Congenital and Acquired Immunodeficiencies

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Outline:

1. Definitions
2. Classification of defects by cell type affected
    a. B-cell syndromes
    b. T-cell syndromes
    c. Combined T and B-cell syndromes
    d. Innate immunity
3. Classification of defects by cell maturation stage most affected
    a. Defects in lymphocyte maturation
    b. Defects in lymphocyte activation
4. Acquired immunodeficiencies
    a. Malnutrition
    b. Radiation exposure
    c. Chemotherapy and Immunosuppressive drugs
    d. Infections of the immune system
    e. Splenectomy

Learning Objectives, after studying this unit you should be able to:

1. Define primary vs. secondary immunodeficiency.
2. Describe the symptoms, gene defects and/or mechanisms resulting in the primary B-cell deficiencies.
3. Describe the symptoms, gene defects and/or mechanisms resulting in the primary T-cell deficiencies.
4. Describe the symptoms, gene defects and/or mechanisms resulting in the primary combined B- and T-cell deficiencies.
5. Describe symptoms, the gene defects and/or mechanisms resulting in the phagocytic deficiencies.
6. Describe the gene defects and mechanisms resulting in deficiencies of innate immunity.
7. Describe the mechanism (if known) and phenotype for acquired immunodeficiency due to age, malnutrition, radiation, immunosuppressive drugs, infection with HIV, measles virus infection, HIV infection, cancers of the lymphoid system, and splenectomy.
8. Use information about laboratory and histological abnormalities and infectious history to create a differential diagnosis of immunodeficiencies for patients.

Reading References:

1. Review of Medical Microbiology and Immunology 14th edition by W. Levinson, under Access Medicine on the MUSC Library website
2. Abbas & Lichtman, Basic Immunology Chapter 12

Disease name	***Type of immune defect***	***Gene defect or etiology***	***Key differentiating characteristics***
X-linked Agammaglobulinemia	B cell	BTK, Bruton's tyrosine kinase	Defect in B cell maturation, absent mature B cells, very low Igs, B1 cell IgM present
Selective Ig Deficiency			
IgA Deficiency			
Common Variable Immunodeficiency (CVID)			
DiGeorge Syndrome			
Hyper IgE syndrome			
Tcell Receptor defects			
IL-12 deficiency			
Chronic mucocutaneous candidiasis			
Chronic granulomatous disease (CGD)			
Bare Lymphocyte syndrome			
Chediak-Higaski syndrome			
Toll Like Receptor defect			
Early Complement deficiencies			
Late Complement deficiencies			
NK cell deficiency			
Leukocyte adhesion deficiency			
SCID			

Reticular dysgenesis			
X-linked Hyper IgM syndrome			
Age related immune impairment			
Malnutrition			
Radiation			
Cancers of the lymphoid system			
Iatrogenic immunosuppression			
Post-measles virus infection			
HIV infection			
Splenectomy			

Congenital and Acquired Immunodeficiencies

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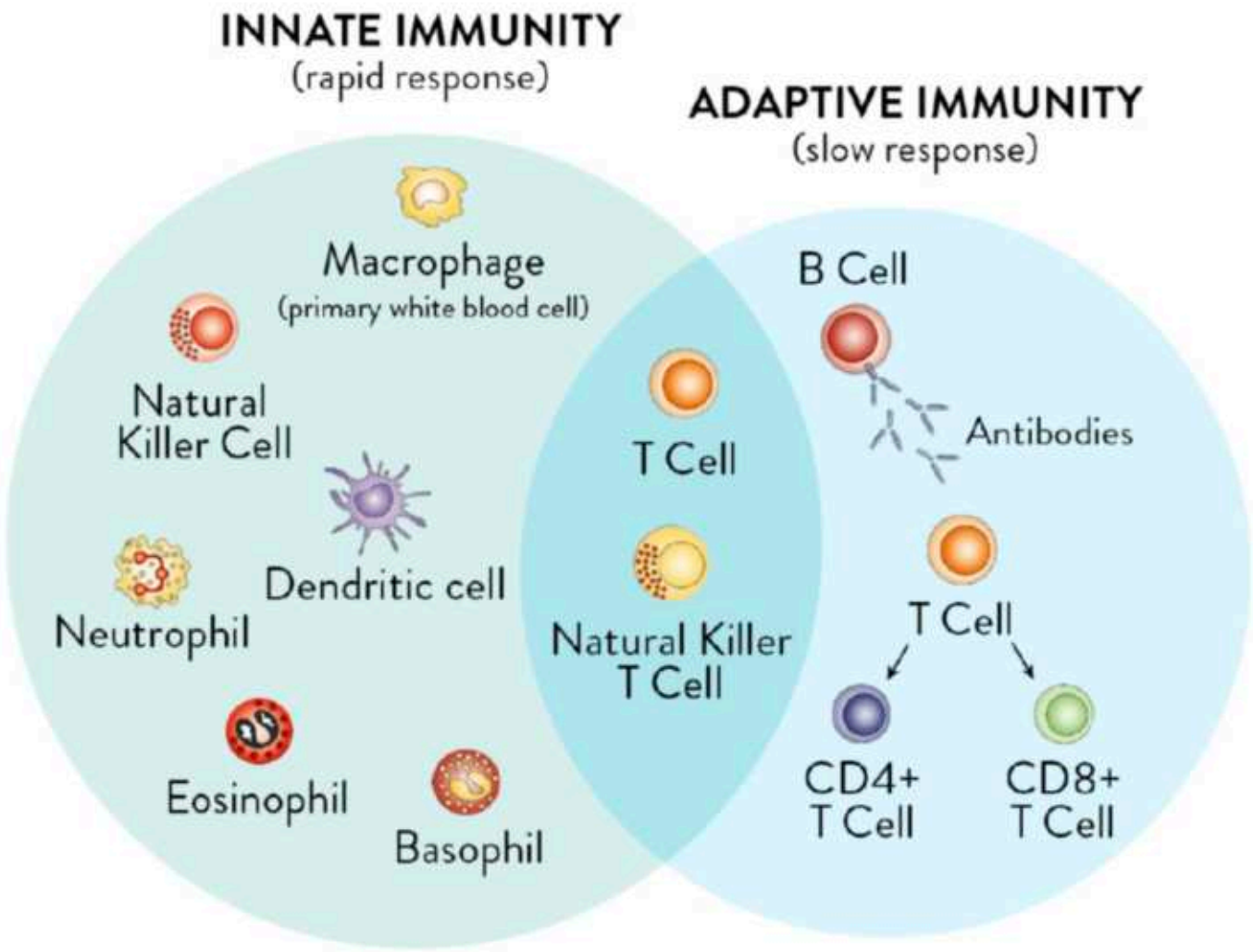
(partial slide credit Dr. Laura Kasman)

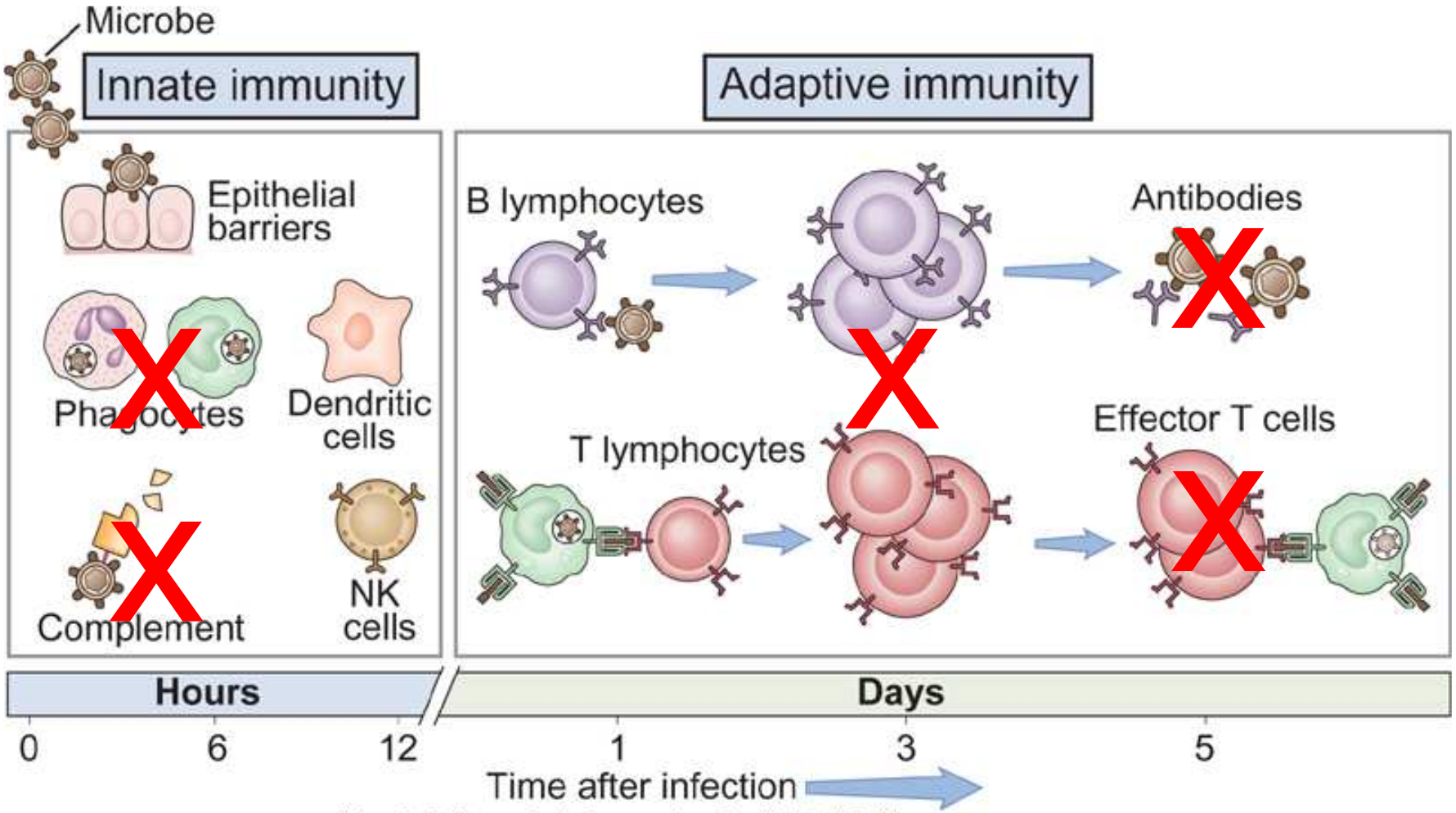
Overview

- Definitions
- Classification of defects by cell types most affected
- Classification of defects by cell maturation stage most affected
- Acquired immunodeficiencies

Immune System



Immunodeficiency can affect any part of the immune system



Primary vs. Secondary Immunodeficiencies

Primary=congenital

- **Definition: Genetic defects** that increase susceptibility to infection
- Estimated frequency in the U.S. is **1 in 700** (Many are subclinical)
- Usually detected in childhood, but *may* be diagnosed later in life
- Vary from mild to life-threatening

Secondary=acquired

- **Definition:** Increased susceptibility to infection due to age, a disease process, or toxic exposures. e.g. :
  - Malnutrition
  - Radiation or chemotherapy
  - Lymphoid cancers, bone marrow metastasis
  - Immunosuppressive drugs
  - Infection of leukocytes
  - Splenectomy

What is an IEI?

