Primary Immunodeficiency syndromes

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Immune system

Innate system:

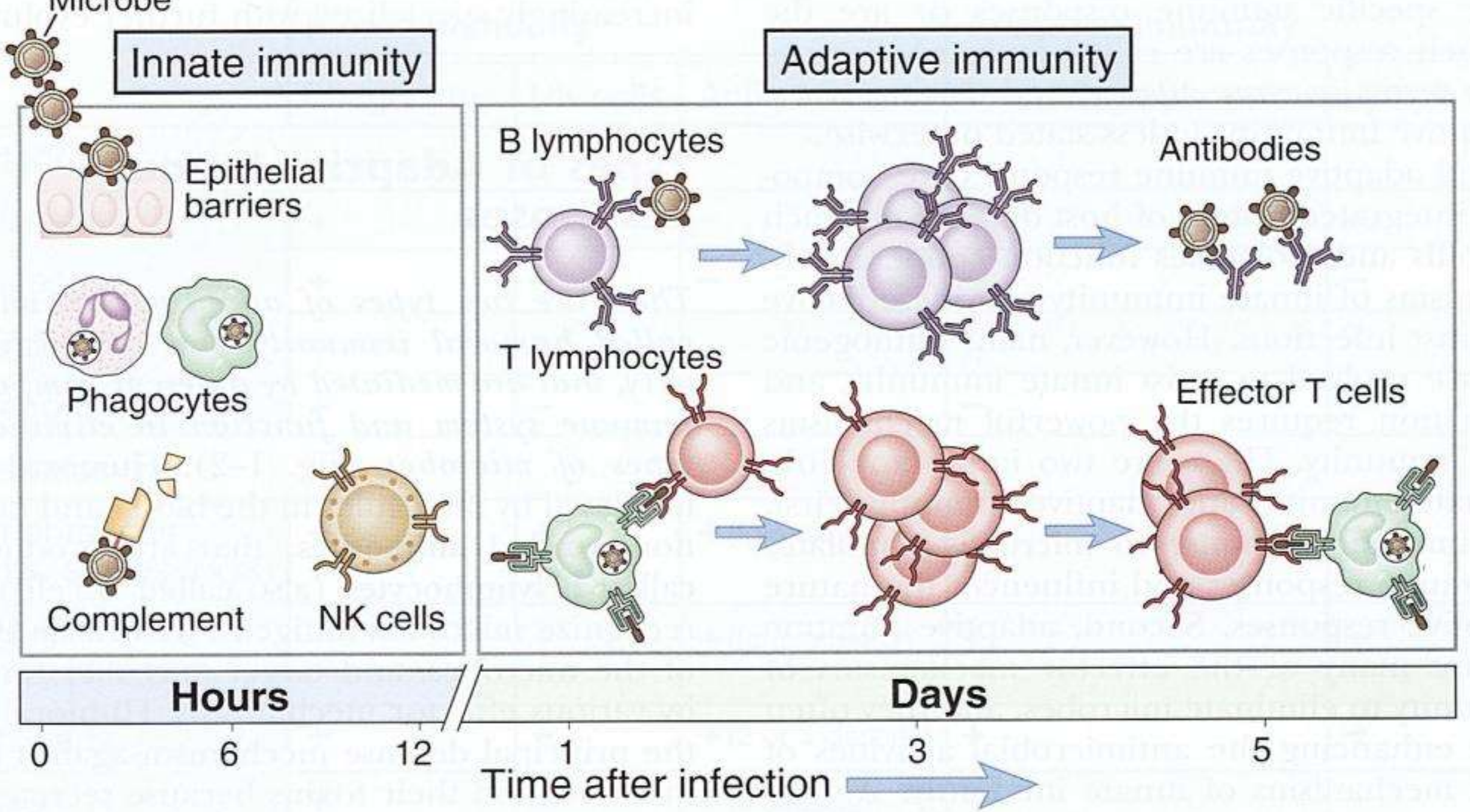
