Immunodeficiency Diseases

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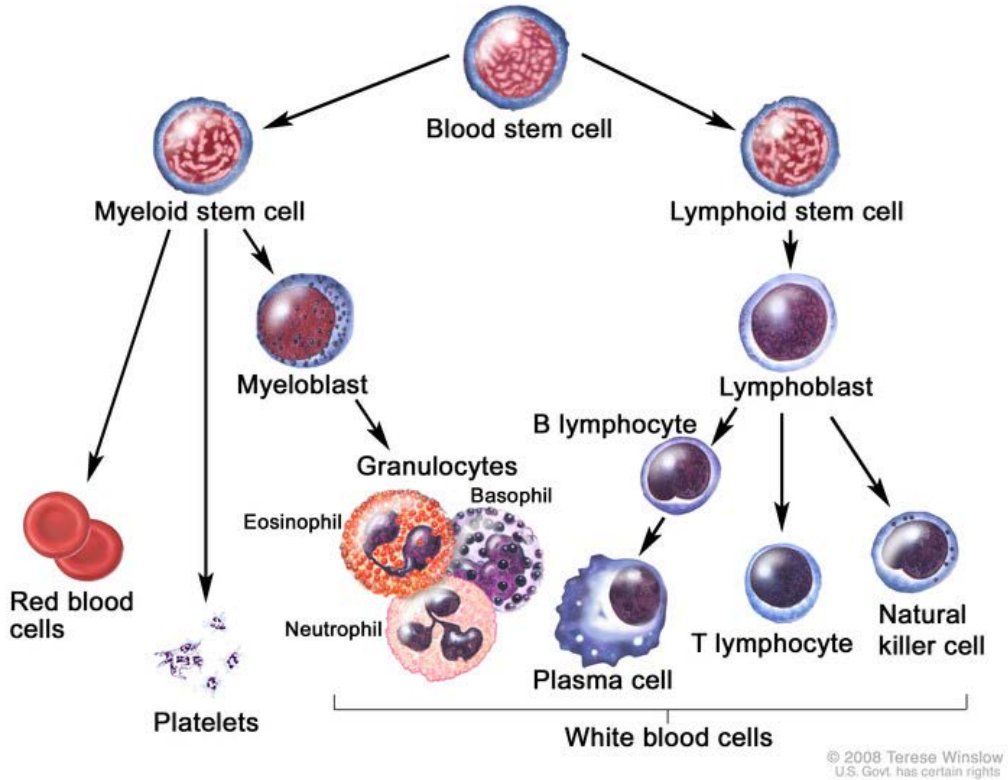
Cells of the immune system

Immune cells originate from a common precursor, and differentiate into several distinct lineages with unique functions.



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- B lymphocytes & plasma cells – humoral immunity
- T lymphocytes – cellular immunity
- Granulocytes & mononuclear phagocytes – phagocytic functions
- Complement

Primary Immunodeficiency Diseases

- Defects in any arm of the immune system can potentially cause an immunodeficiency disease
  - B cell defects – often associated with susceptibility to bacterial infections
  - T cell defects – often associated with susceptibility to intracellular infections (viral, fungal)
  - Combined defects – usually associated with severe disease and profound susceptibility to infections

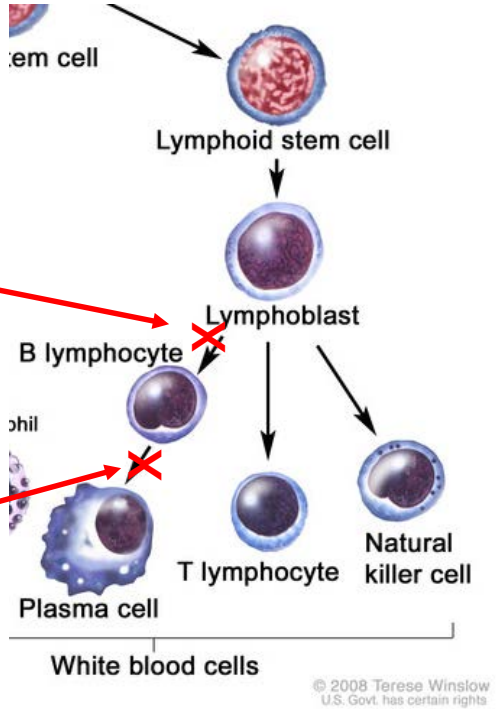
- > 50 different congenital forms of primary immunodeficiency have been described
  - Most are very rare (combined incidence of 2/10,000 births)
    - IgA deficiency is exception (1/600)
  - Many are X-linked (primarily affect males)
  - Most present in early life with infections and failure to thrive

