

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, Peyer patches
 - Allow immune cells to interact with antigen

Lymph node

A 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.

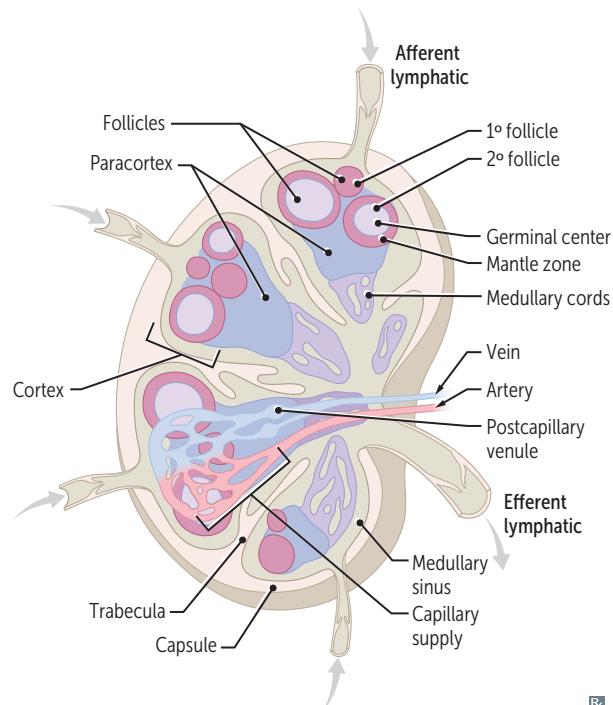
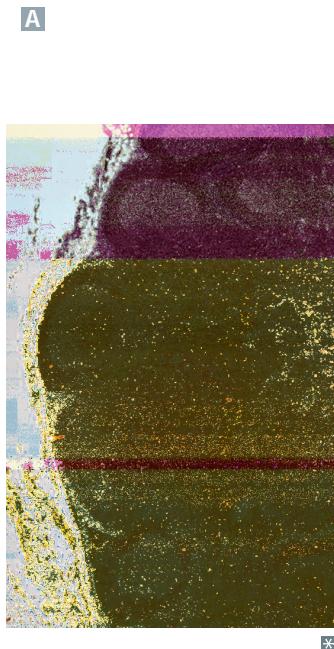
Medulla