(Epithelial Barrier,Phagocyte,

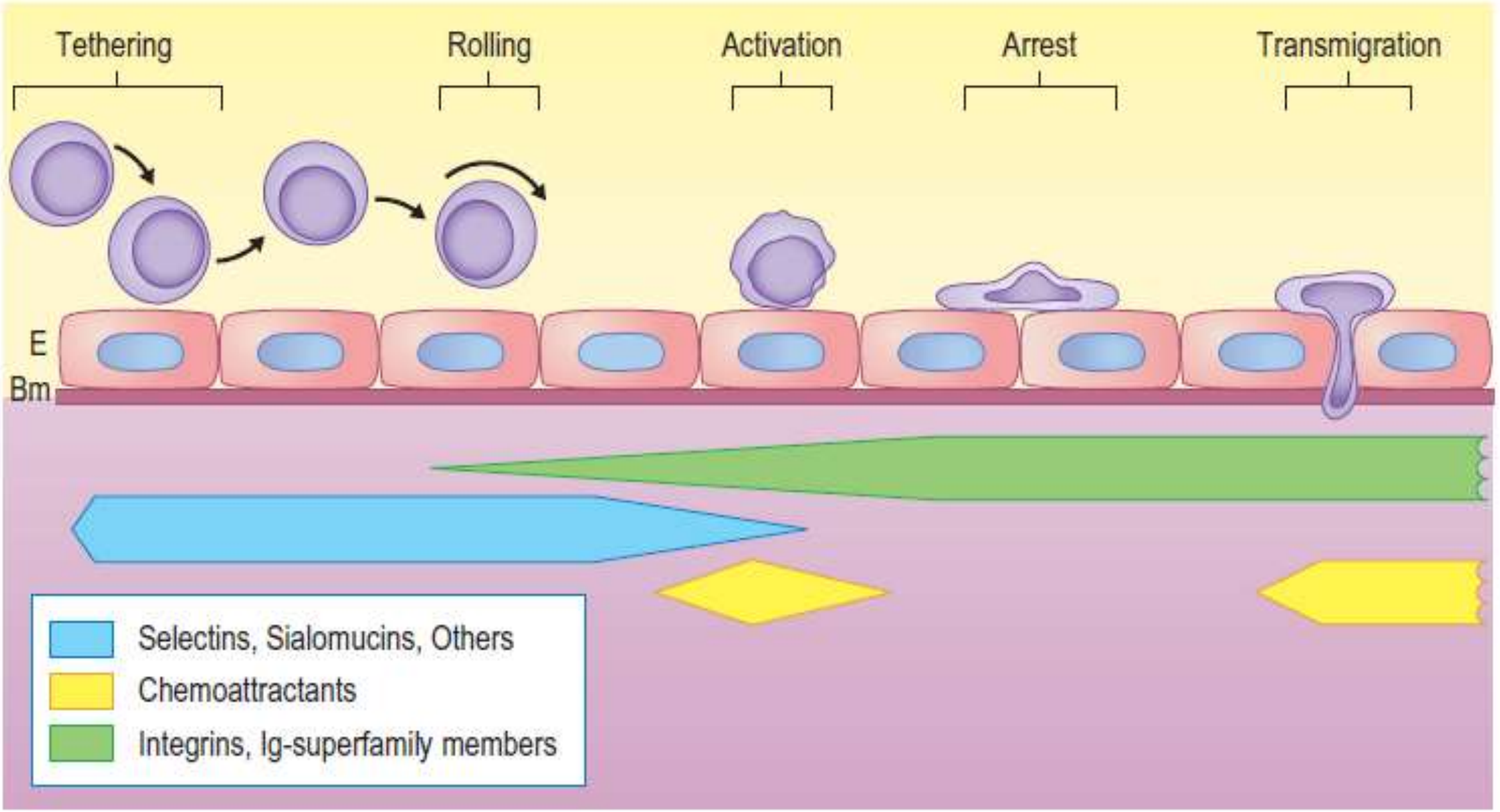
APC, NK cell,Complement Factor)

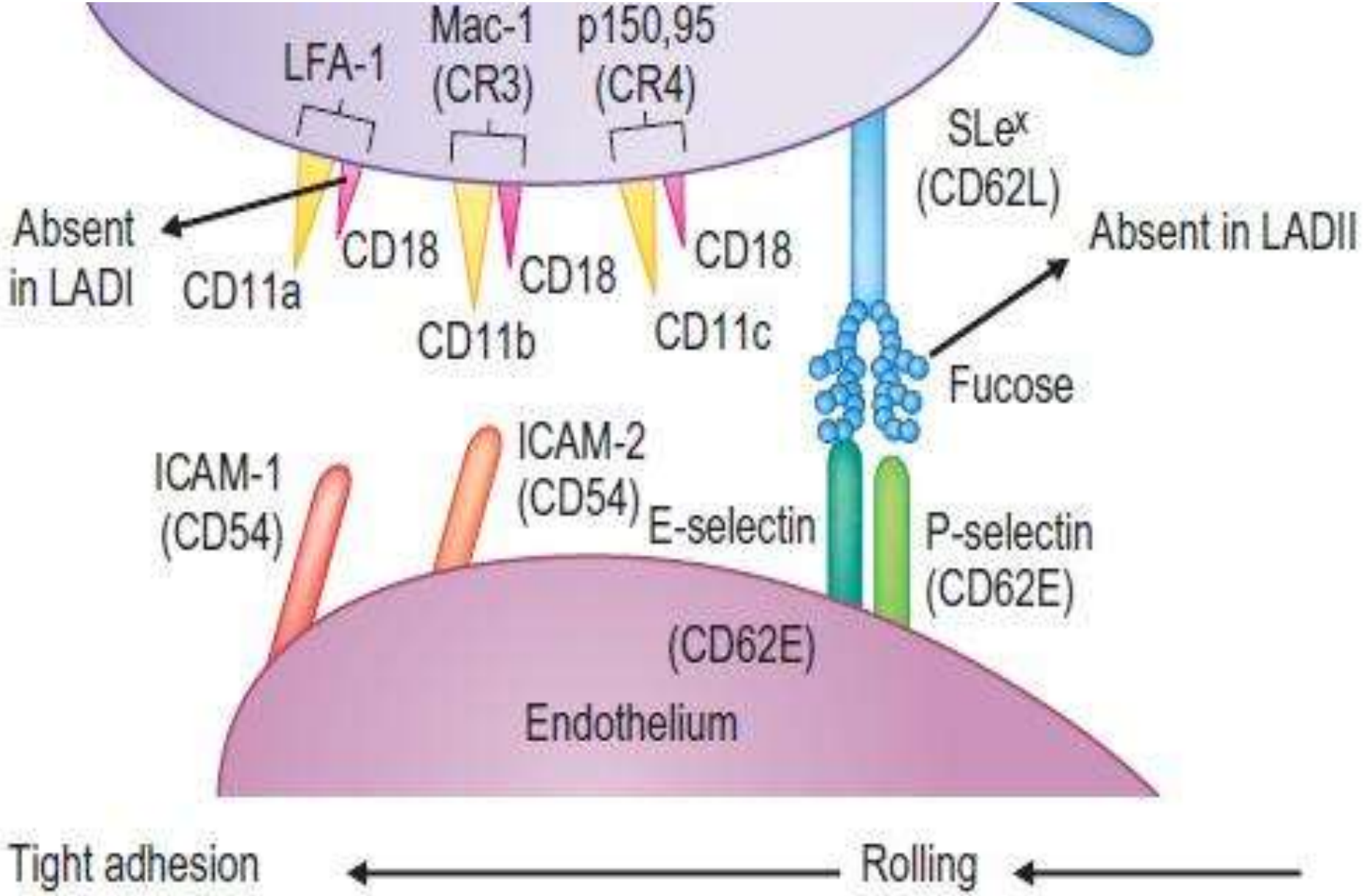
Adaptive system:

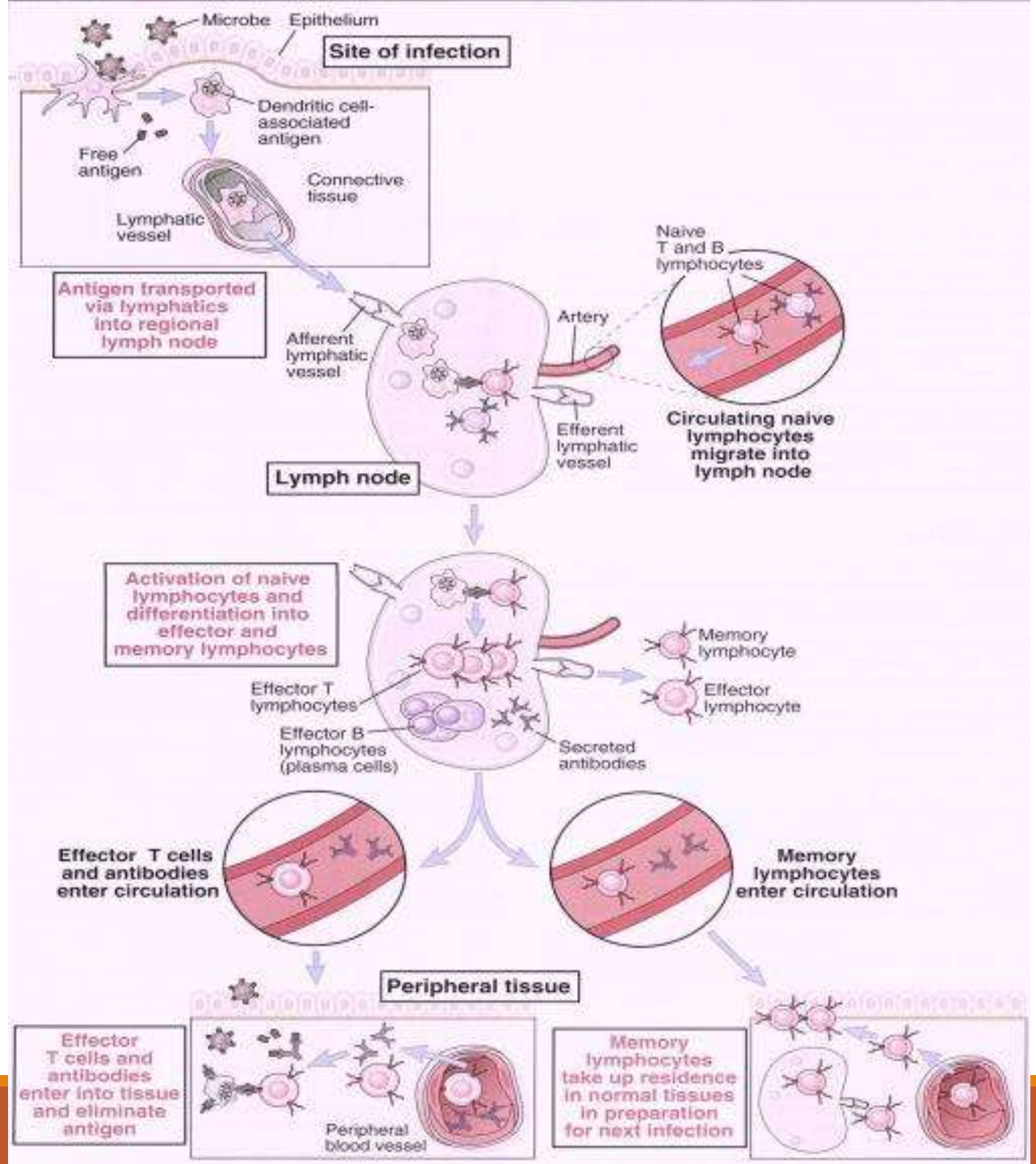
- Tcell maturation in thymus
- B cell maturation in BM,