- Inborn errors of immunity (IEI – formerly called congenital or primary immunodeficiencies, PI, PID or PIDD) are a group of rare, inborn disorders of the immune system that result from:
  - Absent or reduced number of immune cells
  - Absent or reduced function of immune cells
- Increased risk for recurrent or severe infections
- Increased risk for autoimmunity, lymphoproliferation and hyperinflammation (e.g. PIRD)

General manifestations of B-cell, T-cell, and innate immunodeficiencies

Type of immunodeficiency	Histopathologic and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens *in vitro*	Viral and other intracellular microbial infections (e.g., *Pneumocystis jiroveci*, atypical mycobacteria, fungi) Virus-associated malignancies (e.g., EBV-associated lymphomas)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable; pyogenic bacterial infections

IEI and Susceptibility to Infections: Clues to the Immune Defect

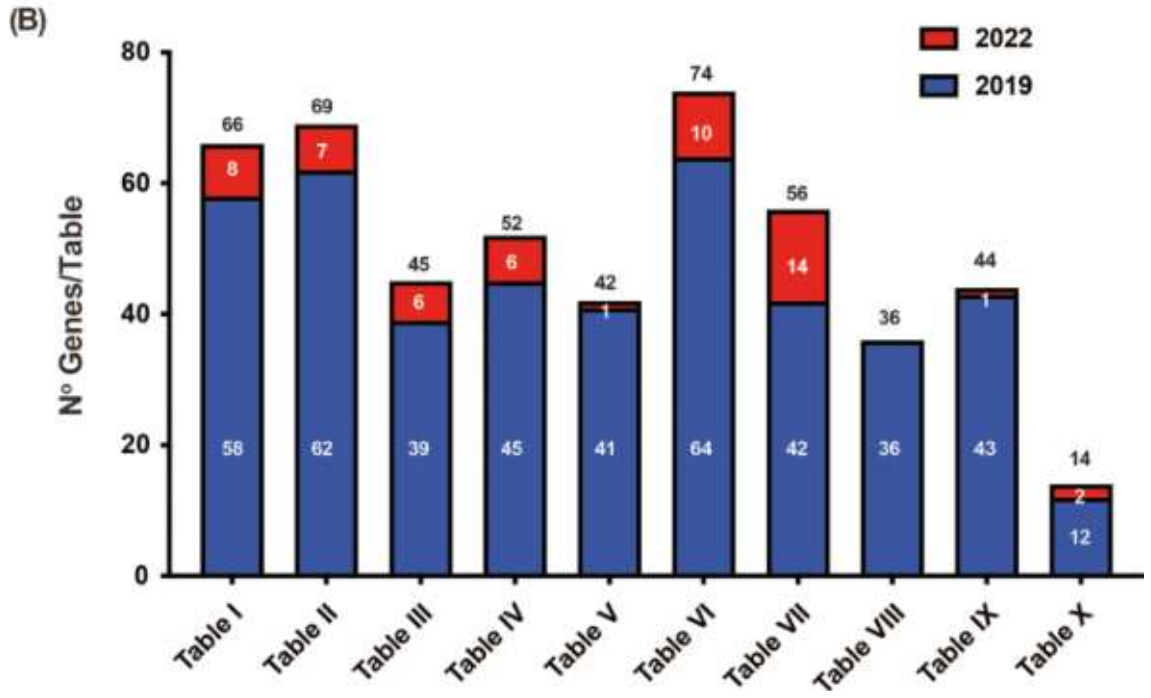
	Bacterial	Viral	Parasitic	Fungal	Mycobact
T cells	X	X	X	X	X
B cells	X	X			
NK cells		X			
PMN cells	X			X	
MN cells	X				X
Complement	X				

Classification by cell types affected

B-cell defects	T-cell defects	Innate immunity
• Agammaglobulinemia • Selective Ig isotype deficiencies • Common Variable Immunodeficiency (CVID)	• DiGeorge Syndrome • TCR defects • IL-12/IL-12 receptor deficiency • Chronic muco-cutaneous candidiasis	• Chronic Granulomatous disease (CGD) • Leukocyte adhesion deficiency (LAD) • Bare lymphocyte syndromes • Chediak-Higashi syndrome • Toll like receptor (TLR) defects • Complement deficiencies
Combined T and B-cell defects		
• Severe combined immunodeficiency (SCID) • Reticular dysgenesis • Job's syndrome (HIES, STAT3 deficiency) • X-linked Hyper IgM syndrome • Wiskott-Aldrich syndrome • Bare lymphocyte syndrome I & II		

Frequency & Distribution of IEI

- Incidence: 1/700-1,000,000 (2:1, ♂:♀)
- Distribution



I. Combined/T-B deficiencies

II. CID + syndromic features

III. Predominantly antibody

IV. Immune dysregulation

V. Phagocytic defects

VI. Intrinsic or Innate

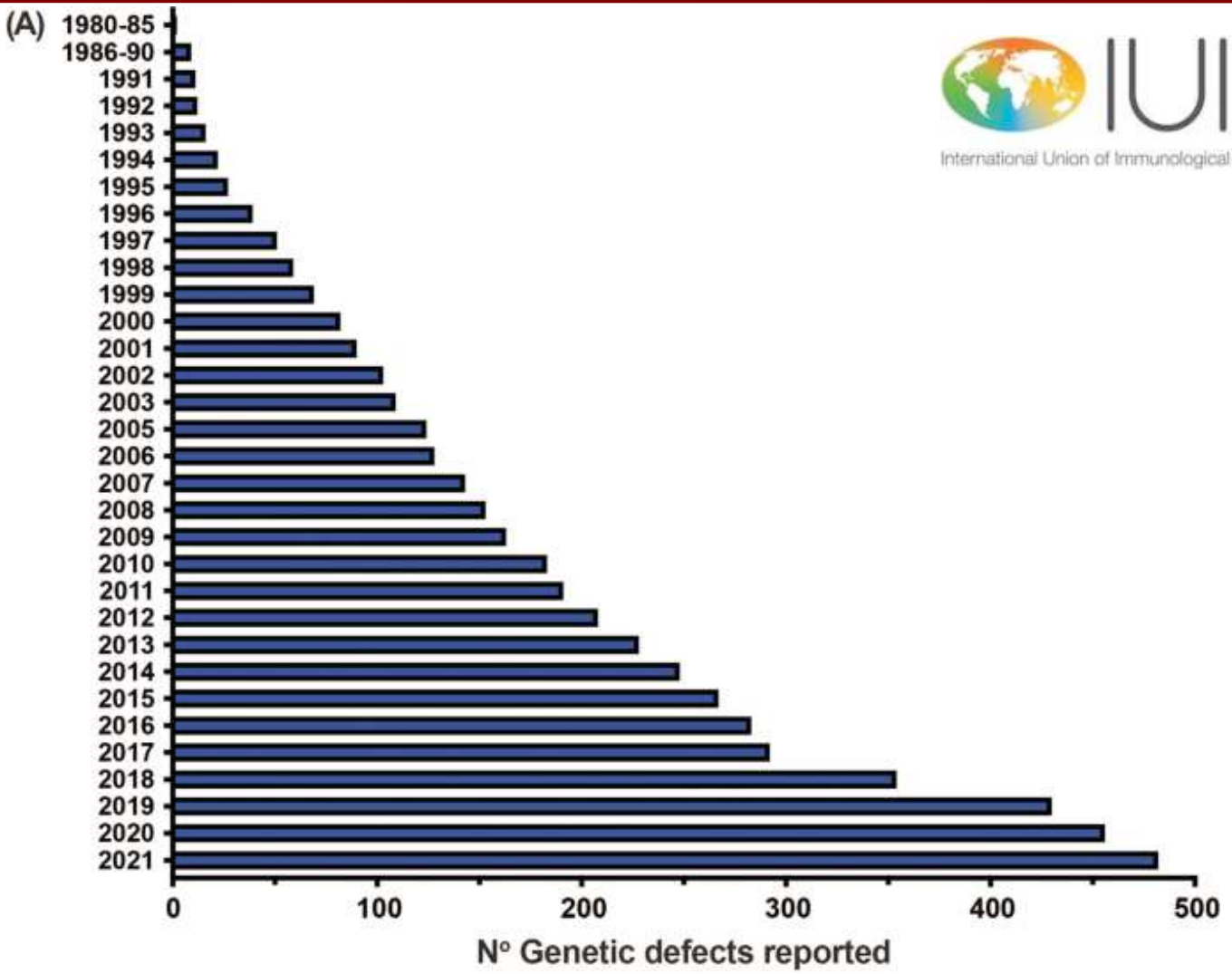
VII. Autoinflammatory disorders

VIII. Complement deficiency

IX. Bone marrow failure

X. Phenocopies of PID

IEI Over the Years

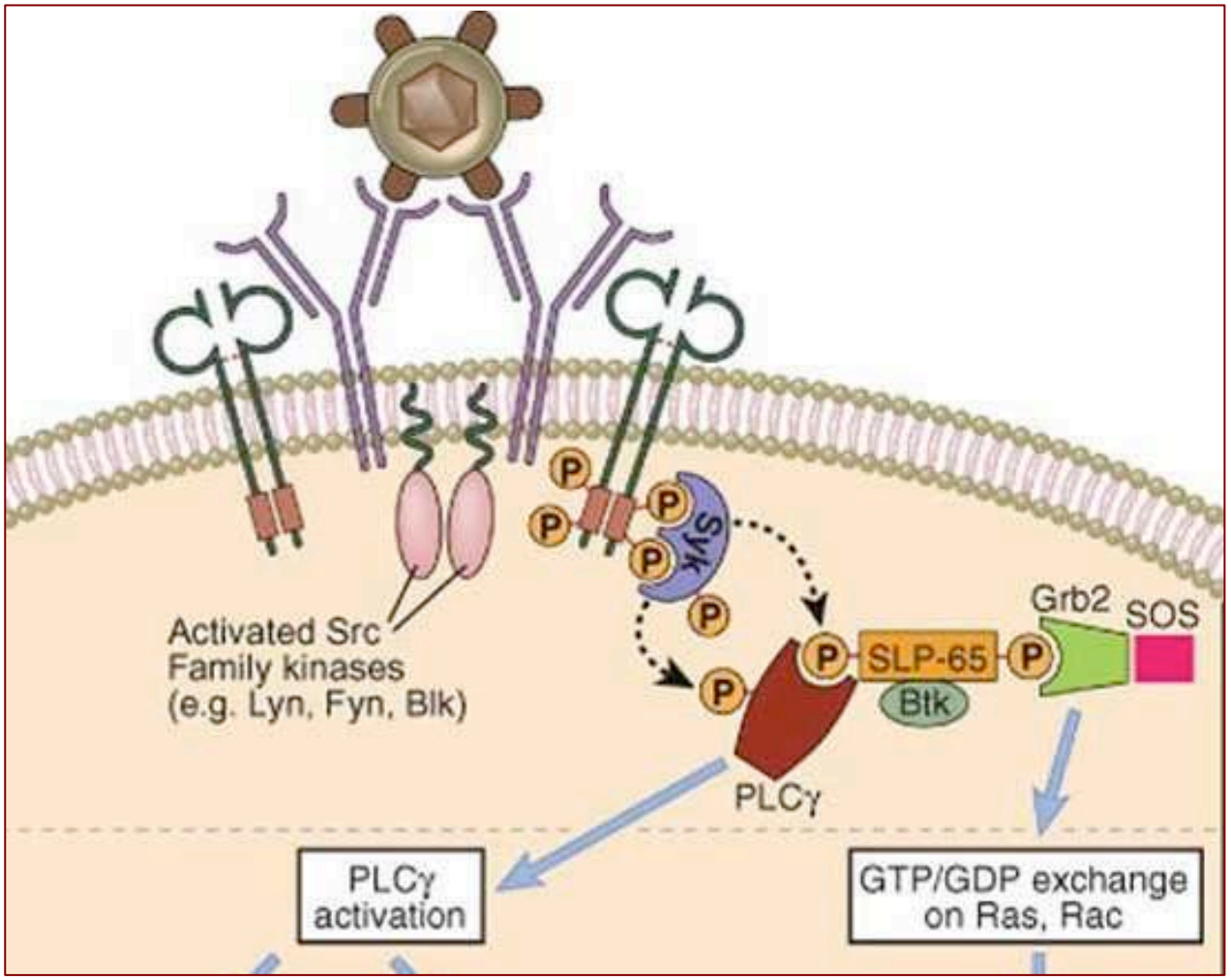


B-cell syndromes

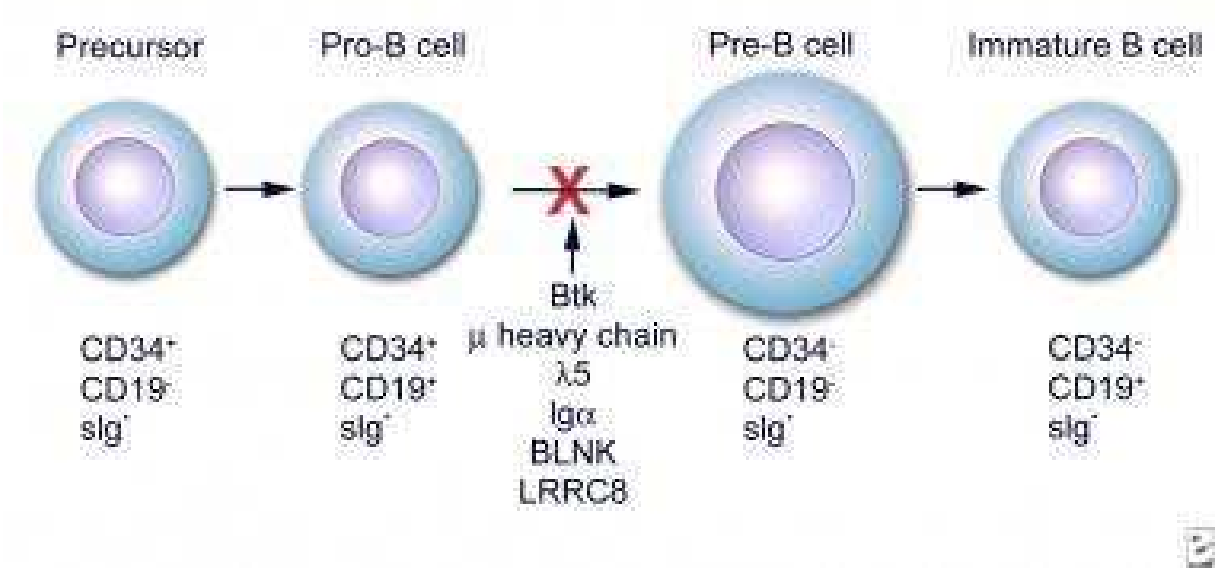
- Agammaglobulinemia
- Selective Ig isotype deficiencies
- Common Variable Immunodeficiency

B-cell syndrome: X-linked agammaglobulinemia (a.k.a. Bruton's agammaglobulinemia)

- Gene defect: Bruton's tyrosine kinase (Btk)
- Mechanism: Btk is essential for signal transduction in pre-B cells from the pre-B cell receptor. No signal, no B-cell survival.