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

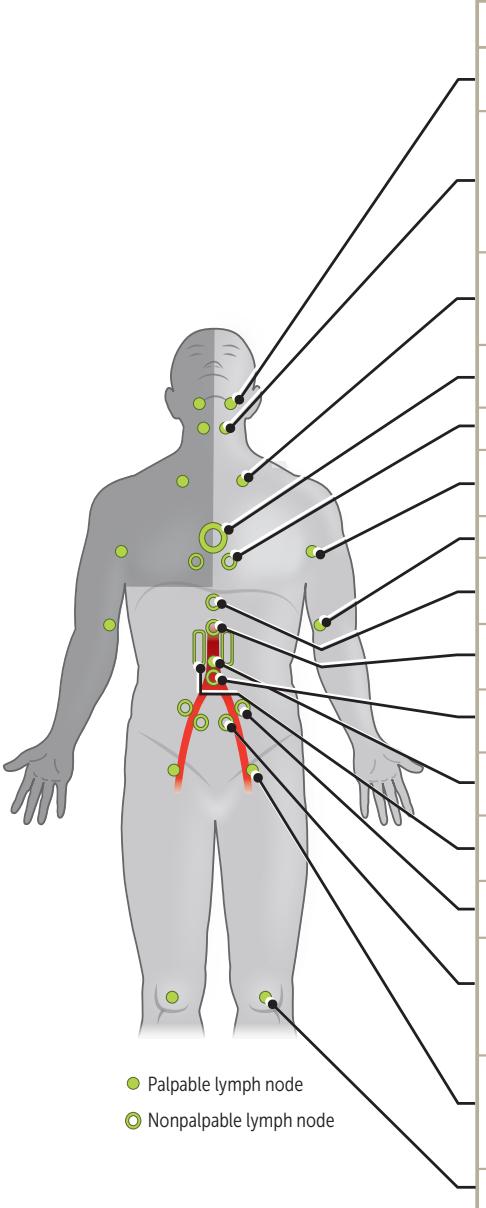
Paracortex

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

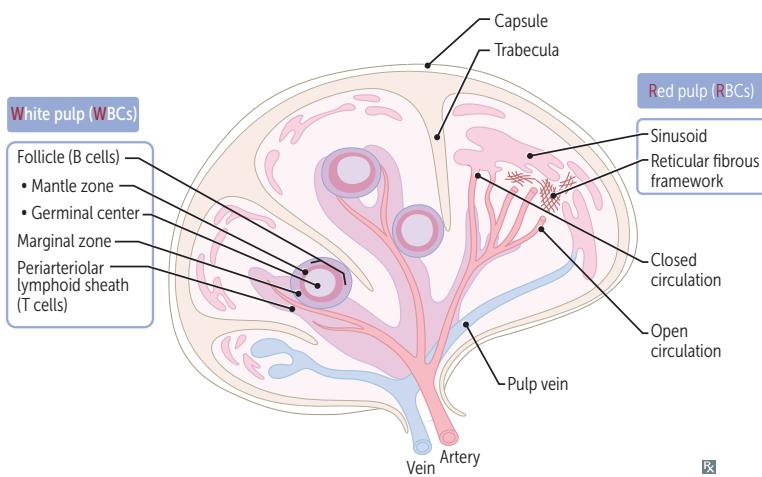


| Lymph node cluster | Area of body drained | Associated pathology |
|--|---|---|
| Submandibular, submental | Oral cavity, anterior tongue, lower lip | Malignancy of and metastasis to the oral cavity |
| Deep cervical | Head, neck, oropharynx | Upper respiratory tract infection Infectious mononucleosis 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.

Postsplenectomy findings:

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

Vaccinate patients undergoing splenectomy or with splenic dysfunction against encapsulated organisms (pneumococci, Hib, meningococci).

Periarteriolar lymphatic sheath

Contains T cells. Located within white pulp.

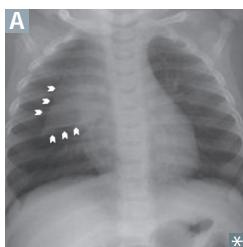
Follicle

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 (asterisks 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.

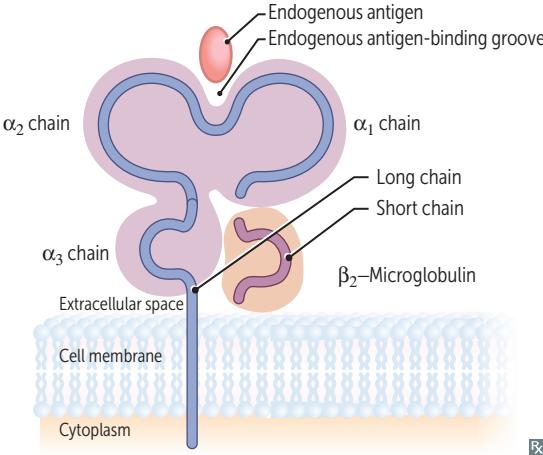
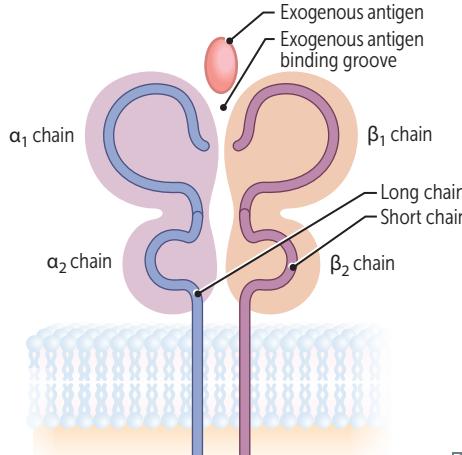
► IMMUNOLOGY—CELLULAR COMPONENTS