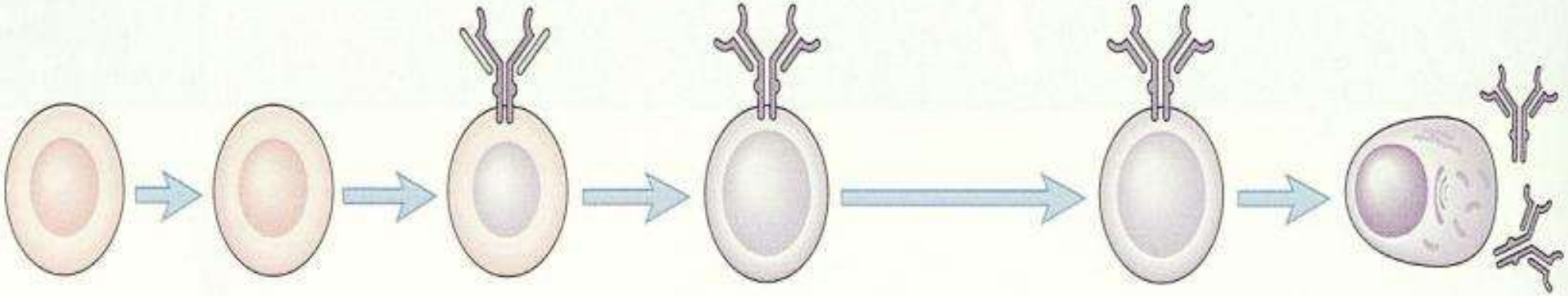
lymphatic tissue


Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
Phagocytes
Complement
NK cells
B lymphocytes
Antibodies
T lymphocytes
Effector T cells
Hours
Days
0
6
12
1
3
5
Time after infection


Tethering
Rolling
Activation
Arrest
Transmigration
E
Bm
Selectins, Sialomucins, Others
Chemoattractants
Integrins, Ig-superfamily members


LFA-1
Mac-1
(CR3)
p150,95
(CR4)
SLe^x
(CD62L)
Absent
in LADI
CD11a
CD18
CD18
CD11b
CD18
CD11c
Absent in LADII
Fucose
ICAM-1
(CD54)
ICAM-2
(CD54)
E-selectin
P-selectin
(CD62E)
(CD62E)
Endothelium
Tight adhesion
Rolling


Microbe
Epithelium
Site of infection
Dendritic cell-associated antigen
Free antigen
Connective tissue
Lymphatic vessel
Antigen transported via lymphatics into regional lymph node
Afferent lymphatic vessel
Artery
Naive T and B lymphocytes
Efferent lymphatic vessel
Circulating naive lymphocytes migrate into lymph node
Lymph node
Activation of naive lymphocytes and differentiation into effector and memory lymphocytes
Memory lymphocyte
Effector lymphocyte
Effector T lymphocytes
Effector B lymphocytes (plasma cells)
Secreted antibodies
Effector T cells and antibodies enter circulation
Memory lymphocytes enter circulation
Peripheral tissue
Effector T cells and antibodies enter into tissue and eliminate antigen
Peripheral blood vessel
Memory lymphocytes take up residence in normal tissues in preparation for next infection



Stage of maturation	Stem cell	Pro-lymphocyte	Pre-lymphocyte	Immature lymphocyte	Mature lymphocyte	Differentiated effector lymphocyte
Major events	Early maturation and growth factor–mediated expansion		Antigen receptor expression	Selection of repertoire; acquisition of functional competence		Performance of effector functions
Anatomic site	Generative organ (bone marrow or thymus)				Peripheral lymphoid organ or tissue	
Antigen dependence	No			Self antigen		Foreign antigen

Classification of immunodeficiency

Combined immunodeficiencies.

Well-defined syndromes with immunodeficiency.

Predominantly antibody deficiencies

Diseases of immune dysregulation.

Congenital defects of phagocyte number, function, or both

Defects in innate immunity.

Autoinflammatory disorders.

Complement deficiencies

Type of infections associated with major categories of PIDs

Organism	Antibody deficiencies	CIDs	Phagocytic defects	Complement deficiencies
Viruses	Enteroviruses	All, especially: CMV, respiratory syncytial virus, EBV, parainfluenza type 3	No	No
Bacteria	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Mycoplasma pneumoniae*	As for antibody deficiencies, also: *Salmonella typhi*, *Listeria monocytogenes*, enteric flora	*S aureus*, *P aeruginosa*, *Nocardia asteroides*, *S typhi*	As for antibody deficiencies: especially *N meningitidis* in deficiency of late components
Mycobacteria	No	Nontuberculous, including BCG	Nontuberculous, including BCG	No
Fungi	No	*Candida* species, *Aspergillus* species, *Cryptococcus neoformans*, *Histoplasmosis capsulatum*	*Candida* species, *Aspergillus* species	No
Protozoa	*Giardia lamblia*	*Pneumocystis jiroveci*, *Toxoplasma gondii*, *Cryptosporidium parvum*	No	No