B-cell syndrome: X-linked agammaglobulinemia (a.k.a. Bruton's agammaglobulinemia)



- Lab Phenotype: Absence of gamma globulin in the blood
  - No peripheral b cells (B2 B-cells) in blood, lymphoid tissues, no germinal centers, no plasma cells
  - Normal T and NK cells, very low Igs

B-cell syndrome: X-linked agammaglobulinemia (a.k.a. Bruton's agammaglobinemia)

- **Clinical Phenotype**
  - Recurrent sinopulmonary infections (*S. pneumo, S. pyogenes, S. aureus, Hib)*
  - Higher risk for chronic diarrhea from *Giardia*
  - Higher risk for developing chronic enterovirus meningoencephalitis
  - Small or no tonsils or lymphadenopathy
  - Autoimmune disorders develop in ~20%
- Lifelong treatment with pooled immunoglobulin therapy (weekly or monthly) is a relatively successful

B-cell syndrome: Selective Ig Isotype deficiencies

- Most common is IgA deficiency (1:700 people)
- Gene defect: varies, but IgA heavy chain genes (IgαC) are normal
- Mechanism: block in differentiation of B-cells to IgA secreting plasma cells
- Phenotype: very low serum IgA with normal or elevated IgM and IgG.
  - Clinically may be normal, or have increased susceptibility to respiratory infections or GI infections
  - May have allergic reaction to IgA positive blood transfusions
  - Increased risk for autoimmune conditions

B-cell syndrome: Selective Ig Isotype deficiencies

- Most common IgG deficiency is IgG3 in adults.
- Gene defect: varies, but IgγC genes are almost always normal
- Mechanism: block in differentiation of B-cells to IgG3 secreting plasma cells
- Phenotype: very low serum levels of a specific IgG isotype
  - Clinically usually normal, but some have increased sinopulmonary bacterial infections

B-cell syndrome:

Common variable immunodeficiency

- **Gene defect**: various, most undefined
- **Mechanism**: heterogeneous, but include intrinsic B-cell defects, deficient T-cell help, excessive Tregs
- **Phenotype**: mature B-cells but impaired memory and class-switched B cells.
  - defined by reduced serum levels of Ig, impaired antibody responses
  - increased sinopulmonary bacterial infections, autoimmune disorders, lymphadenopathy, higher incidence of malignancy

B cell Syndromes to Know

IgA Deficiency	IgG Deficiency	CVID	Specific Antibody Deficiency	Agammaglobulinemia
Normal IgG	Low IgG	Low IgG	Normal IgG	Low IgG
Very low IgA (IgA <7)	Normal IgA	Low IgA	Normal IgA	Low IgA
Normal IgM	Normal IgM	Variable IgM	Normal IgM	Low IgM
Normal B cells	Normal B cells	Usually normal B cells	Normal B cells	No/Very low B cells
Normal Function	Impaired Function	Impaired Function	Impaired Function	Impaired Function

T-cell syndromes

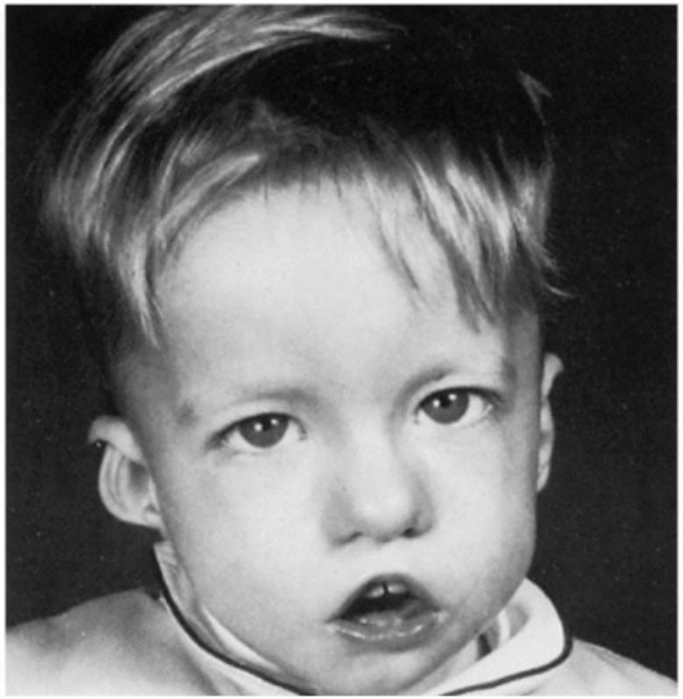
- DiGeorge Syndrome
- TCR defects
- Chronic mucocutaneous candidiasis
- IL-12/IL-12 receptor deficiency

T-cell syndrome:

DiGeorge Syndrome

- **Gene defect:** deletion at chromosome 22q11.2, often the *TBX1* gene encoding the T-box 1 transcription factor

- **Mechanism:** Congenital malformation of 3rd and 4th pharyngeal pouches resulting in absence or hypoplasia of thymus and parathyroid glands



T-cell syndrome:

DiGeorge Syndrome

- **Phenotype:** Abnormal thymic development leads to low or absent T-cells that are unresponsive to polyclonal activators
- Antibody levels are usually normal
- Increased susceptibility to *Mycobacteria*, fungi, viruses (including after live virus vaccination)

T-cell syndrome:

DiGeorge Syndrome

- **Clinical Phenotype**
  - Primary hypoparathyoridism
  - Cleft palate, laryngotracheal anomalies
  - Cardiac defects: Tetralogy of Fallot, Ventral Septal Defect, Interrupted Aortic Arch most common
  - Increased risk of autoimmune conditions
  - Higher risk for ADHD & psychiatric conditions

DiGeorge Syndrome

CATCH-22

Cardiac abnormalities

Abnormal facies

Thymic absence/abnormality, **T** cell abnormality

Cleft palate

Hypocalcemia

Chromosome **22**

Microdeletion in chromosome 22

Thymic hypoplasia → Hypocalcemia → Neonatal Seizure or Tetany

Congenital heart defect

Abnormal facies

Cleft palate

T-cell Syndrome:

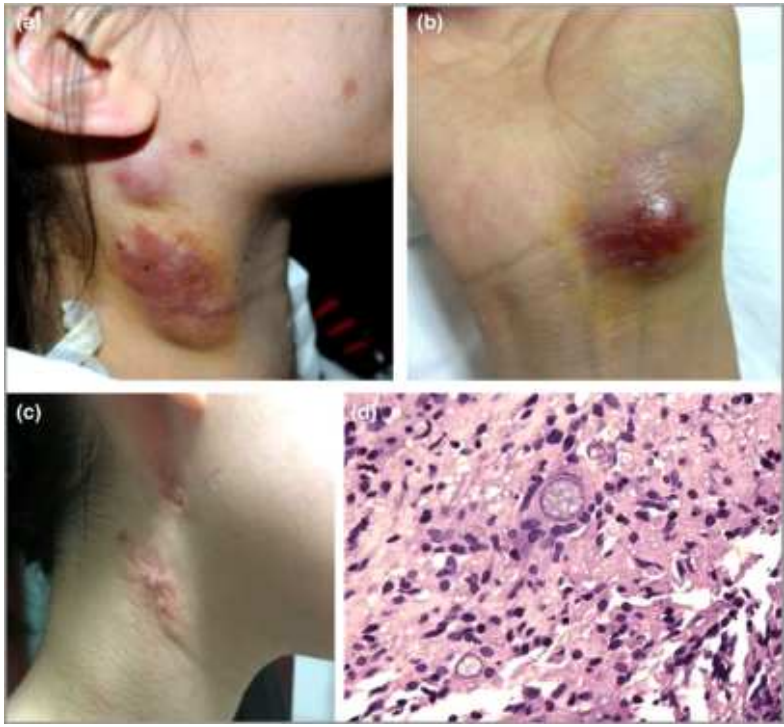
Defects in TCR expression or signaling

- **Gene defect:** CD3 subunits, ZAP70
- **Mechanism:** defective TCR-mediated signaling
- **Phenotype:** Normal or elevated numbers of blood lymphocytes, decreased IL-2, IL-2R, and IFN-γ production
  - Specific case is **chronic mucocutaneous candidiasis (STAT 1 loss of function defect)**- defective T-cell cytokine production results in specific susceptibility to *Candida sp.*

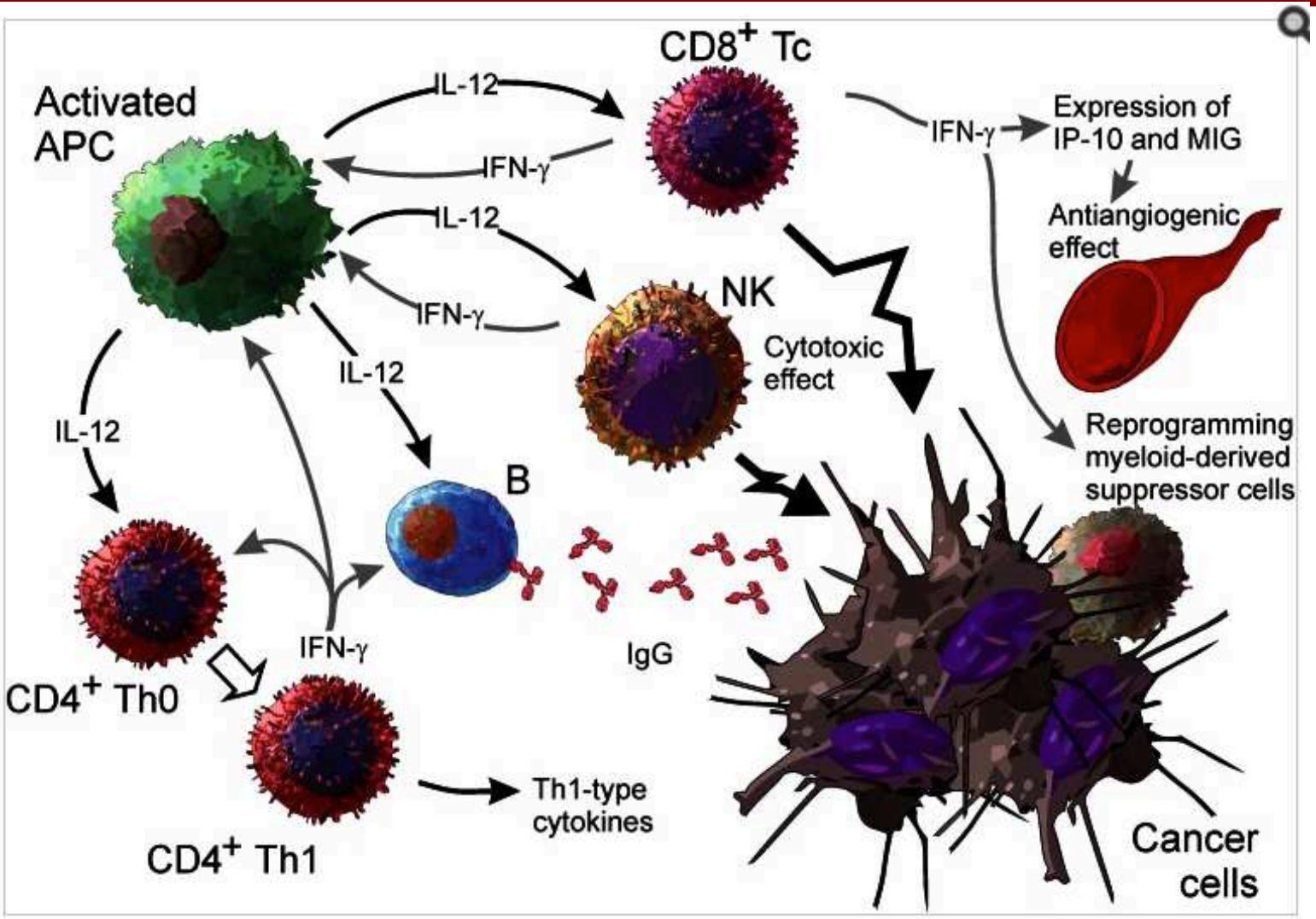
T-cell syndrome:

IL-12/IL-12R deficiency

- Autosomal recessive mutations in ligand or receptor genes
- Decreased Th1 responses
- Low IFN-γ and TNF production
- Disseminated fungal and intracellular bacterial infections most common (e.g. *Mycobacteria, coccidioidomycosis*)
- Fever unexpectedly reduced or absent



Review of Functions of IL-12



Combined B and T-cell syndromes

- Severe combined immunodeficiency (SCID)
- Reticular dysgenesis
- Job's Syndrome (STAT3 deficiency, HIES)
- X-linked Hyper IgM syndrome
- Wiskott-Aldrich syndrome
- Bare lymphocyte syndrome I and II

Clinical Presentation of SCID

"Classic SCID" presents in infancy

- Failure to thrive +/- chronic diarrhea
- Recurrent thrush
- Recurrent, severe & opportunistic infections (PJP, candida, MAI, vaccine-associated disease, CMV)
- Has absent or very low T cells
- B cells are absent or non-functional
- Or exam may be completely normal until infected & critically ill

Genetic Basis of SCID

Cellular phenotype			Gene Defect	Inheritance	% of cases
T-cells	B-cells	NK cells			
Low/Absent	Present	Absent	IL2-Rγ (common γ chain)	X-linked	45-50%
Low/Absent	Present	Absent	Janus-associated kinase-3 (JAK3)	AR	7%
Low/Absent	Present	Present	IL7-Rα	AR	10%
Low/Absent	Present	Present	CD3 ε, δ, or ζ subunits	AR	Rare
Low/Absent	Present	Present	FOXN1	AR	Very rare
Low/Absent	Present	Present	22q11 (athymia in complete Digeorge syndrome)	AD	Very rare
Low/Absent	Present	Variable	CD45	AR	Rare
Low/Absent	Present	Present	Coronin-1A	AR	Very rare
Absent	Absent	Present	RAG1/2	AR	<5%
Absent	Absent	Present	DCLRE1C (Artemis)	AR	<5%
Absent	Absent	Present	Cernunnos (XLF)	AR	Very rare
Absent	Absent	Present	DNA Ligase-4	AR	Very rare
Absent	Absent	Present	DNA PKcs	AR	Very rare
Low/Absent	Low/Absent	Low/Absent	Adenosine deaminase (ADA)	AR	16%
Low/Absent	Low/Absent	Low/Absent	Purine nucleotide phosphorylase (PNP)	AR	Rare
Present	Present	Present	ORAI1	AR	Very rare
Present	Present	Present	STIM1	AR	Very rare

7% failed to identify a pathogenic genetic variant

***Most (but not all) are lymphopenic

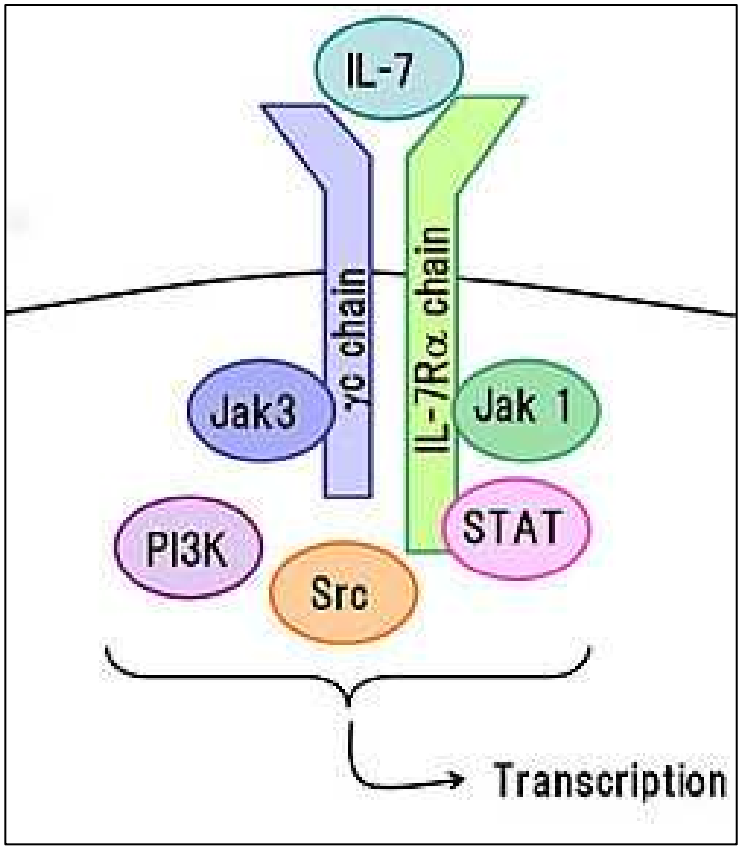
Combined syndrome:
X-linked SCID

- David Vetter, the “Boy in the Plastic Bubble”
- Lived in isolation until he received an unmatched bone marrow transplant from his sister at age 12
- Died of Epstein-Barr virus-induced cancer 4 months later

Combined syndrome:

X-linked SCID

- **Genetic Defect:** absent common cytokine receptor γc chain
- **Mechanism:** IL-7 signals not received, so very few T-cells begin maturation
- Low T, normal or increased B, low serum Ig, low NK



Also common to IL-2, IL4, IL-9, IL-15

Combined syndrome:

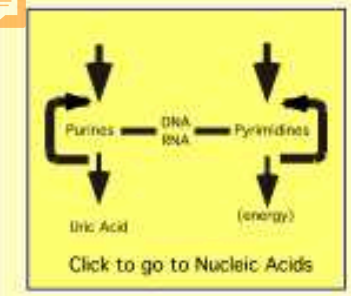
Autosomal recessive SCID (ADA)

- Gene defect: Adenosine deaminase (ADA)
- ADA Mechanism: build up of metabolites of purine synthesis (dATP) inhibits ribonucleotide reductase, a master regulator of DNA synthesis rate (mostly harms rapidly dividing cells)
- Cell death at lymphoid progenitor cell stage: loss of T, B, and NK cells.

Combined syndrome:

Autosomal recessive SCID (PNP)

- Gene defect: purine nucleoside phosphorylase, *PNP* gene
- PNP Mechanism: same as ADA, but block is at a different step
- Very similar in phenotype to ADA deficiency
- Both can be treated with enzyme replacement injection



Adenosine Deaminase Deficiency

Deficiency of adenosine deaminase, the first enzyme in the breakdown of adenosine nucleotides, causes Severe Combined Immunodeficiency Syndrome, or SCIDS, probably by blocking Ribonucleotide Reductase via excess dATP buildup.

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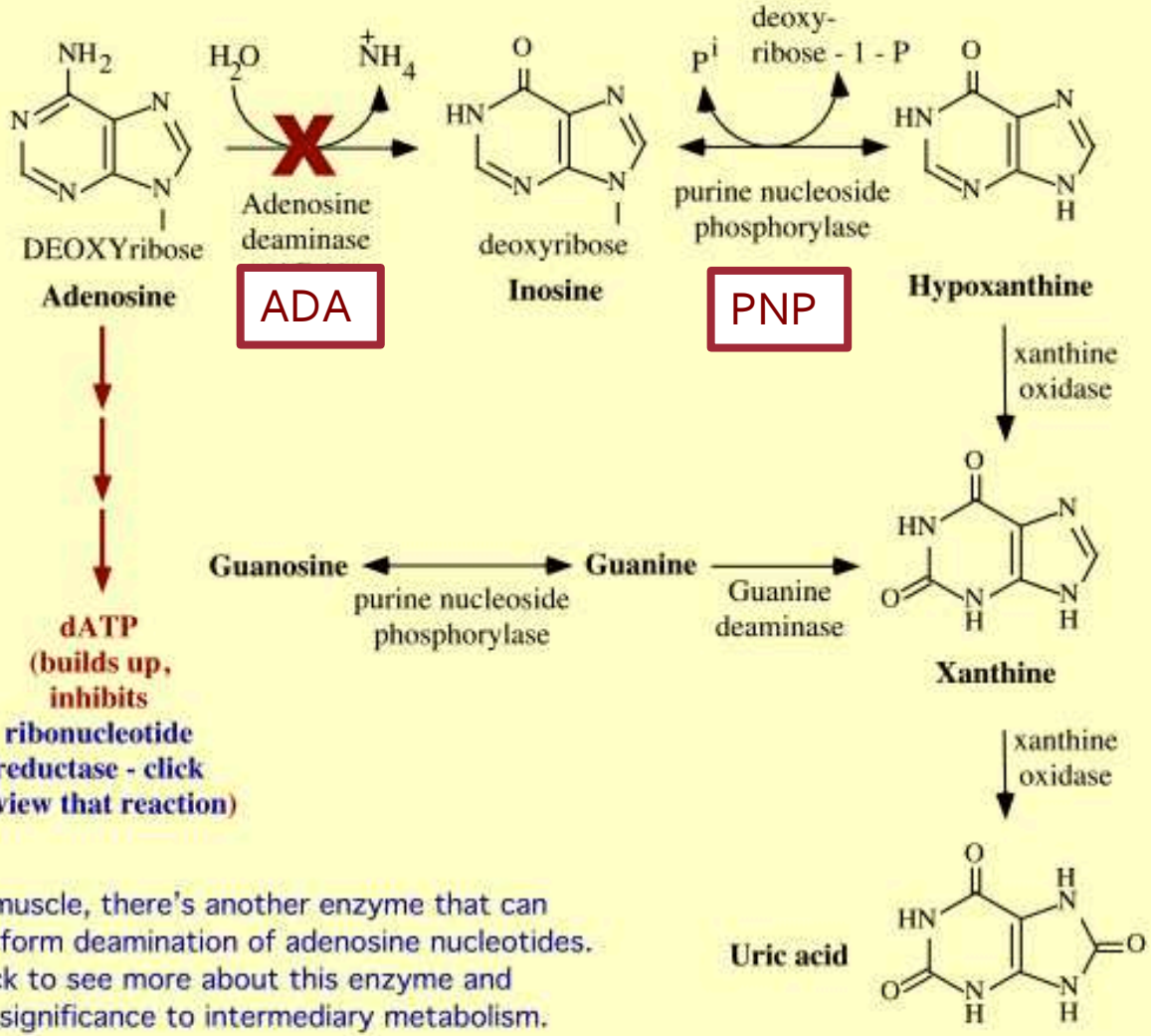


Severe Combined Immunodeficiency Syndrome, a profound lack of both cell-mediated and humoral immunity, is due to nonproliferation of both Blymphocytes and T lymphocytes.

It is thought that dATP build up especially in lymphocytes, and that consequently ribonucleotide reductase is in inhibited, blocking any proliferation in those cell types.

NCBI
Click to go to OMIM

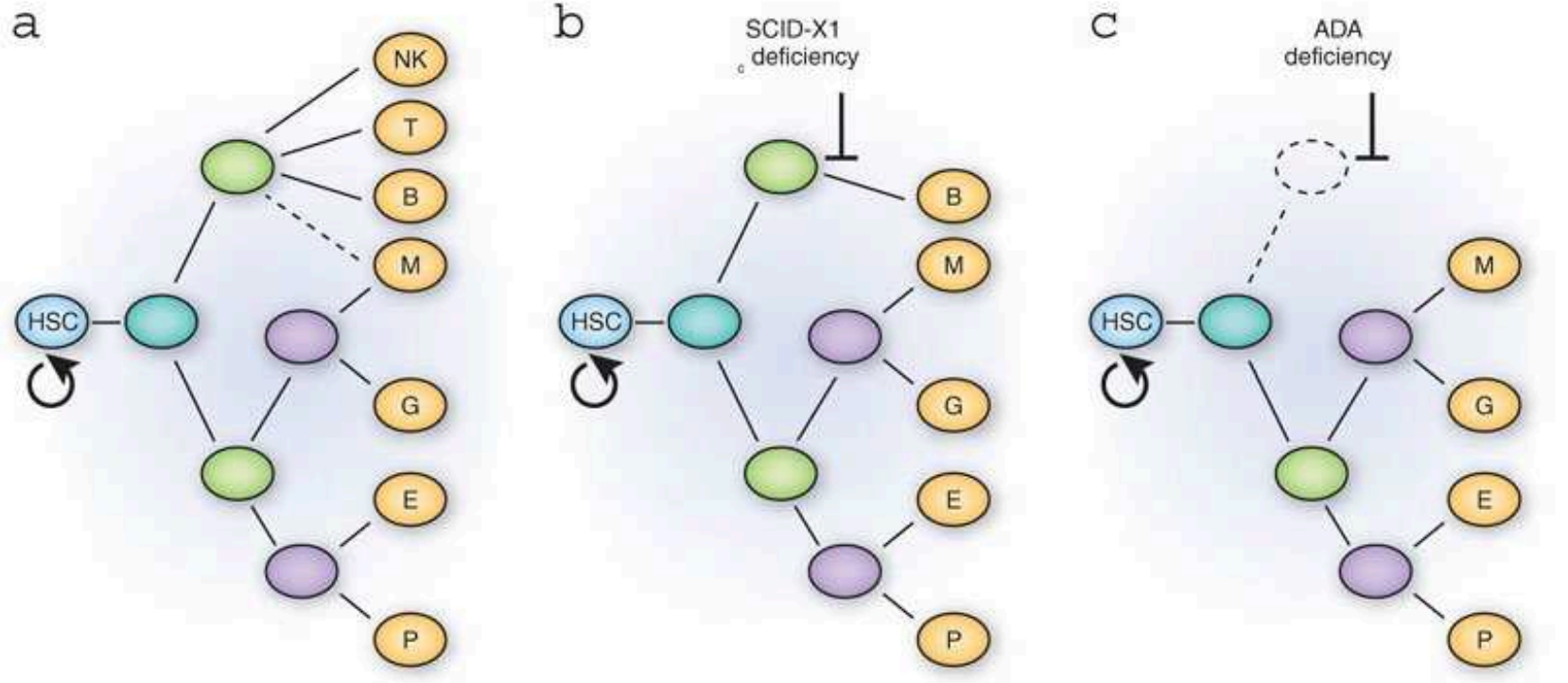
In muscle, there's another enzyme that can perform deamination of adenosine nucleotides. Click to see more about this enzyme and its significance to intermediary metabolism.