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-associated molecular patterns (PAMPs) and lead to activation of NF-κB. Examples of PAMPs: LPS (gram \ominus bacteria), flagellin (bacteria), nucleic acids (viruses) | Memory cells: activated B and T cells; subsequent exposure to a previously encountered antigen \rightarrow stronger, quicker immune response |
| 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 | TCR and CD4 |
| STRUCTURE | 1 long chain, 1 short chain | 2 equal-length chains (2 α, 2 β) |
| 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, A nyklosing spondylitis, I BD-associated arthritis, R eactive arthritis | PAIR |
| B57 | Abacavir hypersensitivity | |
| DQ2/DQ8 | Celiac disease | I ate (8) too (2) much gluten at Dairy Queen |
| 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) |

Functions of natural killer cells

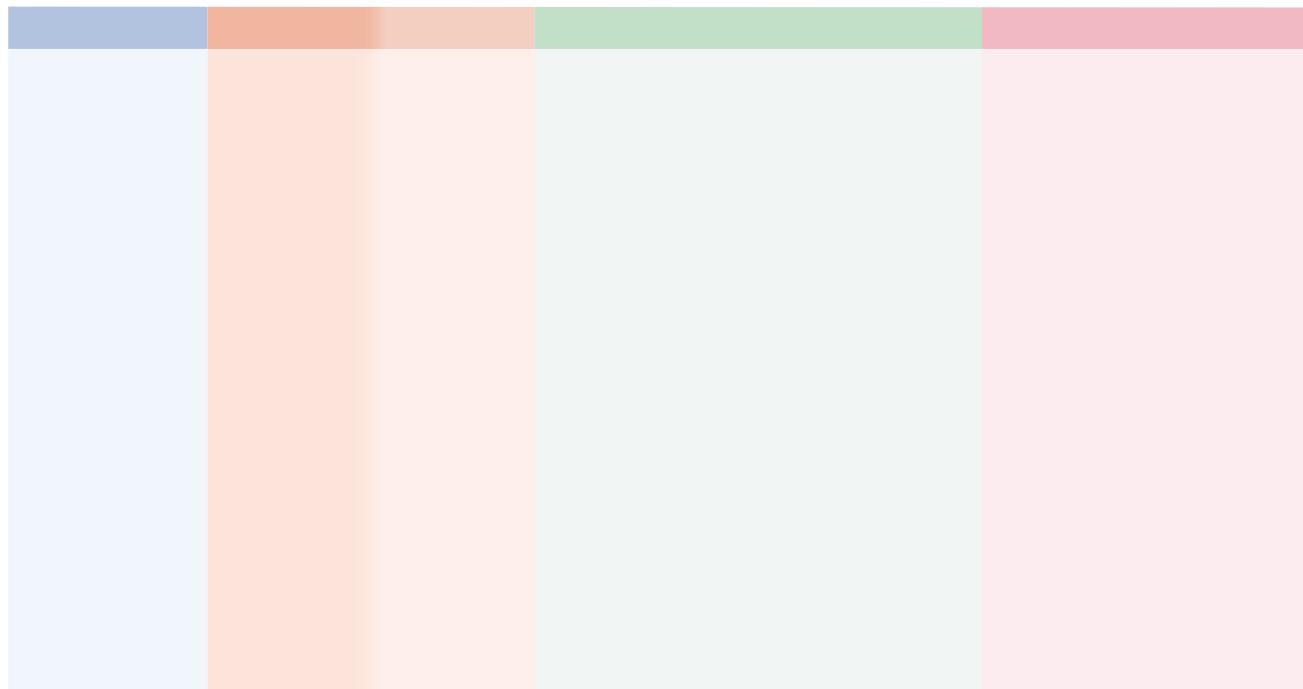
Lymphocyte member of innate immune system.
Use perforin and granzymes to induce apoptosis of virally infected cells and tumor cells.
Activity enhanced by IL-2, IL-12, IFN- α , and IFN- β .
Induced to kill when exposed to a nonspecific activation signal on target cell and/or to an absence of an inhibitory 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).
Delayed cell-mediated hypersensitivity (type IV).
Acute and chronic cellular organ rejection.
Rule of 8: MHC II \times CD4 = 8; MHC I \times CD8 = 8.