Table 73-1 Antibody Deficiency Diseases

DISORDER	GENETICS	ONSET	MANIFESTATIONS	PATHOGENESIS	ASSOCIATED FEATURES
Agammaglobulinemia	X-linked, AR	Infancy (6–9 mo)	Recurrent infections, sinusitis, pneumonia, meningitis (encapsulated bacteria, enteroviruses)	Arrest in B-cell differentiation (pre-B level); mutations in: *Btk* gene (X-linked); μ chain, BLNK, Igα, Igβ, Vpre-B, and λ5 (AR)	Lymphoid hypoplasia
Common variable immunodeficiency	AR; AD; sporadic	Second to third decade	Sinusitis, bronchitis, pneumonia, chronic diarrhea	Arrest in plasma cell differentiation, mutations in ICOS, TACI, CD19	Autoimmune disease, RA, SLE, Graves disease, ITP, malignancy, granulomatous disease
Transient hypogammaglobulinemia of infancy		Infancy (3–7 mo)	Recurrent viral and pyogenic infections	Unknown; delayed plasma cell maturation	Frequently in families with other immunodeficiencies
IgA deficiency	Variable	Variable	Sinopulmonary infections; can be normal	Failure of IgA expression	IgG subclass deficiency common, autoimmune diseases
IgG subclass deficiency	Variable	Variable	Sinopulmonary infections; can be normal	Defect in IgG isotype production	IgA deficiency, ataxia telangiectasia, polysaccharide antibody deficiency
IgM deficiency	Variable	First year	Variable (normal to recurrent sinopulmonary infections and meningitis)	Defective helper T cell–B cell interaction	Whipple disease, regional enteritis, lymphoid hyperplasia
Specific antibody deficiency, IgA deficiency	Variable	After 2 years of age	Sinopulmonary infections	Unknown	IgG subclass deficiency
Hyper-IgM syndrome	AR	Variable	Sinopulmonary infections	Defect in AID, UNG	Autoimmunity

Table 72-3	Clinical Characteristics of Primary Immunodeficiencies
B-CELL DEFECTS	
Recurrent pyogenic infections with extracellular encapsulated organisms, such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and group A streptococcus	
Otitis, sinusitis, recurrent pneumonia, bronchiectasis, and conjunctivitis	
Few problems with fungal or viral infections (except enterovirus and poliomyelitis)	
Diarrhea common, especially secondary to infection with *Giardia lamblia*	
Minimal growth retardation	
Compatible with survival to adulthood or for several years after onset unless complications occur	

B cell Development

Stem cell **Pro B cell**

Pro B cell **Pre B cell**

Pre B cell **Immature B cell**

Immature B cell **Mature B cell**

Mature B cell **Plasma cell**

XLA

Frequency

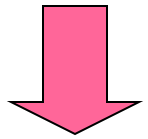
1/50,000 - 1/100,000

Etiology: Mutation in BTK gene

Chro X q 22

Pro B cell

Pre B cell Arrest



Specific manifestation of XLA

Tonsillar Atrophy

Meningoencephalitis with enteroviruses

Paralysis after live polio vaccine

Dermatomyositis like syndrom

Increased of GI cancer

Lab Finding

IgG < 100mg/dl

B cell < 1%

Mutation analysis of BTK

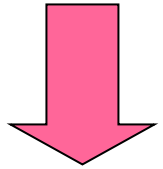
gene

CVID

- **Frequency:**

1/10,000 - 1/50,000

B cell :



Plasma cell arrest

CVID Genetic

ICOS deficiency

CD 19 Deficiency

BAFFR Deficiency

TACI Deficiency

X –LP (SH2DIA)

LRBA deficiency

CD27 deficiency

Clinical Manifestation

GI Symptom :

malabsorption,Gluten sensitive entropathy,Giardial infection,

Nodular Lymphoid Hyperplasia Mycoplasma infection

Autoimmune :

SLE, Hemolytic anemia , Neutropenia, alopecia areata

Malignancy :