- When suspected, diagnosis can be accomplished using a standard set of laboratory tests
  - Immunoglobulin levels, cell counts and phenotypes, and (rarely) functional assays

B cell immunodeficiency syndromes

Different blockages in the B cell maturation process will lead to different clinical syndromes

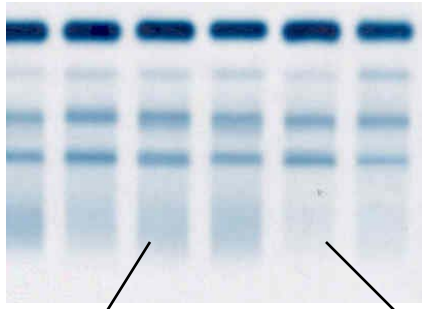
- Transient hypogammaglobulinemia of infancy
- Bruton's (X-linked) agammaglobulinemia
- IgA deficiency
- Common variable immunodeficiency (CVID)

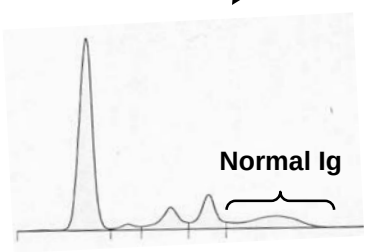


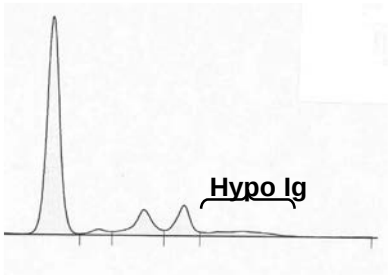
Clinical symptoms have some similarities between disease states (recurrent bacterial infections), but severity varies with different syndromes

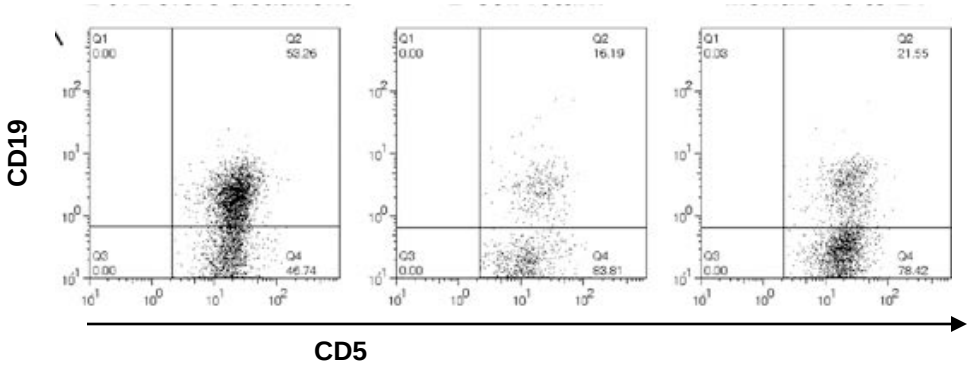
Diagnostic tests for B-cell deficiencies

- Screening tests:
  - Qualitative immunoglobulin measurements (SPEP, MPA)
  - Quantitative immunoglobulin measurements
  - CBC
- Confirmatory tests:
  - Flow cytometry
  - Histology of lymphoid tissues