Figure 1. FROM [20 years of gene therapy for SCID Alain Fischer, Salima Hacein-Bey-Abina & Marina Cavazzana-Calvo*Nature Immunology 11, 457–460 (2010) doi:10.1038/ni0610-457*]

Normal hematopoesis

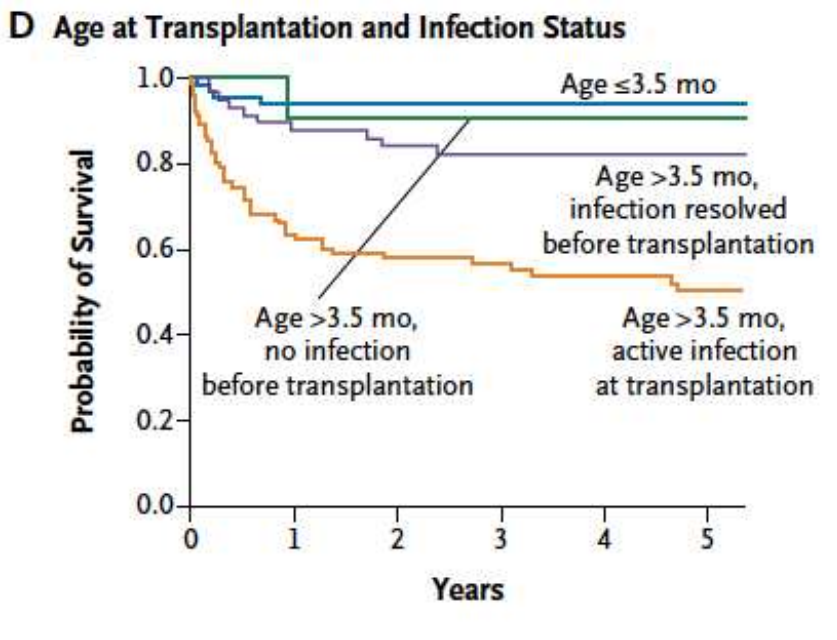
X-linked SCID

ADA or PNP SCID



Management of SCID

- Treatment
  - Hematopoietic stem cell transplantation can be curative (ideally before DOL 100)
  - ADA-SCID should be started on enzyme replacement then ideally gene therapy
  - All babies with SCID should be started on immunoglobulin replacement, prophylactic antibiotics (Bactrim/Atovaquone) & antifungal, synagis if in season



Combined Syndrome:
Reticular dysgenesis

- **Gene defect:** a mitochondrial gene, ak2
- **Mechanism:** assumed to be at the level of the myeloid – lymphoid **stem cell**
- **Phenotype:** most severe form of SCID
  - Absence of T lymphocytes
  - Absence of B lymphocytes
  - Absence of most myeloid cells, including granulocytes
  - Death in early infancy

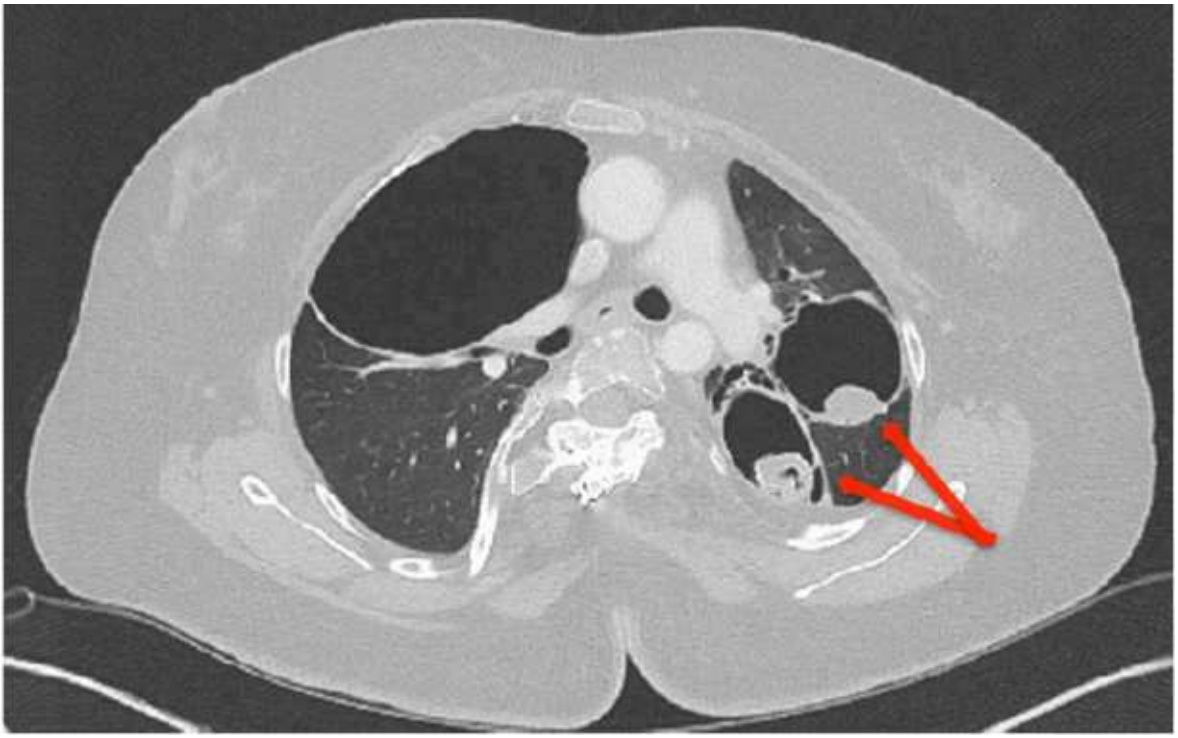
Combined Syndrome:

Job's Syndrome (HIES)

- Due to autosomal dominant *STAT3* loss of function mutations
- High serum IgE levels, low IFN-γ, low Th17
- **Phenotype:** triad of severe eczema, recurrent cold Staphylococcal abscesses, and recurrent sinopulmonary infections

Combined Syndrome:

Job's Syndrome (HIES)

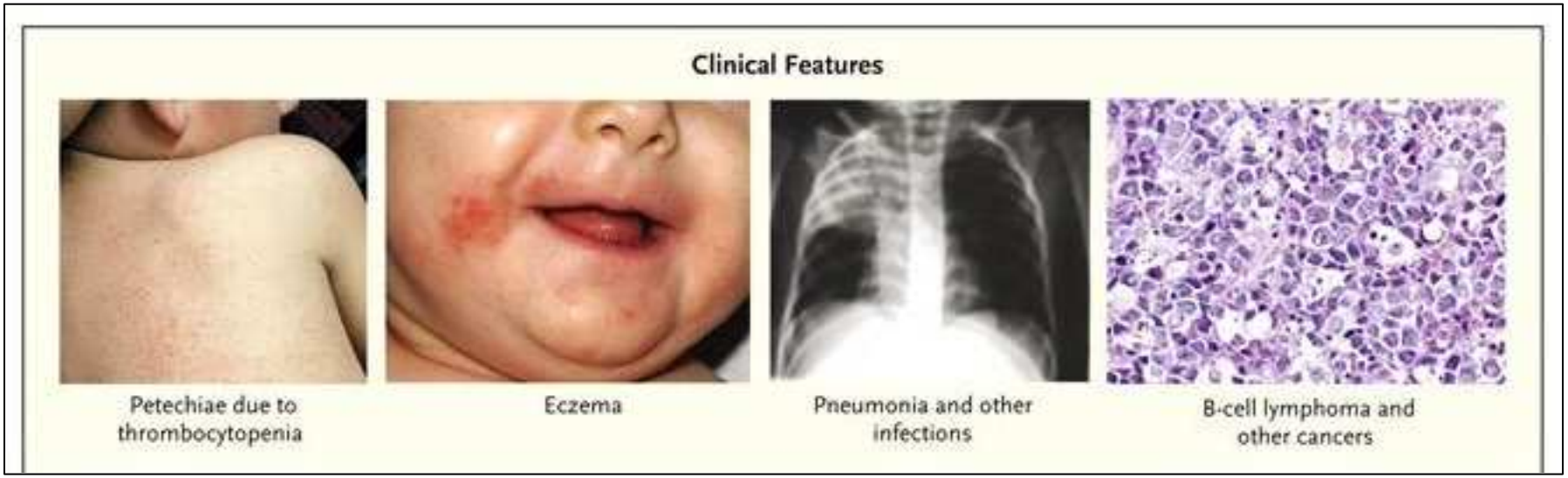


Combined Syndrome:
X-linked Hyper IgM syndrome

- **Gene defect:** CD40L
- **Mechanism:** lack of CD40L on T helper cells leads to defective T-cell help for B-cell and macrophage activation
- **Phenotype:** Normal B and T-cell numbers
  - No isotype switching so that IgM is the major serum antibody
  - Severe deficiency of cell-mediated immunity against intracellular microbes.

Combined syndrome:

Wiskott-Aldrich Syndrome



- X-linked recessive in *WAS* gene
- IgM low, IgA and IgE high
- Thrombocytopenia, eczema, increased infections with encapsulated bacteria, lymphomas

Combined Syndrome:
Bare lymphocyte syndrome (Class I)

- **Gene defect:** TAP 1, TAP 2
- **Mechanism:** Decreased MHC I expression on all cells
- **Phenotype**: defective CD8+T-cell activation. Strangely, have increased susceptibility to respiratory bacterial infections, not viruses.