Differentiation of T cells

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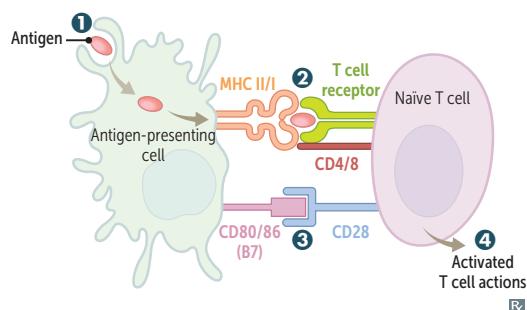
T- and B-cell activation

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

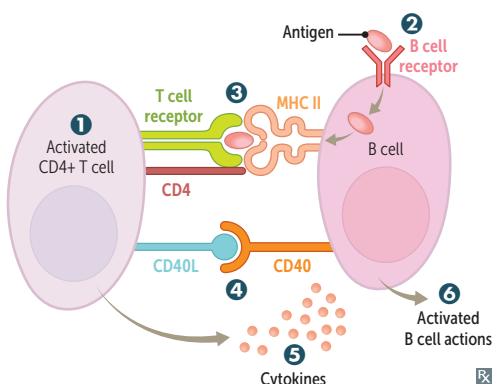
Two signals are required for T-cell activation, B-cell activation, and class switching.

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.





Immunoglobulin isotypes

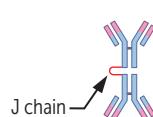
All isotypes can exist as monomers. Mature, naïve B cells prior to activation express IgM and IgD on their surfaces. They may differentiate in germinal centers of lymph nodes by isotype switching (gene rearrangement; induced by cytokines and CD40L) into plasma cells that secrete IgA, IgG, or IgE. “For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



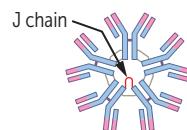
Main antibody in 2° response to an antigen. Most abundant isotype in serum. Fixes complement, opsonizes bacteria, neutralizes bacterial toxins and viruses. Only isotype that crosses the placenta (provides infants with passive immunity that starts to wane after birth). “IgG Greets the Growing fetus.”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

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—microbe surface molecules.

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

C5a—neutrophil chemotaxis.

Neisseria species. Deficiency results in

C5b-9 (MAC)—cytolysis.

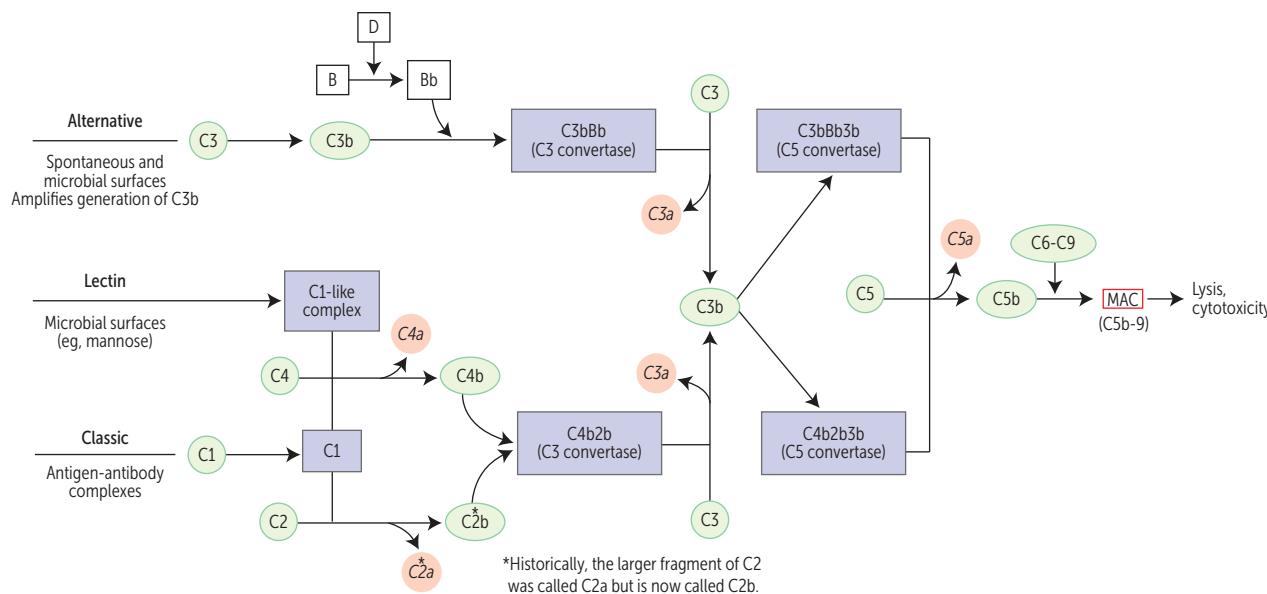
recurrent infection.