Transient hypogammaglobulinemia of infancy

- Immunoglobulins show age-related development in normal infancy
  - IgG: Adult levels at birth (maternal), drops by 2-3 mos, returns to adult levels by 5 yrs
  - IgM: Low at birth, adult by 1 yr
  - IgA: Low at birth, adult by adolescence

- Infants with THI show prolonged nadir of IgG levels
  - Disease presents at 2-6 months as maternal IgG is cleared
  - Bacterial respiratory and/or skin infections
  - IgG depressed more than IgA and IgM
  - Usually resolves spontaneously by 9-15 months

- Mechanism of disease isn't known
  - Delayed maturation of immune system components?

Diagnosis is made by clinical presentation with persistently decreased immunoglobulin levels when compared to age-specific reference ranges.

Selective immunoglobulin deficiencies

- IgA deficiency
  - Most common congenital immunodeficiency (1/600 caucasians)
  - Vast majority of patients are asymptomatic
    - Picked up incidentally on immunoglobulin screening for other causes
    - When symptomatic, tend to be GI/respiratory infections
  - Transfusion reactions to IgA can be seen in these patients
    - Known patients should receive IgA-free products, or washed cells.

- Isolated IgG subclass deficiencies
  - Normal IgG is mixture of 4 subclasses (70% IgG1, 20% IgG2, 6% IgG3, 4% IgG4)
  - Selective losses of one subclass can lead to total IgG being normal, but patient with some subtle defects
    - IgG2 deficient may have specific infections with encapsulated bacteria

Severe B-cell deficiencies

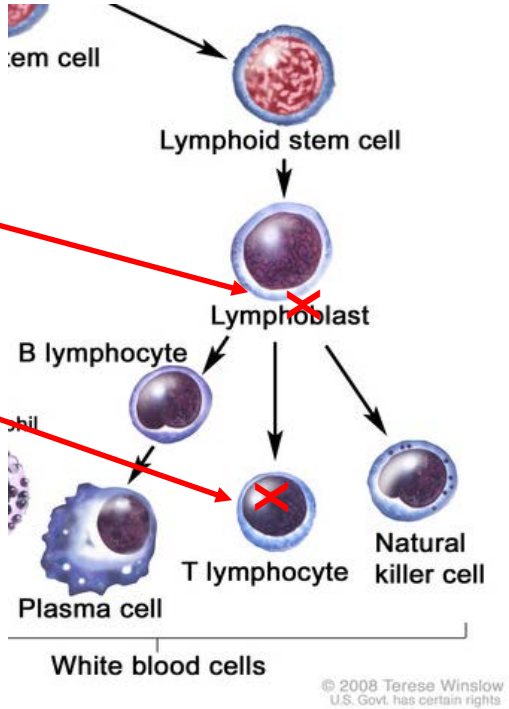
- X-linked (Bruton's) agammaglobulinemia
  - Mutation leading to differentiation block at pre-B cell stage
  - Presents in infancy with recurring bacterial infections
    - Tonsils and adenoids small/absent, lymph nodes w/o germinal centers
    - Lack all immunoglobulins of all classes (IgG, IgA, IgM)
    - No B cells in circulation or in lymph nodes – pre-B cells in marrow
  - Disease caused by defect in Bruton tyrosine kinase (BTK) gene on X chromosome
    - Almost entirely seen in male patients

- Common variable immunodeficiency (CVID)
  - Family of disorders characterized by blocks in plasma cell maturation from B cells
  - Age of onset varies from childhood to elderly
    - Hypogammaglobulinemia coupled with recurrent infections
    - Usually IgA and IgG deficiency
    - Associated with increased autoimmune and cancer risks
  - Diagnosed by clinical symptoms (recurrent infections) and persistently low IgG
    - Unlike Bruton's – CVID patients will have normal #'s of B cells

T cell immunodeficiency syndromes

T cell defects will lead to a loss of cellular immunity, and an increase susceptibility to intracellular pathogens such as viruses.