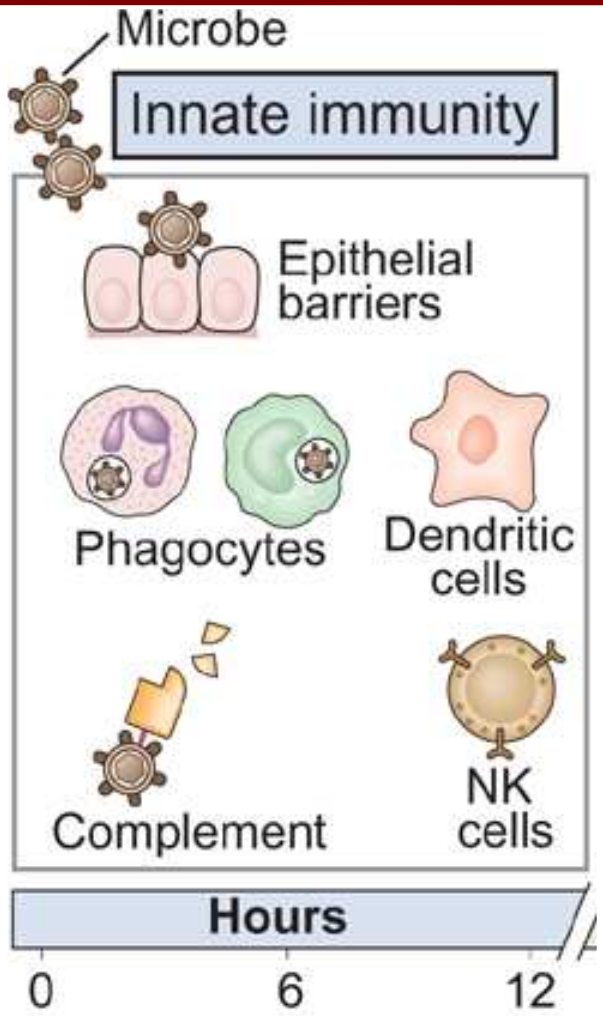
Combined Syndrome:

Bare lymphocyte syndrome (Class I)

Combined Syndrome:
Bare lymphocyte syndrome (Class II)

- **Gene defect:** transcription factors regulating MHC II expression
- **Mechanism:** low or absent MHC II expression on macrophage, dendritic and B-cells
- **Phenotype**: defective CD4+T-cell activation, cell mediated immunity, and humoral immune responses to proteins

Review of effectors of innate immunity



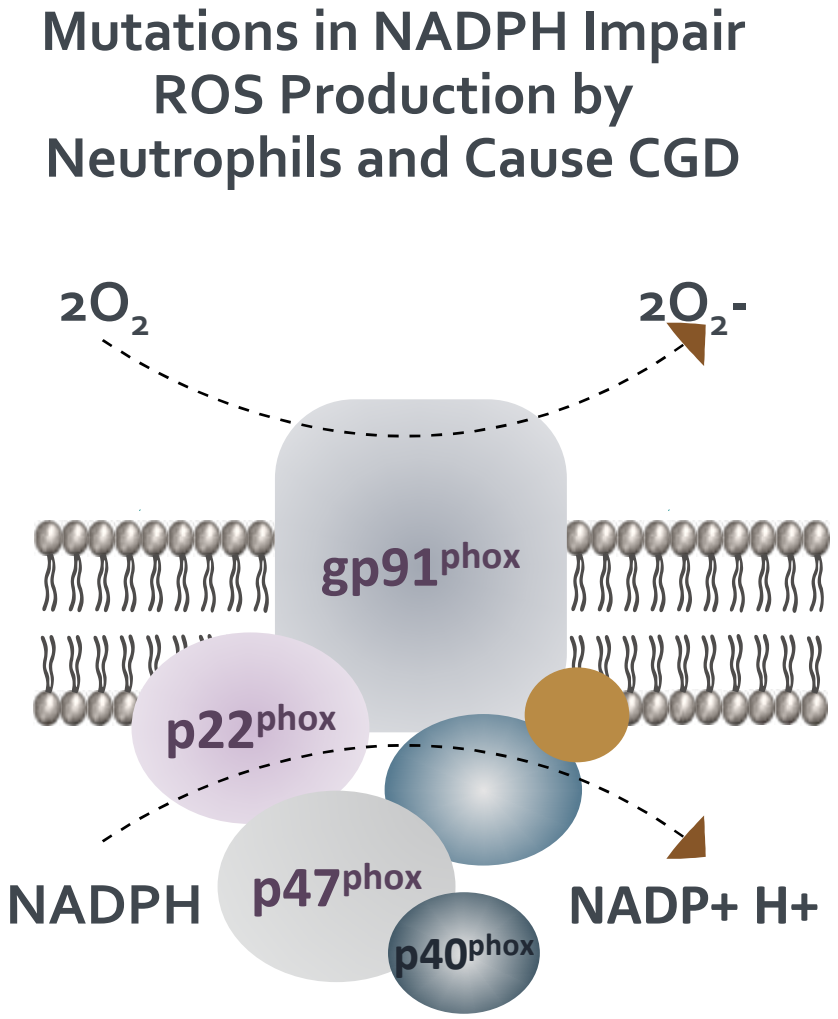
- Professional phagocytes
  - Monocytes
  - Macrophage
  - Granulocytes
- NK cells
- Complement

Congenital defects of Innate Immunity

- Chronic Granulomatous Disease
- Leukocyte Adhesion Deficiency
- Complement deficiencies
- Chediak-Higashi Syndrome
- Toll-like receptor defects

Chronic Granulomatous Disease (CGD)

- **Genetic defect** in NADPH oxidase, needed for generation of superoxide ions and hydrogen peroxide
  - Phagocytes cannot readily kill ingested bacteria or fungi (*especially catalase positive organisms*)
  - Persistent microbial antigens induce a persistent T helper response, and granulomas form



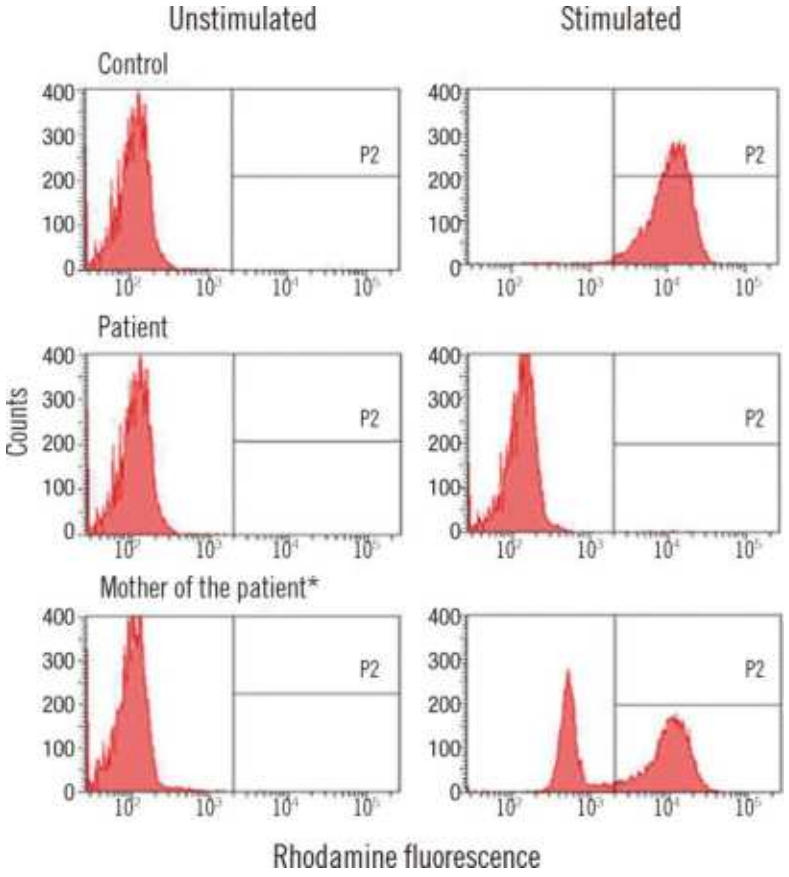
Clinical Presentation of CGD

- Severe recurrent bacterial and fungal infections
  - Pneumonias & empyemas, skin abscesses, osteomyelitis, suppurative lymphadenitis
  - Organisms: *Staph aureus, Serratia marscecens, Nocardia, Burkholderia cepacia, Aspergillus*
- Granulomas
- Poor wound healing after surgery
- High rate of IBD, perianal fistulas & abscesses

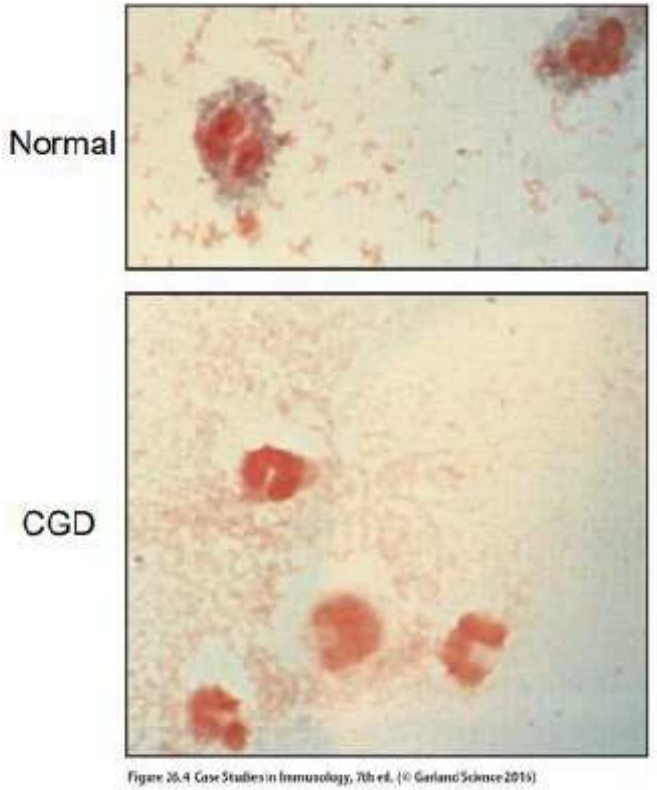
Diagnosis of CGD

- The most common form (67%) of CGD is X-linked and involves a defect in the 91-kDa chain of cytochrome b_{558}.
- Lab evaluation
  - Dihydrorhodamine-123 assay
    - Using flow cytometry, this is a quantitative assessment of NADPH oxidase activity
    - Can distinguish between X-linked CGD and AR forms, as well as carriers
  - Nitroblue tetrazolium (NBT) dye
    - Using light microscopy and NBT dye, this is a qualitative assessment of NADPH oxidase activity
    - NBT turns from yellow to dark blue when it combines with released H+

Lab Evaluation of CGD



DHR

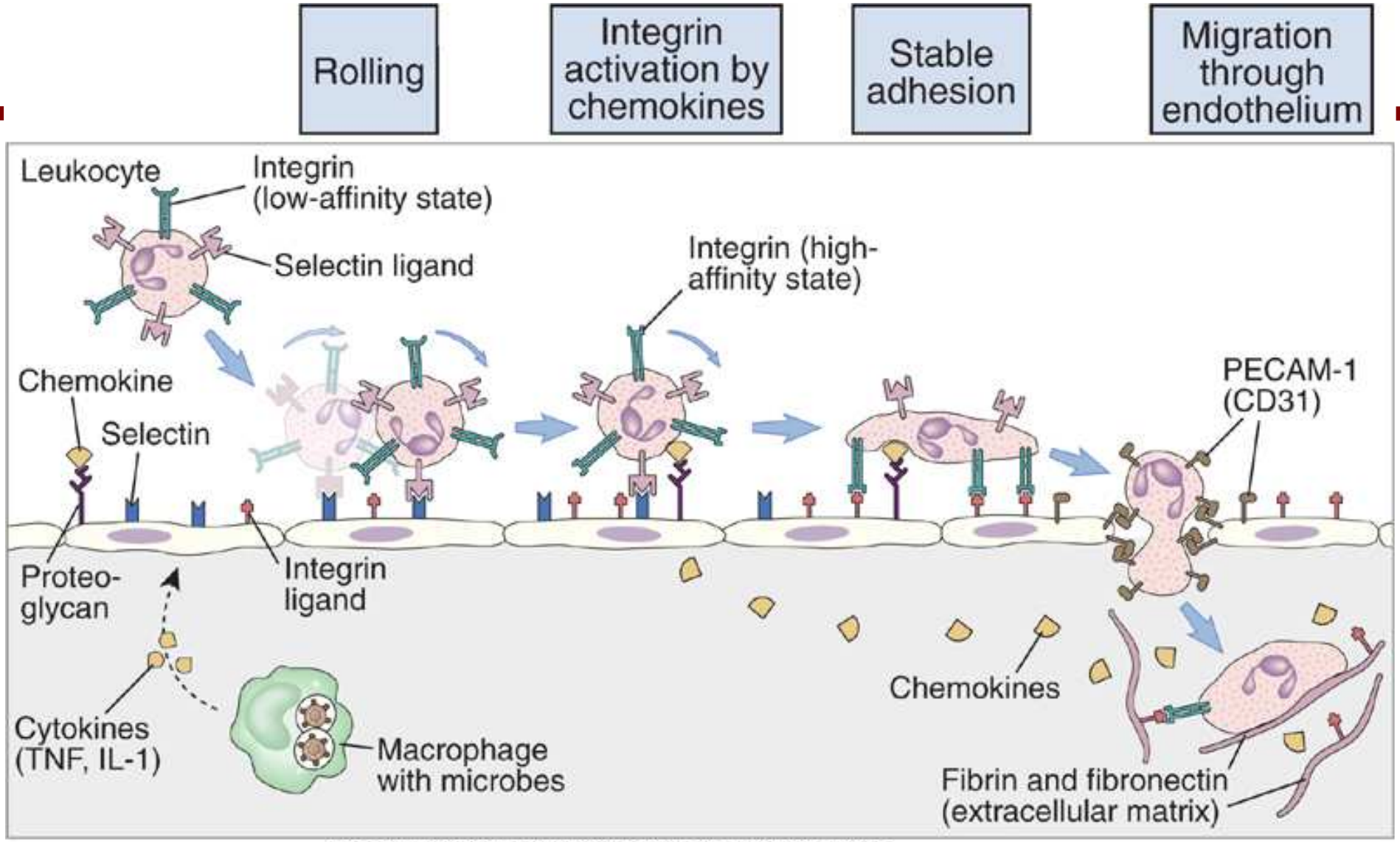


NBT

Leukocyte Adhesion Deficiency (I,II, III)