Lymphoma, Stomach cancer

Diagnosis

IgG <200 mg / dl

B cell Normal

R/out other genetic defect

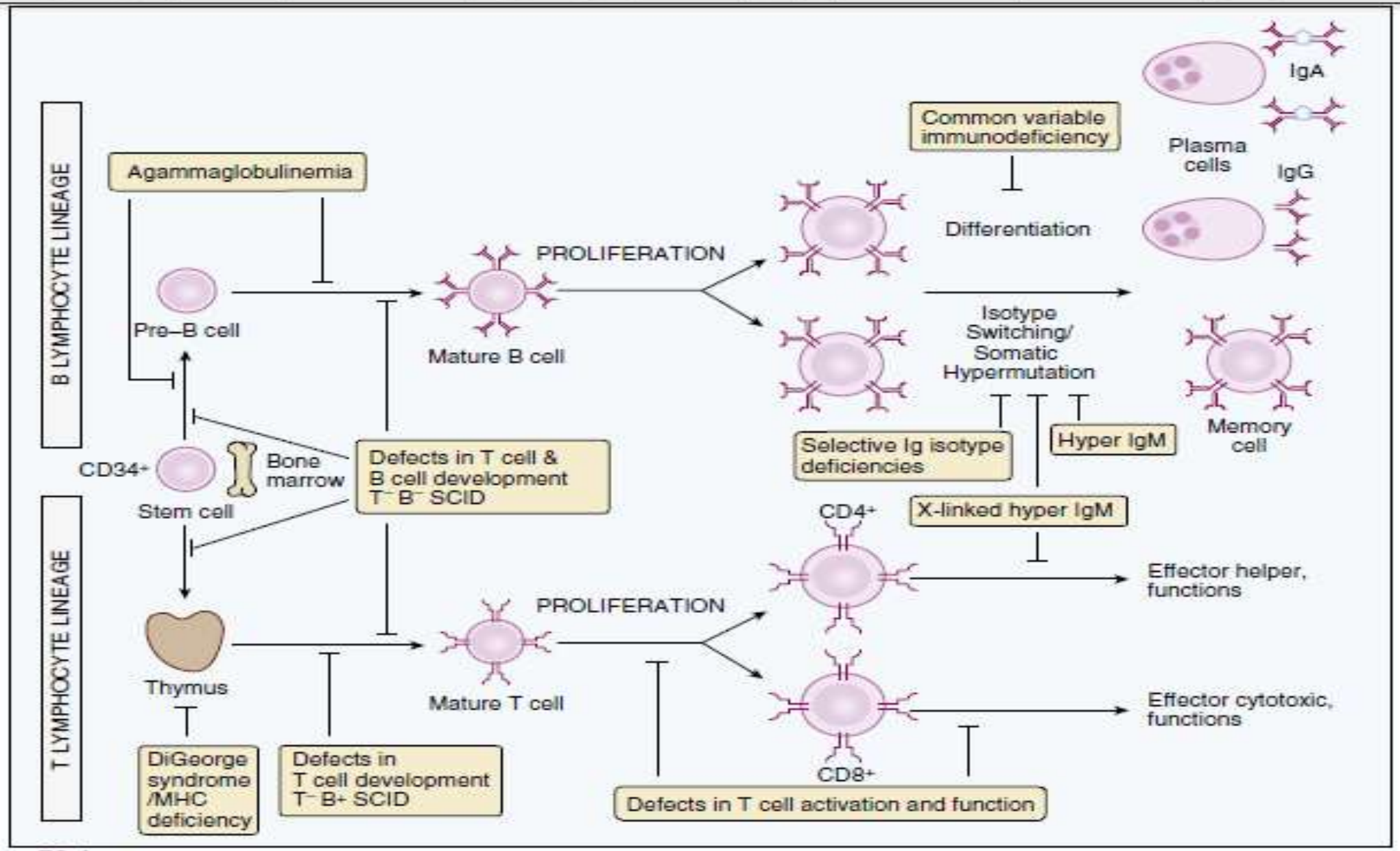


Figure 73-1 Sites of cellular abnormalities in congenital immunodeficiencies. In primary immunodeficiency diseases, the maturation or activation of B or T lymphocytes may be blocked at different stages. ⊥ Inhibition; *B*, B lymphocyte; *T*, T lymphocyte. *(Adapted from Abbas AK, Lichtman*

Table 72-5 Tests for Suspected Immune Deficiency

GENERAL
Complete blood count, including hemoglobin, differential white blood cell count and morphology, and platelet count
Radiographs to document infection in chest, sinus, mastoids, and long bones, if indicated by clinical history
Cultures, if appropriate

ANTIBODY-MEDIATED IMMUNITY

Quantitative immunoglobulin levels: IgG, IgA, IgM, IgE, Isohemagglutinin titers (anti-A, anti-B, measures IgM function)

Specific antibody levels:

Protein antigens: diphtheria, tetanus

Protein-conjugated antigens: *Haemophilus influenzae*, *Streptococcus pneumoniae* (conjugate vaccine)

Polysaccharide antigens: *S. pneumoniae* (unconjugated vaccine)