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

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 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**).

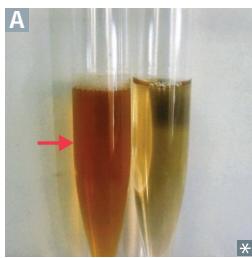
Terminal complement deficiencies (C5–C9) ↑ susceptibility to recurrent *Neisseria* bacteremia.

Complement regulatory protein deficiencies

C1 esterase 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**.

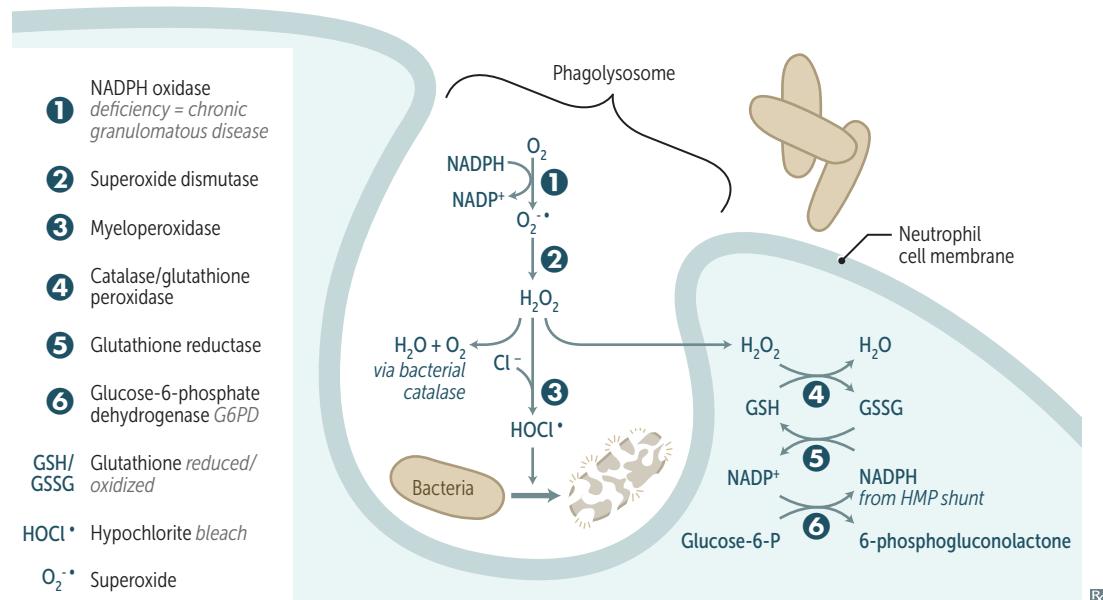
Can cause atypical venous thrombosis (eg, Budd-Chiari syndrome; portal vein, cerebral, or dermal thrombosis).



| | | |
|--------------------------------|--|---|
| 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 Kute -phase protein production. |
| Interleukin-6 | Causes fever and stimulates production of acute-phase proteins. | |
| Tumor necrosis factor- | Activates endothelium. Causes WBC recruitment, vascular leak. | Causes cachexia in malignancy. Maintains granulomas in TB. IL-1, IL-6, TNF- α can mediate fever and sepsis. |
| Interleukin-8 | Major chemotactic factor for neutrophils. | “Clean up on aisle 8.” Neutrophils are recruited by IL-8 to clear infections. |
| 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. | |
| Interleukin-3 | Supports growth and differentiation of bone marrow stem cells. Functions like GM-CSF. | |
| From Th1 cells | | |
| Interferon- | 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 IgG 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 C . | 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 thir EE n 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.