- **Gene defects**: β chain of β2 integrins (CD18), GDP fucose transporter, Kindlin 3
- **Mechanism:** defective leukocyte migration into tissues, making them unable to appropriately respond to injury or infection
- **Phenotype: :** leukocytosis with defective recruitment of lymphocytes to areas of infection. Recurrent bacterial and fungal infections. Usually die from infections by age 2 if severe.
  - Marked neutrophilia but no PMNs in pus

Review: How leukocytes enter the site of infection



Leukocyte Adhesion Deficiency (I,II, III)

Complement deficiencies

- C1q, C1r, C1s, C4, and C2 deficiency→ phenotype is sepsis, bacteremia, and systemic lupus erythematosus
- C5-C9 (terminal pathway) deficiency→ phenotype is increased susceptibility to invasive *Neisseria* infections
- Alternative or MBL pathway deficiencies→ phenotype is frequent encapsulated bacterial infections

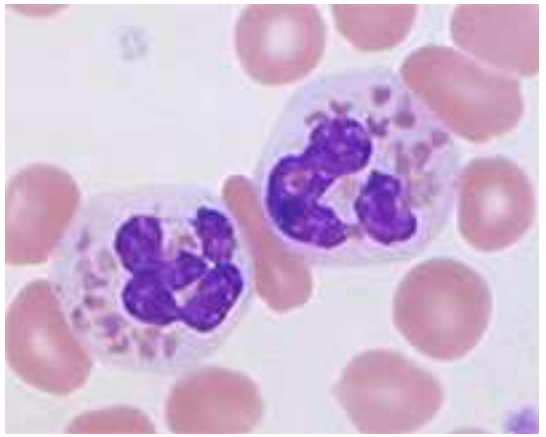
Complement regulator deficiencies

C1-inhibitor deficiency ~1 in 25,000 people	**Hereditary angioedema (autosomal dominant)**  Swollen right hand during a hereditary angioedema attack. 
Factor H or Factor I haploinsufficiency	Predisposition to atypical hemolytic uremic syndrome and age-related macular degeneration
Homozygous Factor H deficiency	C3 overconsumption and increased risk of pyogenic bacterial infections

Chediak-Higashi Syndrome

- **Gene defect:** LYST gene (lysosomal trafficking regulator)
- **Mechanism:** defective lysosomal granule exocytosis
- **Phenotype**: defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, natural killer cells, cytotoxic T cells, and many other cell types.
  - recurrent infections by pyogenic bacteria

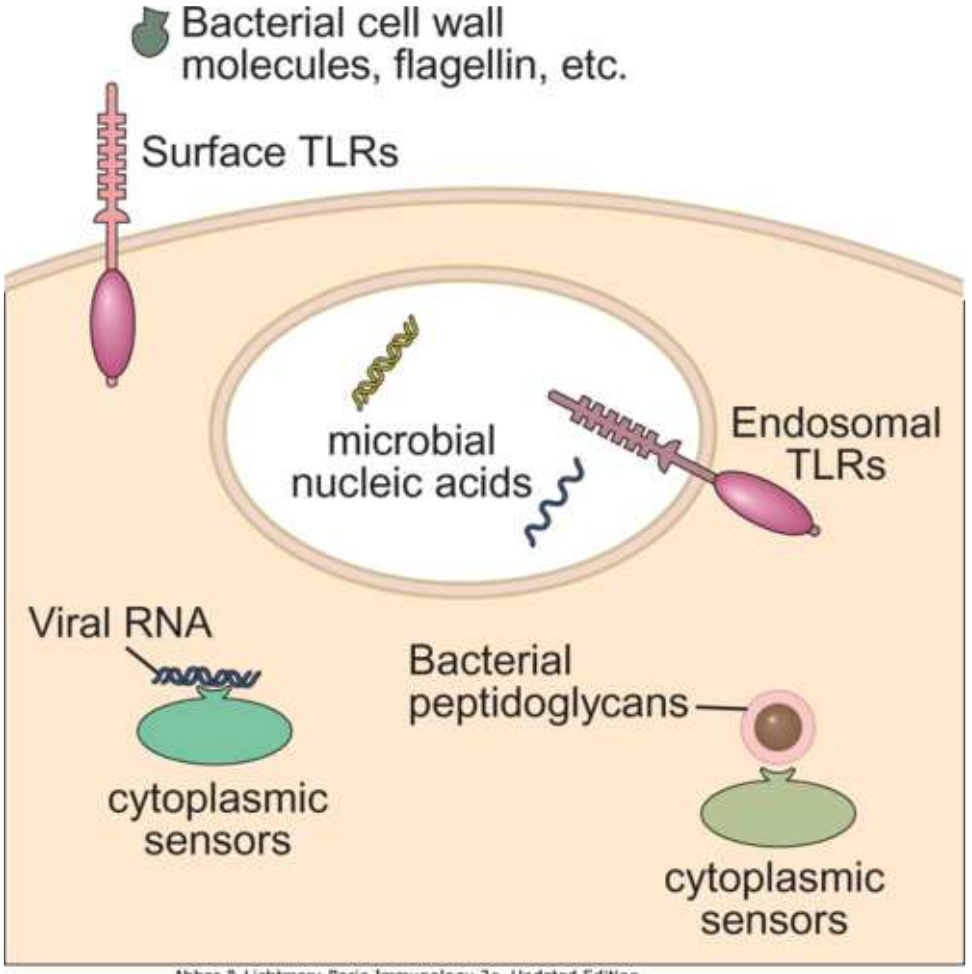
Chediak-Higashi Syndrome



- Also associated with albinism and neuropathies
- Note giant lysosomes in PMNs

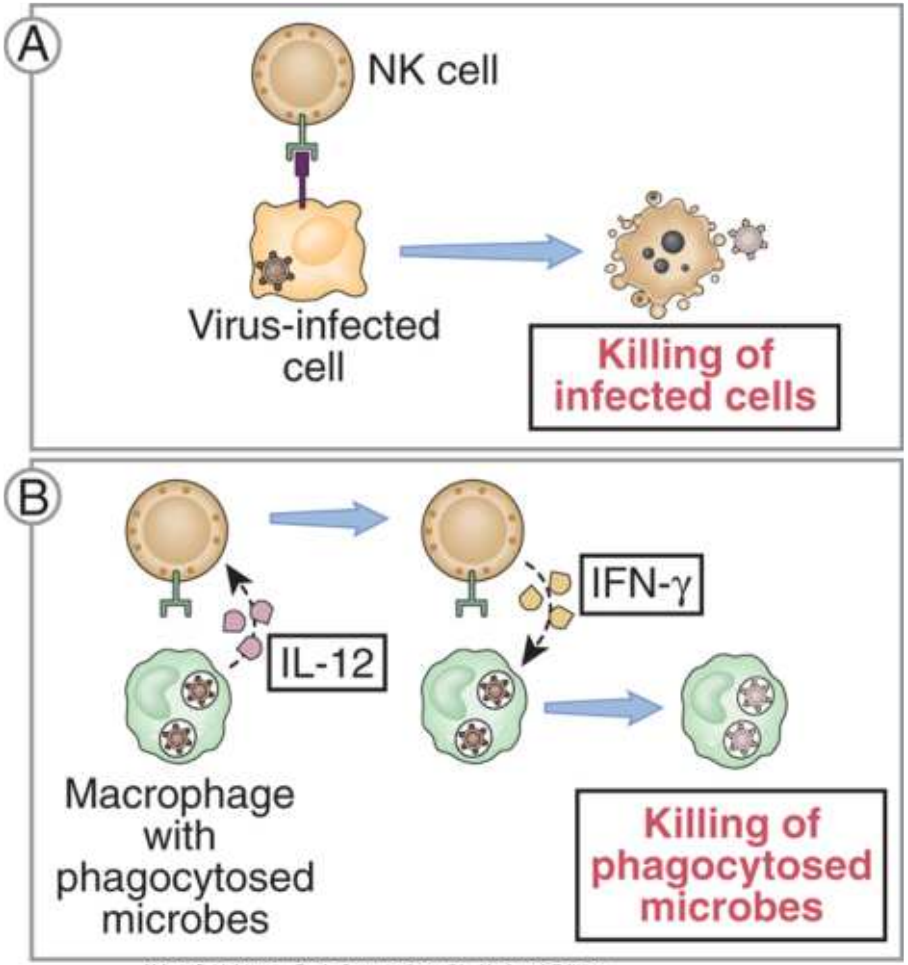
Toll-like Receptor Defects

- Best known defect with a known phenotype is in a TLR signaling protein, IRAK4 (Toll and interleukin-1 receptor-associated kinase-4)
- Type I IFN signaling defects result in specific viral susceptibilities



NK cell Deficiencies

- Multiple mutations can produce this deficiency
- Main phenotype: Increased susceptibility to severe herpesvirus infections
- NK cells are also very low to absent in some forms of SCID



Classification of primary immunodeficiencies by cell stage defect

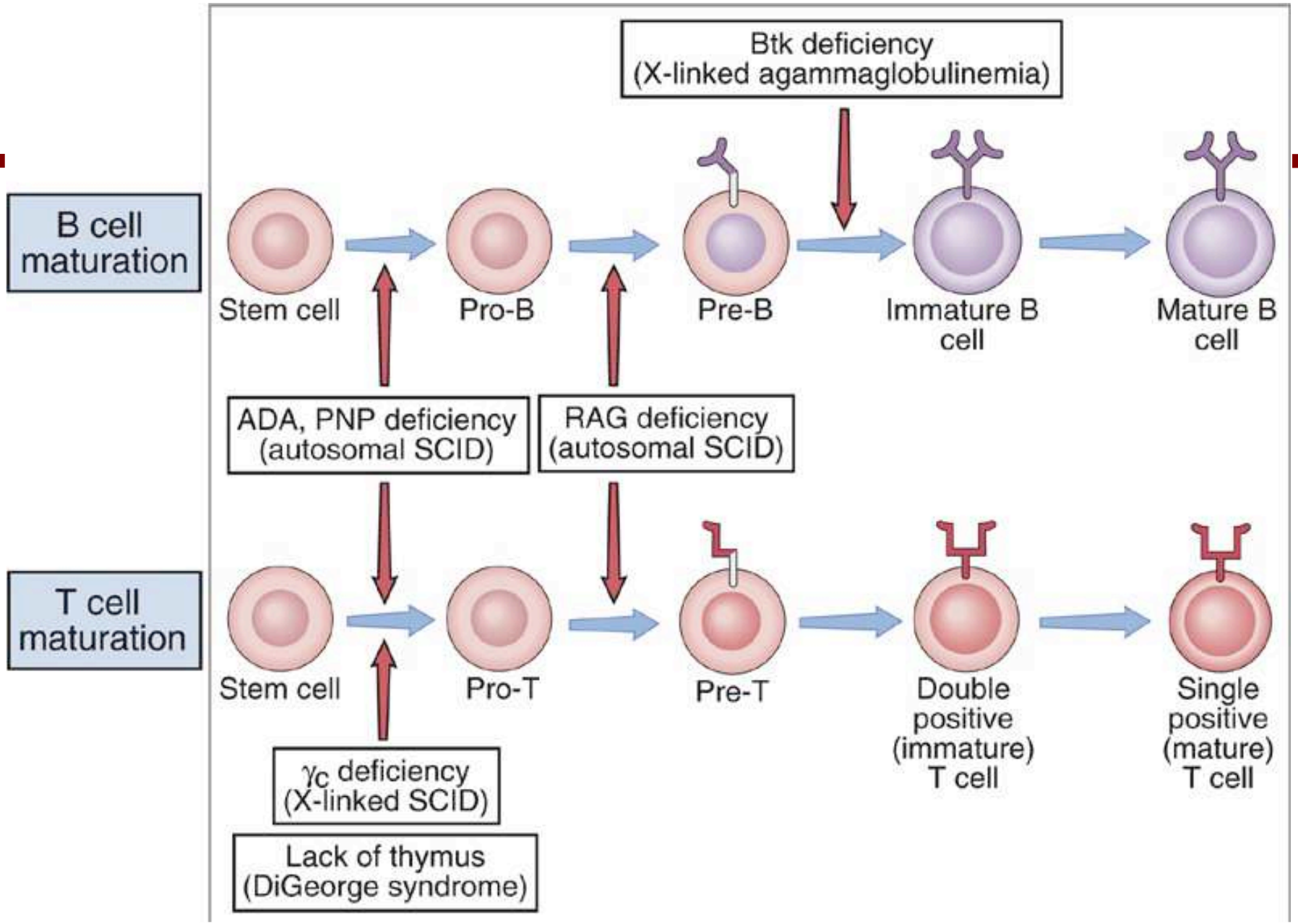
1. defects in lymphocyte maturation

2. defects in lymphocyte activation and effector functions

Defects in lymphocyte maturation

- Severe-combined immunodeficiency (SCID)
  - **X-linked SCID**
  - **Autosomal recessive SCID (ADA or PNP defects)**
  - **Autosomal recessive SCID (other defects)**
  - Reticular dysgenesis
- B-cell only deficiencies
  - **X-linked agammaglobulinemia**
  - Ig Heavy chain deletions
- T-cell only deficiencies
  - **DiGeorge syndrome**