B-cell numbers and subsets by flow cytometry

Table 73-2 Combined Immunodeficiency Diseases

DISORDER	GENETICS	ONSET	MANIFESTATIONS	PATHOGENESIS	ASSOCIATED FEATURES
Hyper-IgM syndrome (see Table 73-1)	X-linked, AR	First year	Sinopulmonary infections, opportunistic infections, *Pneumocystis jiroveci*	Defect in CD40 ligand (X-linked) or CD40 (AR)	Neutropenia, liver disease, cancer
DiGeorge anomaly	22q11.2 (or 10p) deletion	Newborn, early infancy	Hypocalcemic tetany, pyogenic infections, partial or complete T-cell deficiency	Hypoplasia of third and fourth pharyngeal pouch	Congenital heart disease (aortic arch anomalies), hypoparathyroidism, micrognathia, hypertelorism
Severe combined immunodeficiency (T^-B^+ SCID)	X-linked; AR	1–3 mo	Candidiasis, all types of infections, failure to thrive, chronic diarrhea	Mutation in IL-2Rγ chain, Jak3 kinase, ZAP-70, IL-7Ra, CD3 subunits	GVHD from maternal-fetal transfusions, severe GVHD from nonirradiated blood transfusion
Severe combined immunodeficiency (T^-B^- SCID)	AR	1–3 mo	Same as T^-B^+ SCID	Mutation in RAG1/2, Artemis, ADA/PNP deficiency	Same as T^-B^+ SCID ADA deficiency: chondro-osseous dysplasia PNP deficiency: neurologic disorders
Omenn syndrome	AR	1–3 mo	Same as T^-B^- SCID, exfoliative erythroderma, lymphadenopathy, hepatosplenomegaly	Hypomorphic mutations in SCID-causing genes (RAG1/2, Artemis)	Restricted T-cell receptor heterogeneity, eosinophilia, elevated IgE
Reticular dysgenesis (T^-B^-SCID)	AR	1–3 mo	Same as T^-B^- SCID	Defective maturation of common stem cells due to *AK2* mutations	Agammaglobulinemia, alymphocytosis, agranulocytosis
Bare lymphocyte syndrome (MHC class I deficiency)	AR	First decade	Sinopulmonary infections	Mutation in TAP1 or TAP2 (transporter associated with antigen processing)	Decreased CD8 T cells, chronic lung inflammation
Bare lymphocyte syndrome (MHC class II deficiency)	AR	Early infancy	Respiratory tract infections, chronic diarrhea, viral infections in central nervous system	Mutations in CIITA, RFX5, RFXAP, and RFX-B (DNA binding factors)	Decreased CD4 T cells, autoimmune disease

Table 73-3 Other Immunodeficiency Diseases

DISORDER	GENETICS	ONSET	MANIFESTATIONS	PATHOGENESIS	ASSOCIATED FEATURES
Wiskott-Aldrich syndrome	X-linked, (Xp11.22)	Early infancy	Thrombocytopenia, atopic dermatitis, recurrent infections	53-kD protein (*WASP*) defect	Polysaccharide antibody deficiency, small platelets, decreased cell-mediated immunity, lymphoproliferation
Ataxia-telangiectasia	AR (11q22.3)	2–5 yr	Recurrent otitis media, pneumonia, meningitis with encapsulated organisms	*ATM* gene mutation Disorder of cell cycle checkpoint and of DNA double-strand break repair	Neurologic and endocrine dysfunction, malignancy, telangiectasis; sensitivity to radiation
Nijmegen breakage syndrome	AR (8q21)	Infancy	Sinopulmonary infections, bronchiectasis, urinary tract infections	Defect in chromosomal repair mechanisms; hypomorphic mutation in *NBS1* (Nibrin)	Sensitivity to ionizing radiation; microcephaly with mild neurologic impairment; malignancy
Cartilage-hair hypoplasia (short-limbed dwarf)	AR (9p13–21)	Birth	Variable susceptibility to infections	Mutation in *RMRP*	Metaphyseal dysplasia, short extremities
Chronic mucocutaneous candidiasis (APECED)	AR	3–5 yr	Candidal infections of mucous membranes, skin, and nails	Mutations in *AIRE* gene	Autoimmune endocrinopathies
X-linked-lymphoproliferative syndromes	X-linked	Variable	Variable decrease in T, B, and NK cell function, hypogammaglobulinemia	Mutation in *SH2D1A* (SAP: SLAM-associated protein) or *XIAP*	Life-threatening Epstein-Barr virus infection, lymphoma or Hodgkin disease, aplastic anemia, lymphohistiocytic disorder
Hyper-IgE syndrome	AD, AR	Variable	Skin and pulmonary abscesses, fungal infections, eczema, elevated IgE	Mutation in STAT3 (AD), TYK2 (AR), and DOCK8 (AR)	Coarse facial features, failure to shed primary teeth, frequent fractures (STAT3), viral and other infections (TYK2 and DOCK8)

AD, Autosomal dominant; AR, autosomal recessive; NK, natural killer.

T-CELL DEFECTS
Recurrent infections with less virulent or opportunistic organisms, such as fungi, *Candida* sp mycobacteria, viruses, and protozoa as well as bacteria
Growth retardation, malabsorption, diarrhea, and failure to thrive common
Anergy
Susceptible to graft-versus-host disease from nonirradiated blood or from maternal engraftment
Fatal reactions may occur from live virus or bacille Calmette-Guérin vaccination.
High incidence of malignancy

CELL-MEDIATED IMMUNITY

Lymphocyte count and morphology

Delayed hypersensitivity skin tests (*Candida*, tetanus toxoid, mumps): measure T-cell and macrophage function

T-cell and NK cell numbers and subsets by flow cytometry
T-lymphocyte functional analyses (mitogen responses, cytokines)