- DiGeorge syndrome
- PNP deficiency



Because of T cell's role in B cell development, can sometimes see effects on humoral immunity as well

Diagnostic tests for T-cell deficiencies

- Screening tests:
  - CBC with diff
  - Skin testing (PPD, Candida)
  - Quantiferon testing

- Confirmatory tests:
  - Flow cytometry (T cell subsets)
  - Functional assays (Cylex)
  - Enzyme assays (PNP)

T-cell deficiency syndromes

- DiGeorge syndrome
  - Fetal developmental abnormality of 3rd and 4th pharyngeal pouches
  - Widespread defects in many organs, including a lack of thymic development
    - Thymus is organ responsible for T-cell maturation
    - Lack of thymus results in absence or reduced # of mature T cells
  - Neonatal presentation with tetany (hypoPTH), cardiac defects
    - Will get recurrent viral and fungal infections

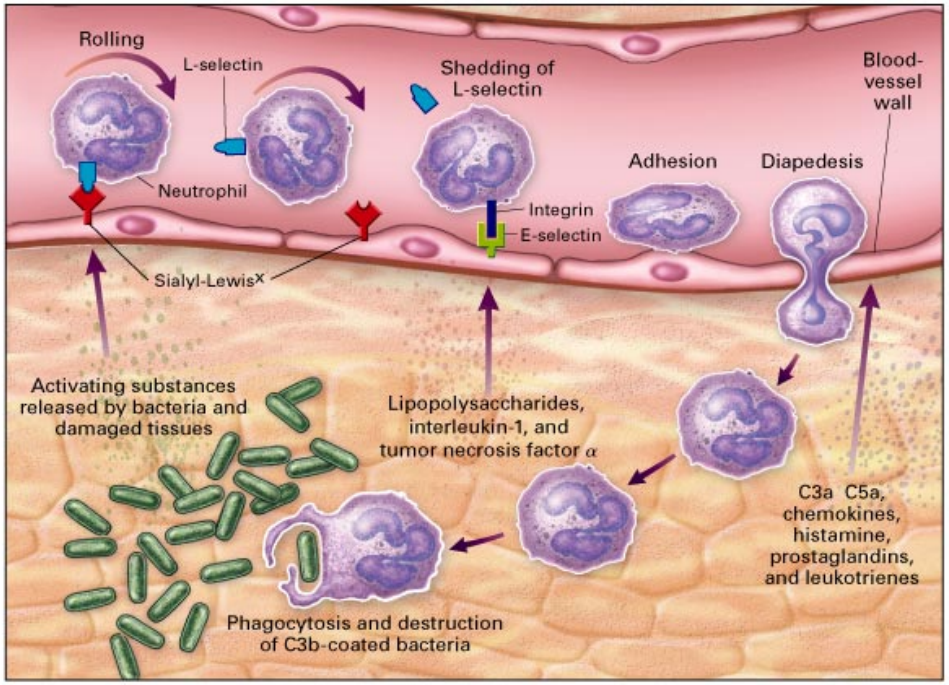
- Purine Nucleoside Phosphorylase (PNP) deficiency
  - Rare autosomal recessive disorder
  - Mutation in PNP blocks purine metabolism, leading to accumulation of toxic precursors
    - Progressive reduction in T cell populations over time as toxin accumulates
  - Presents in infancy with recurrent infections, failure to thrive
    - Can be mistaken for HIV because of selective T cell losses

Combined immunodeficiency syndromes

- Severe Combined Immunodeficiency (SCID)
  - Class of rare diseases that affect both T and B cell functions
    - X-linked (50% of SCID cases) – ILg chain signalling defect
    - ADA deficiency (20%) – toxin accumulation in purine synthesis
  - Present early in infancy with recurrent infections of any kind
    - Decreased #s of B and T cells
    - Low to absent immunoglobulins
    - No responses to antigen challenges (skin tests)
  - Mortality by 2 unless BMT, enzyme replacement (for ADA)
- Wiskott-Aldrich
  - X-linked disease with immunodeficiency, eczema, thrombocytopenia
  - Distinctive laboratory finding (in addition to low platelets) is lack of isohemagluttanins.
- Ataxia-Telangiectasia
  - Autosomal recessive disease with immunodeficiency, ataxia, and telangiectasias.
  - Usually distinguised by associated clinical signs

Neutrophil function disorders

Neutrophils serve as a first line of non-specific defense to invading organisms.