Interferons

IFN- α , IFN- β , IFN- γ .

| | |
|-----------------|--|
| 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, chronic granulomatous disease. |
| 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 |

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 mechanism of self-tolerance.

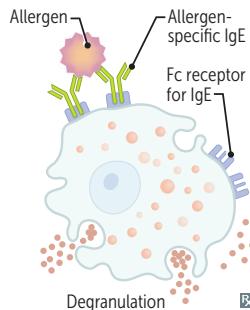
Passive vs active immunity

| | 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 | Microorganism rendered nonpathogenic but retains capacity for transient growth within inoculated host. MMR and varicella vaccines can be given to people living with HIV without evidence of immunity if CD4+ cell count ≥ 200 cells/mm ³ . | Pros: induces cellular and humoral responses. Induces strong, often lifelong immunity. Cons: may revert to virulent form. Contraindicated in pregnancy and patients with immunodeficiency. | Adenovirus (nonattenuated, given to military recruits), typhoid (Ty21a, oral), polio (Sabin), varicella (chickenpox), smallpox, BCG, yellow fever, influenza (intranasal), MMR, rotavirus. “Attention teachers! Please vaccinate small, Beautiful young infants with MMR routinely!” |
| Killed or inactivated vaccine | Pathogen is inactivated by heat or chemicals. Maintaining epitope structure on surface antigens is important for immune response. Mainly induces a humoral response. | Pros: safer than live vaccines. Cons: weaker cell-mediated immune response; mainly induces a humoral response. Booster shots usually needed. | Hepatitis A, Typhoid (Vi polysaccharide, intramuscular), Rabies, Influenza (intramuscular), Polio (SalK). A TRIP could Kill you. |
| Subunit, recombinant, polysaccharide, and conjugate | All use specific antigens that best stimulate the immune system. | Pros: targets specific epitopes of antigen; lower chance of adverse reactions. Cons: expensive; weaker immune response. | 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), <i>Haemophilus influenzae</i> type b, herpes zoster. |
| Toxoid | Denatured bacterial toxin with an intact receptor binding site. Stimulates immune system to make antibodies without potential for causing disease. | Pros: protects against the bacterial toxins. Cons: antitoxin levels decrease with time, thus booster shots may be needed. | <i>Clostridium tetani</i> , <i>Corynebacterium diphtheriae</i> . |
| mRNA | A lipid nanoparticle delivers mRNA, causing cells to synthesize foreign protein (eg, spike protein of SARS-CoV-2). | Pros: high efficacy; induces cellular and humoral immunity. Safe in pregnancy. Cons: local and transient systemic (fatigue, headache, myalgia) reactions are common. Rare myocarditis, pericarditis particularly in young males. | SARS-CoV-2 |

Hypersensitivity types

Four types (**ABCD**): **A**naphylactic and **A**topic (type I), **Anti**Body-mediated (type II), **I**mune **C**omplex (type III), **D**elayed (cell-mediated, type IV). Types I, II, and III are all antibody-mediated.

Type I**hypersensitivity**

Anaphylactic and atopic—two phases:

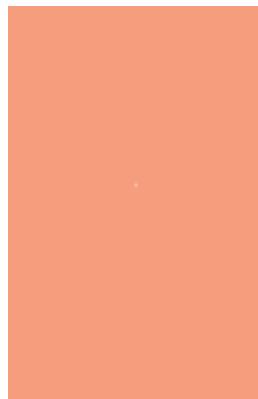
- Immediate (minutes): antigen crosslinks preformed IgE on presensitized mast cells → immediate degranulation → release of histamine (a vasoactive amine), tryptase (marker of mast cell activation), and leukotrienes.
- Late (hours): chemokines (attract inflammatory cells, eg, eosinophils) and other mediators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

First (type) and **F**ast (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.

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

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).