NK cell cytotoxicity assays

Table 74-1 Phagocytic Disorders

NAME	DEFECT	COMMENT
Chronic granulomatous disease	Bactericidal	X-linked recessive (66%), autosomal recessive (33%); eczema, osteomyelitis, granulomas, abscesses caused by *Staphylococcus aureus*, *Burkholderia cepacia*, *Aspergillus fumigatus*
Chédiak-Higashi syndrome (1q42l-44)	Bactericidal plus chemotaxis; poor natural killer function	Autosomal recessive; oculocutaneous albinism, neuropathy, giant neutrophilic cytoplasmic inclusions; malignancy, neutropenia
Hyperimmunoglobulin E (Job syndrome)	Chemotaxis, opsonization	Autosomal dominant (STAT3 mutation), autosomal recessive (TYK2, DOCK8 mutation), eczema, staphylococcal abscesses, granulocyte and monocyte chemotaxis affected
Myeloperoxidase deficiency	Bactericidal, fungicidal	Reduced chemiluminescence; autosomal recessive (1:4000); persistent candidiasis in diabetic patients
Glucose-6-phosphate dehydrogenase deficiency	Bactericidal	Phenotypically similar to chronic granulomatous disease
Burns, malnutrition	Bactericidal plus chemotaxis	Reversible defects
Lazy leukocyte syndrome	Chemotaxis	Normal bone marrow cells but poor migration; granulocytopenia
Leukocyte adhesion deficiency	Adherence, chemotaxis, phagocytosis; reduced lymphocyte cytotoxicity	Delayed separation or infection of umbilical cord; lethal bacterial infections without pus; autosomal recessive; neutrophilia; deficiency of LFA-1, Mac-1, CR3
Shwachman-Diamond syndrome	Chemotaxis, neutropenia	Pancreatic insufficiency, metaphyseal chondrodysplasia; autosomal recessive

CR3, Complement receptor 3; *LFA-1*, leukocyte function-associated antigen type 1; *Mac-1*, macrophage 1 antigen.

Congenital Disorders
Kostmann syndrome (HAX-1, G6PC3, ELA-2, G-CSF, GFI-1)
Cyclic neutropenia (ELA-2)
Cartilage hair hypoplasia
Shwachman-Diamond syndrome
Diamond-Blackfan syndrome
Griscelli syndrome
Chédiak-Higashi syndrome
WHIM syndrome (warts, hypogammaglobulinemia, infections, myelokathexis) Glycogen storage disease type Ib Methylmalonicacidemia

NEUTROPHIL DEFECTS
Recurrent dermatologic infections with bacteria such as *Staphylococcus*, *Pseudomonas*, and *Escherichia coli*, and fungi such as *Aspergillus*
Subcutaneous, lymph node, lung, and liver abscesses Pulmonary infections common, including abscess and pneumatocele formation, contributing to chronic disease
Bone and joint infection common
Delayed separation of umbilical cord
Absence of pus at site(s) of infection Poor wound healing

CGD

Pathogenesis NADPH Oxidase Defect

Mutation :

- **X Linked gp 91(70%)**
- **AR P22, P47 ,P67**

Clinical Manifestation

Bacterial infection with catalase + Microbe

- Lung Infection, Lung Abcesses,

- Liver Abcesses, Lymphadenitis

Fungal Infection: Aspergilous, Nocardia

GI problem: GI obstraction ,Malabsorption

GUT problem: bladder Granulomatosis, Uretral obstraction

Diagnosis

NBT

DHR test

PHAGOCYTOSIS

Neutrophil cell count and morphology

Nitroblue tetrazolium dye test/dihydrorhodamine 123 using flow cytometry

Staphylococcal killing, chemotaxis assay

Myeloperoxidase stain

COMPLEMENT DEFECTS

Recurrent bacterial infections with extracellular encapsulated organisms, such as *S. pneumoniae* and *H. influenzae*

Susceptibility to recurrent infections with *Neisseria meningitides*

Increased incidence of autoimmune disease

Severe or recurrent skin and respiratory tract infection

Warning signs of PID:

4 or more new ear infections within 1 year

2 or more new sinus infections within 1 year.

Two or more months on antibiotic with little effect.

Two or more pneumonia per year

Failure of an infant to gain weight or grow normally.

Recurrent ,deep abscesses of the skin or internal organs.

Persistent thrush in mouth or fungal infections on skin.

Need for IV antibiotic to clear infections.

Two or more deep-seated infections includings septicemia

A family history of PID

Table 73-4	General Management of Patients with Immunodeficiency
Avoid transfusions with blood products unless they are irradiated and cytomegalovirus-negative.	
Avoid live virus vaccines, especially in patients with severe T-cell deficiencies or agammaglobulinemia, and in household members.	
Use prophylaxis to *Pneumocystis jiroveci* (*carinii*) in T-cell immunodeficiency, and in X-linked hyper-IgM, consider antifungal prophylaxis in T-cell immunodeficiency.	
Follow pulmonary function in patients with recurrent pneumonia.	
Use chest physiotherapy and postural drainage in patients with recurrent pneumonia.	
Consider using prophylactic antibiotics because minor infections can quickly disseminate.	
Examine diarrheal stools for *Giardia lamblia* and *Clostridium difficile*.	
Avoid unnecessary exposure to individuals with infection. Boil water for T-cell defects and hyper-IgM syndrome (*Cryptosporidium* risk).	
Use immunoglobulin for severe antibody deficiency states (400–600 mg/kg q3–4 wk IV).	