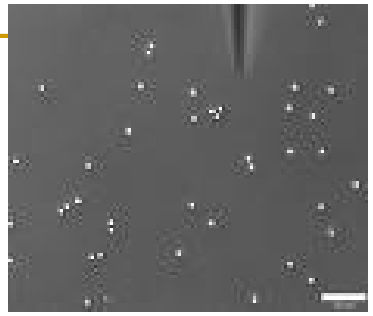


http://www.chronicprostatitis.com/images/f3.jpg

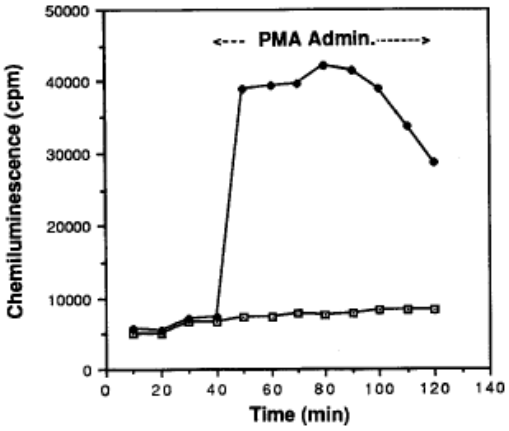
- Neutrophil activity requires multiple phases:
  - Initial adhesion to vascular walls at site of infection.
  - Extravasation across wall to enter tissue.
  - Ingestion of microbial pathogens.
  - Oxidative burst to kill pathogens.
- Defects in all of these phases have been described clinically (although all are rare)

Diagnostic tests for neutrophil disorders

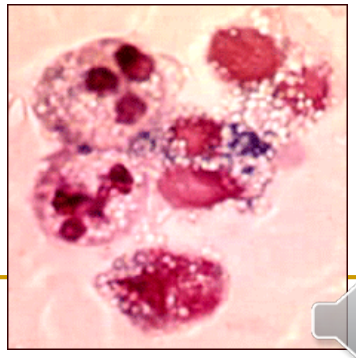
- Functional testing:
  - Chemotaxis – tests cell migration
    - Cell suspension placed in well in agarose gel – migration toward chemoattractant in neighboring well measured



  - Superoxide production – tests oxidative metabolism
    - Cells stimulated with PMA and conversion of substrate by peroxide evaluated



  - NBT (nitroblue tetrazolium) – tests phagocytosis and oxidative metabolism
    - Cells phagocytose endotoxin-NBT, and oxidation reduces NBT to blue subtrate. Count % of blue cells.



Neutrophil functional disorders

- Chronic granulomatous disease
  - Most common neutrophil abnormality (70% X-linked, remainder autosomal recessive)
  - Various molecular mechanisms, leading to defective oxidative burst
    - Process by which neutrophil stimulation produces reactive oxygen molecules that destroy phagocytosed bacteria
  - Disease presents in 1st year of life with severe bacterial infections
    - Often fatal in childhood

- Leukocyte adhesion deficiencies
  - Normal microbial activity, but inability of neutrophils to migrate to site of infection
  - Most defects due to mutations in adhesion receptors on monocytes/neutrophils
    - CD18, CD11, LAD II
  - In addition to chronic infections, patients show delayed wound healing

Conclusions

- Diseases have been associated with losses of virtually all parts of the immune system
- Most primary immunodeficiency diseases are rare – a large # of them are X-linked.
- Laboratory testing for many of these diseases is straightforward (quantitative Ig levels, cell counts, and flow cytometry)
- Functional assays can be used to fully define characteristics of a disease, but are rarely used.