Examples:

- Goodpasture syndrome
- Rheumatic fever
- Hyperacute transplant rejection

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

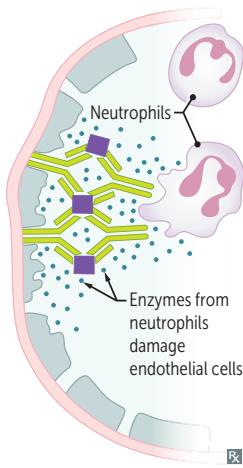
Examples:

- Myasthenia gravis
- Graves disease
- Pemphigus vulgaris

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

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:

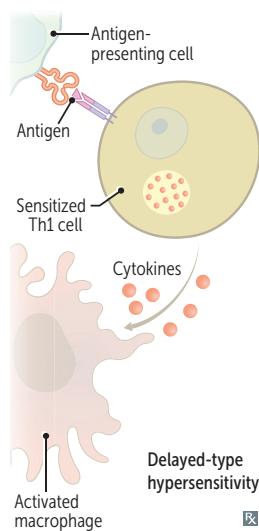
- SLE
- Rheumatoid arthritis
- Reactive arthritis
- Polyarteritis nodosa
- Poststreptococcal glomerulonephritis
- IgA vasculitis

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).

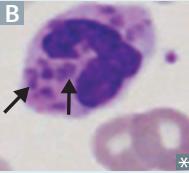
Autoantibodies

| 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 | PRESNTATION | 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 | Cause unknown Most common 1° immunodeficiency | 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 | Mutation in WAS gene; 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) | Defect in LFA-1 integrin (CD18) protein on phagocytes; impaired migration and chemotaxis; autosomal recessive | 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 Recurrent infections and granulomas | Abnormal dihydrorhodamine (flow cytometry) test (↓ green fluorescence) Nitroblue tetrazolium dye reduction test (obsolete) fails to turn blue |

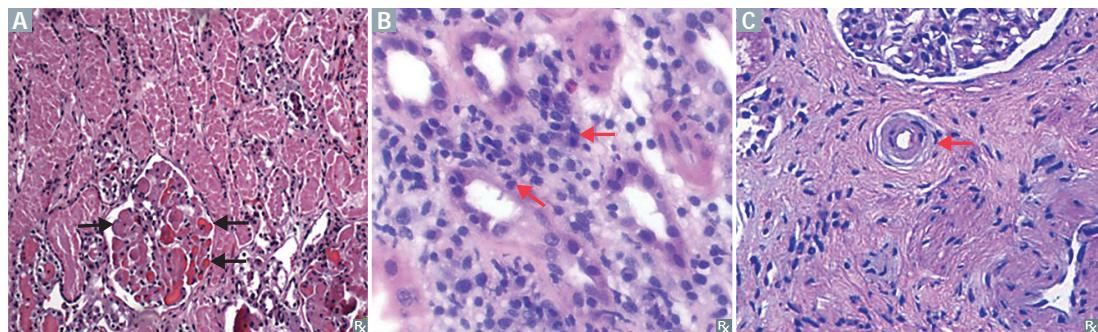
Infections in immunodeficiency

| 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 Neisseria 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.