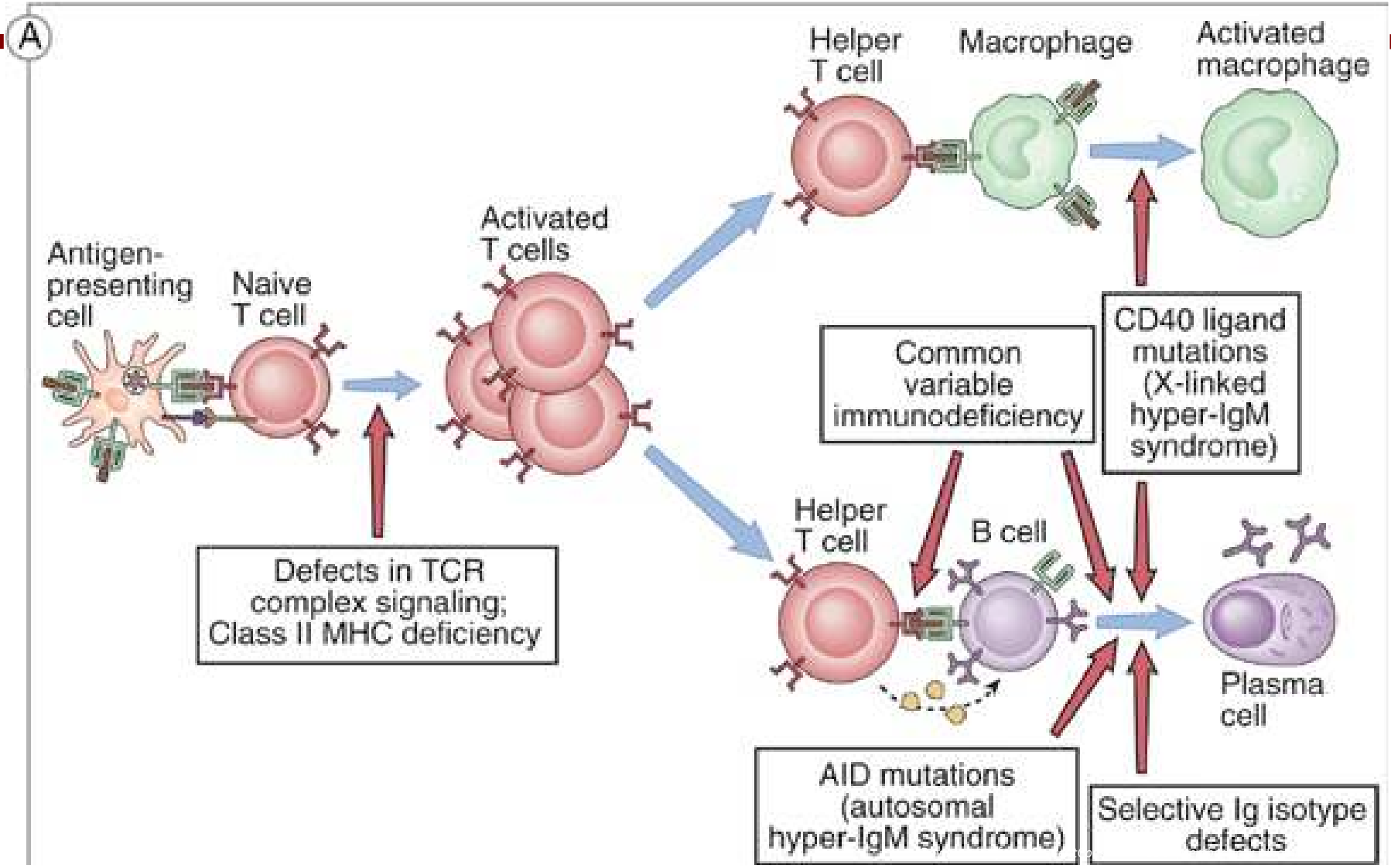
Summary of immune maturation defects



Defects in lymphocyte activation

- **X-linked Hyper IgM syndrome**
- Job's syndrome (HIES, STAT3 deficiency)
- **Common Variable Immunodeficiency**
- Bare lymphocyte syndrome
- Defects in TCR expression or signaling

Summary of activation–effector defects



Diagnosis of Primary Immunodeficiencies

B-cell defects

- Reduced serum Ig
- Reduced responses to vaccines
- Reduced B-cell counts
- Absent or small follicles in lymphoid tissues

T-cell defects

- Reduced T-cell counts
- Reduced responses to polyclonal T-cell activators
- Deficient DTH reactions

Secondary / acquired deficiencies

Acquired / Secondary Immunodeficiencies

- Increased susceptibility to infection as a result of:
  - Age
  - Malnutrition (protein or caloric)
  - Radiation and/or cancer chemotherapy
  - Cancers of the lymphoid system, metastasis into bone marrow
  - Treatment with immunosuppressive drugs
  - Infection of cells of the immune system
  - Splenectomy

Effect of age on immunity

- Newborn to age 2:
  - unable to produce an effective humoral response to T-independent Ag (e.g. polysaccharides)
  - More susceptible to herpesvirus infections
- Elderly (>70)
  - Thymic atrophy results in reduced T-cell responses, reduced response to vaccines, increased autoimmunity

Protein-Calorie Malnutrition

- Chronic starvation (marasmus/cachexia) itself does not cause immunodeficiency
- Kwashiorkor can cause immunodeficiency
  - Body mass is usually preserved, at least initially
  - Cell-mediated immunity is depressed, severe lymphopenia and loss of DTH responses
  - Accompanying edema can result in cellulitis

Acquired / Secondary Immunodeficiencies

- Radiation/ chemotherapies that kill rapidly dividing cells
  - Mechanism: reduced stem cell populations
- Cancers of the lymphoid system, metastasis into bone marrow
  - Mechanism: reduced environment for lymphocyte precursor development

Secondary / Acquired immunodeficiency

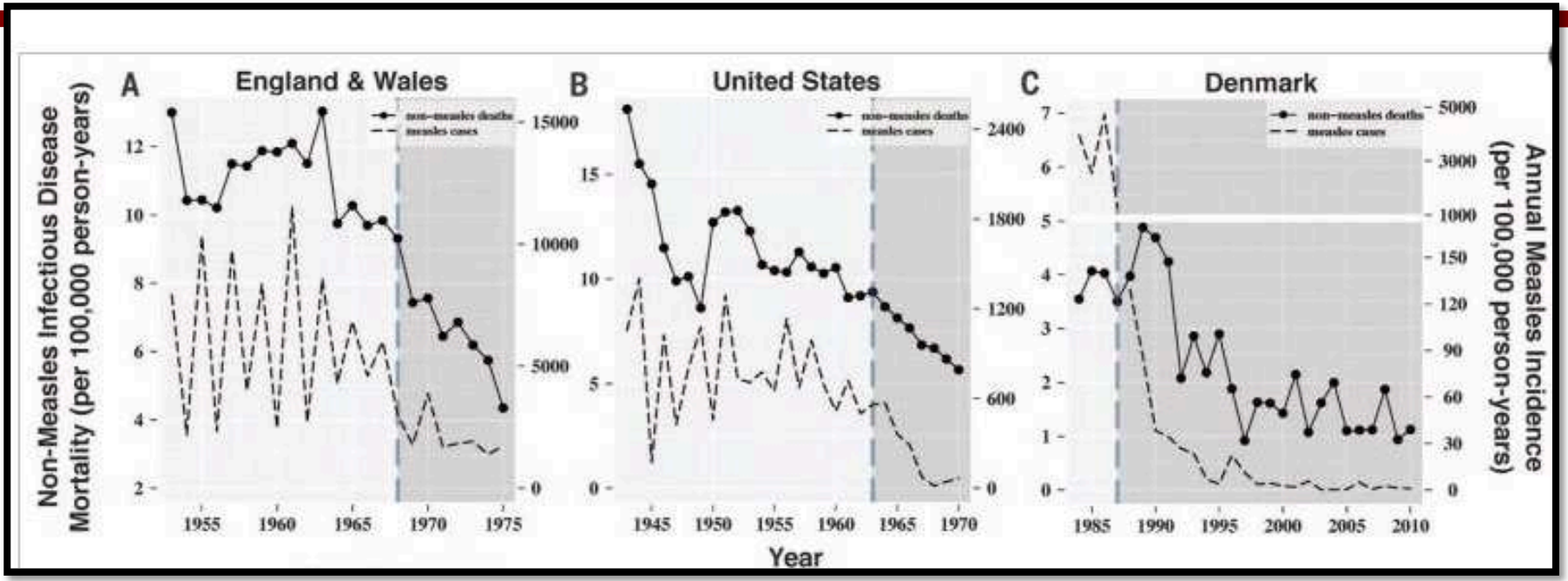
- Treatment with immunosuppressive drugs
  - Transplant recipients
  - Treatment for autoimmune diseases, inflammatory conditions **including anti-cytokine antibodies**
  - Cancer chemotherapies

- Tens of thousands of people in the U.S. are in this group

Infection of cells of the immune system

- *The* Acquired ImmunoDeficiency Syndrome (HIV-mediated AIDS) – depletes CD4+ T-cells
- Measles virus – suppresses T-cell proliferation and responsiveness via a soluble virokine
- Cytomegalovirus infected myeloid precursors and encodes IL-10 mimic (IL-10 is an immunosuppressive cytokine)

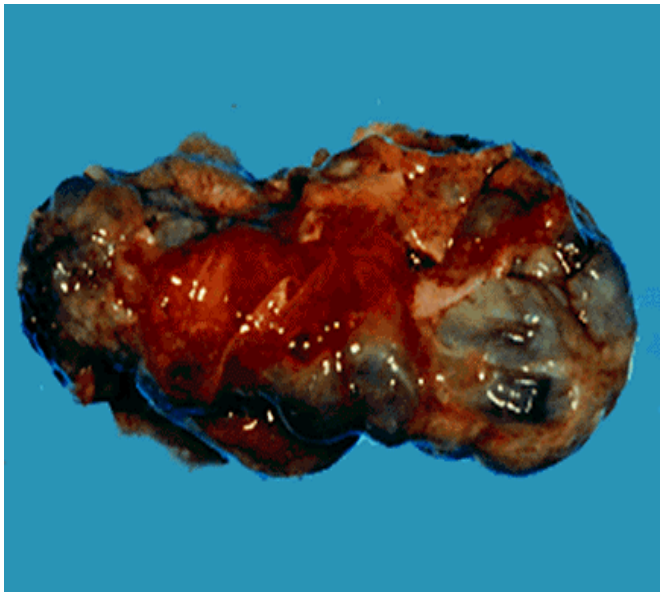
Post-measles immunodeficiency lasts 2-3 years



- Measles virus receptor is expressed on memory B and T-cells, so a measles infection wipes out previously acquired immune memory
- Memory must be rebuilt by subsequent exposures

Splenectomy

- Reduced ability to clear encapsulated micro-organisms
- Individuals with sickle-cell anemia are functionally asplenic due to recurrent infarcts



- Surgical splenectomy is also indicated after trauma to the spleen and other conditions

Summary

- Primary/congenital immunodeficiencies
- Secondary/acquired immunodeficiencies
- Any element of the immune system can be affected
- Presentation is usually an abnormal frequency of certain types of infection, but some present as autoimmunity

questions

Question: T-cell deficiencies are most often associated with infections of which of the following types?

A. Extracellular pathogens
B. Intracellular pathogens
C. Sepsis
D. Skin infections

Question: A patient has a history of frequent fungal infections. A T-cell deficiency is suspected, but flow cytometric analysis to quantify lymphocyte subgroups shows normal results. What is the most likely explanation for this result?

A. Defective antigen presentation
B. Defective complement function
C. Defective T-cell maturation
D. Defective T-helper cell effector function
E. Defective cytotoxic T-cell effectors

Question: Enzymatic steps in purine synthesis are indicated on the diagram. Which one is deficient in the most common form of autosomal severe combined immunodeficiency (SCID)?

A. A

B. B

C. C

D. D

E. E