GVHD Type IV hypersensitivity reaction	Maculopapular rash, jaundice, diarrhea, hepatosplenomegaly Usually in bone marrow and liver transplants (rich in lymphocytes) Potentially beneficial in bone marrow transplant for leukemia (graft-versus-tumor effect) For patients who are immunocompromised, irradiate blood products prior to transfusion to prevent GVHD



▶ IMMUNOLOGY—IMMUNOSUPPRESSANTS

Immunosuppressants Agents that block lymphocyte activation and proliferation. Reduce acute transplant rejection by suppressing cellular immunity (used as prophylaxis). Frequently combined to achieve greater efficacy with ↓ toxicity. Chronic suppression ↑ risk of infection and malignancy.



DRUG	MECHANISM	INDICATIONS	TOXICITY	NOTES
Cyclosporine	Calcineurin inhibitor; binds cyclophilin Blocks T-cell activation by preventing IL-2 transcription	Psoriasis, rheumatoid arthritis	Nephrotoxicity, hypertension, hyperlipidemia, neurotoxicity, gingival hyperplasia, hirsutism	Both calcineurin inhibitors are highly nephrotoxic, especially in higher doses or in patients with ↓ renal function
Tacrolimus (FK506)	Calcineurin inhibitor; binds FK506 binding protein (FKBP) Blocks T-cell activation by preventing IL-2 transcription	Immunosuppression after solid organ transplant	Similar to cyclosporine, ↑ risk of diabetes and neurotoxicity; no gingival hyperplasia or hirsutism	
Sirolimus (Rapamycin)	mTOR inhibitor; binds FKBP Blocks T-cell activation and B-cell differentiation by preventing response to IL-2	Kidney transplant rejection prophylaxis specifically Sir Basil's kidney transplant	"Pansirtopenia" (pancytopenia), insulin resistance, hyperlipidemia; not nephrotoxic	Kidney "sir-vives." Synergistic with cyclosporine Also used in drug-eluting stents
Basiliximab	Monoclonal antibody; blocks IL-2R		Edema, hypertension, tremor	

Immunosuppressants (continued)

DRUG	MECHANISM	INDICATIONS	TOXICITY	NOTES
Azathioprine	Antimetabolite precursor of 6-mercaptopurine Inhibits lymphocyte proliferation by blocking nucleotide synthesis	Rheumatoid arthritis, Crohn disease, glomerulonephritis, other autoimmune conditions	Pancytopenia	6-MP degraded by xanthine oxidase; toxicity ↑ by allopurinol Pronounce “azathio-purine”
Mycophenolate mofetil	Reversibly inhibits IMP dehydrogenase, preventing purine synthesis of B and T cells	Glucocorticoid-sparing agent in rheumatic disease	GI upset, pancytopenia, hypertension Less nephrotoxic and neurotoxic	Associated with invasive CMV infection
Glucocorticoids	Inhibit NF-κB Suppress both B- and T-cell function by ↓ transcription of many cytokines Induce T cell apoptosis	Many autoimmune and inflammatory disorders, adrenal insufficiency, asthma, CLL, non-Hodgkin lymphoma	Cushing syndrome, osteoporosis, hyperglycemia, diabetes, amenorrhea, adrenocortical atrophy, peptic ulcers, psychosis, cataracts, avascular necrosis (femoral head)	Demargination of WBCs causes artificial leukocytosis Adrenal insufficiency may develop if drug is stopped abruptly after chronic use

Recombinant cytokines and clinical uses

CYTOKINE	AGENT	CLINICAL USES
Bone marrow stimulation		
Erythropoietin	Epoetin alfa (EPO analog)	Anemias (especially in renal failure) Associated with ↑ risk of hypertension, thromboembolic events
Colony stimulating factors		
Thrombopoietin	Filgrastim (G-CSF), sargramostim (GM-CSF) Romiplostim (TPO analog), eltrombopag (think “elthrombopag.” TPO receptor agonist)	Leukopenia; recovery of granulocyte and monocyte counts Autoimmune thrombocytopenia Platelet stimulator
Immunotherapy		
Interleukin-2	Aldesleukin	Renal cell carcinoma, metastatic melanoma
Interferons	IFN-α	Chronic hepatitis C (not preferred) and B, renal cell carcinoma
	IFN-β	Multiple sclerosis
	IFN-γ	Chronic granulomatous disease

▶ NOTES