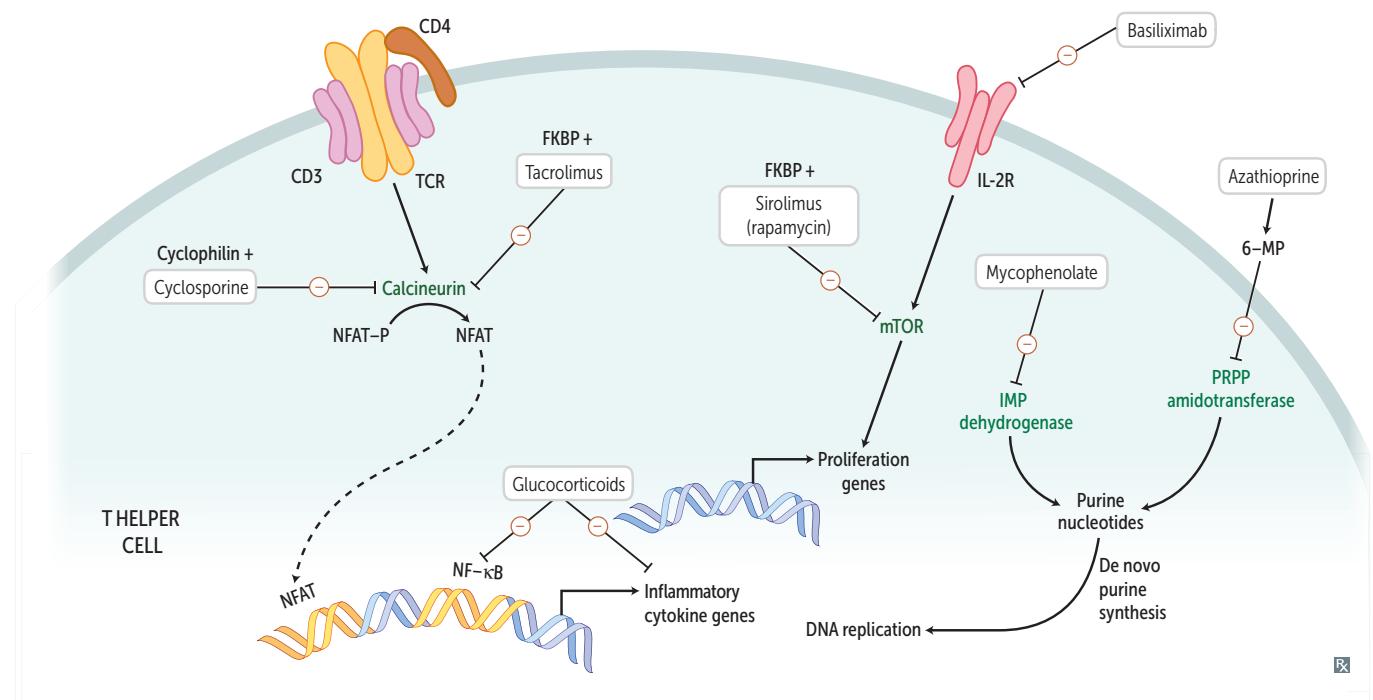
Transplant rejection

| 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 (most importantly HLA-A, -B, and -DR antigens) ↑ 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 IFN-β IFN-γ | Chronic hepatitis C (not preferred) and B, renal cell carcinoma Multiple sclerosis Chronic granulomatous disease |

Therapeutic antibodies

| AGENT | TARGET | CLINICAL USE | NOTES |
|---|-----------------------|---|---|
| Autoimmune disease therapy | | | |
| Adalimumab, certolizumab, golimumab, in iximab | Soluble TNF- α | IBD, rheumatoid arthritis, ankylosing spondylitis, psoriasis | Pretreatment screening (TB, HBV, HCV, VZV, EBV, CMV) due to risk of reactivation Etanercept is a decoy TNF- α receptor and not a monoclonal antibody |
| Eculizumab | Complement protein C5 | Paroxysmal nocturnal hemoglobinuria | Associated with \uparrow risk of meningococcal infection |
| Guselkumab | IL-23 | Psoriasis | |
| Ixekizumab, secukinumab | IL-17A | Psoriasis, psoriatic arthritis | |
| Natalizumab | α 4-integrin | Multiple sclerosis, Crohn disease | α 4-integrin: WBC adhesion Risk of PML in patients with JC virus |
| Ustekinumab | IL-12/IL-23 | Psoriasis, psoriatic arthritis | |
| Vedolizumab | α 4-integrin | IBD | Gut-specific anti-integrin, preventing migration of leukocytes to the gastrointestinal tract |
| Other applications | | | |
| Denosumab | RANKL | Osteoporosis; inhibits osteoclast maturation (mimics osteoprotegerin) | Denosumab helps make dense bones |
| Emicizumab | Factor IXa and X | Hemophilia A | Bispecific; mimics factor VIII |
| Omalizumab | IgE | Refractory allergic asthma; prevents IgE binding to Fc ϵ RI | |
| Palivizumab | RSV F protein | RSV prophylaxis for high-risk infants | Palivizumab— virus |