Primary Immunodeficiencies

- ADA
- PNP
- ZAP 70
Overview of the Primary Immunodeficiencies:

- “Pure” T Cell Disorders
- “Pure” B Cell Disorders
- Severe Combined Immunodeficiency (SCID)
- Combined Immunodeficiencies
- Phagocyte Deficiencies
- Complement Deficiencies

Patterns of Infection in Immunodeficiencies:

- B Cell: recurrent sinopulmonary and GI infections beginning after 3-4 mo.
- T Cell and Severe Combined Immunodeficiency (SCID): opportunistic infections beginning early in infancy (thrush, diarrhea, failure to thrive); Milder forms termed Combined Immunodeficiency (CID)
- Phagocyte deficiencies: deep tissue infections with high-grade bacterial pathogens
- Complement: some infections, primarily with encapsulated organisms and Neisseriae
**T Cell Immunodeficiencies:**

- **“Pure” T Cell Deficiencies:**
  - DiGeorge/Velocardiofacial syndrome
  - T cell receptor deficiencies
  - Zap 70 deficiency

**DiGeorge/Velocardiofacial Syndrome**

- Conotruncal cardiac malformation
- Hypoparathyroidism
- Thymic hypoplasia leading to variable immunodeficiency
- Other features:
  - Cleft palate in VCF syndrome
  - Characteristic facies
  - Deletion in 22q11 in > 80%
  - Small percentage with mutations in chromodomain helicase-DNA binding protein 7 (CHD7) on chromosome 10, associated with much more severe congenital malformations (CHARGE syndrome) and complete absence of thymus (Sanka M et al 2007)
  - Affected gene(s) on chromosome 22 is a transcription factor in the T-box family called *Tbx1*
DiGeorge Syndrome: Cardiac Abnormalities

- Interrupted aortic arch 27%
- Truncus arteriosus 25%
- Tetrology of Fallot 22%
Severe Combined Immunodeficiency Syndromes (SCID)

- X-linked SCID ($\gamma_c$ deficiency)
- Jak3 kinase deficiency
- IL-7R$\alpha$ deficiency
- CD45 deficiency
- Adenosine deaminase deficiency
- Bare lymphocyte syndrome (MHC Class I/II deficiency)
- RAG1/RAG2 deficiency
- T cell receptor deficiencies
  - CD3$\gamma$ or $\varepsilon$
- Zap 70 deficiency
- IL-2R$\alpha$ (CD25) deficiency

Common Features of Severe Combined Immunodeficiency (SCID)

- Failure to thrive
- Onset of infections in the neonatal period
- Opportunistic infections
- Chronic or recurrent thrush
- Chronic rashes
- Chronic or recurrent diarrhea
- Paucity of lymphoid tissue
Severe Combined Immunodeficiency
Common Laboratory Features

- Hypogammaglobulinemia
- Absence of antibody responses to immunizations
- Absent mitogen responses
- Low or absent T cells
- Often low or absent B cells

Severe Combined Immunodeficiency
Treatment

- Bone marrow transplantation, preferably from a histocompatible sibling
- Gene therapy
B Cell Immunodeficiencies:

- Bruton’s (X-linked) Agammaglobulinemia (Bruton’s tyrosine kinase (btk) deficiency)
- Autosomal Recessive Hyper-IgM Syndrome
  - AID (activation-induced cytidine deaminase)
  - UNG (uracil DNA glycosylase)
- B Cell Receptor and Signaling Deficiencies:
  - μ heavy chain mutations
  - Pseudo-light chain deficiency (λ5/V-preB)
  - CD79B (Igβ) deficiency
  - BLNK deficiency
  - NEMO deficiency – X-linked hyper-IgM with ectodermal dysplasia
- Common Variable Immunodeficiency (CVID) (TACI, BAFF-R, CD19, ICOS)
- Selective IgA Deficiency
- IgG Subclass Deficiency
IgG Subclass – IgA-D – CVID
Polar Ends of a Common Disease?

- IgA deficiency frequently coexists with IgG subclass deficiency, especially IgG2 and IgG4
- Linkage to Class III region of HLA
- 50% incidence of IgA-D in children of patients with CVID
- Occasionally IgA deficient patients have been noted to progress to CVID

Common Variable Immunodeficiency

- Panhypogammaglobulinemia, usually with lymphadenopathy and splenomegaly
- No clear abnormalities in T and B cells
- Chronic/recurrent respiratory infections, & diarrhea, especially due to *Giardia*
- Tendency to develop autoimmunity and lymphoid malignancies
- Linkage to HLA Class III Region in 2/3 of patients
- Four genes identified: ICOS (B7h), BAFF-R, CD19, and TACI (co-stimulatory molecules on T and B cells)
IgG Subclass and IgA Deficiencies
Patterns of Illness

- Chronic/recurrent upper respiratory infections, especially sinusitis
- Tendency to develop respiratory and gastrointestinal allergies and autoimmunity

Combined Immunodeficiencies

- Wiskott-Aldrich Syndrome: eczema, thrombocytopenia, immunodeficiency (WAS)
- Ataxia-Telangiectasia: DNA repair disorder, isotype switch defect (ATM)
- Hyper-IgM Syndrome: isotype switch defect, T cell dysfunction (CD40, CD40-L)
- X-linked Lymphoproliferative Disorder: fulminant infectious mono, hypogammaglobulinemia, lymphoma (SH2D1A/SAP, XIAP)
- Chronic Mucocutaneous Candidiasis: chronic superficial fungal infections, autoimmunity (AIRE)
- Hyper-IgE syndrome: markedly elevated IgE with bacterial & fungal infections (STAT3)
Hyper-IgE Syndrome

- Dominant negative mutations in STAT3
- Diffuse defects in cytokine receptor responses
- Markedly elevated IgE with relatively normal immunoglobulins and antibody responses
- Peripheral eosinophilia
- Invasive infections with extracellular bacteria and fungi
- Absent TH17 cells

*Milner J et al Nature 2008*

Other Cellular Immunodeficiencies:

- Defective NK and CTL function: Familial Hemophagocytic Lymphohistiocytosis
- Defects in the interferon-gamma (IFN γ)/interleukin-12 (IL-12) pathway
Familial Hemophagocytic Lymphohistiocytosis (FHL):

- Defective NK and cytotoxic T cell (CD8+ T cell) killing leading to infiltration of the liver, spleen, bone marrow, and central nervous system by activated T cells and macrophages
- Defective genes: perforin (PRF1) (up to 50%), Munc13-4 (UNC13D) (20-30%), syntaxin 11 (STX11) (10-20%)
- Diagnosis: flow cytometry for intracellular perforin, functional killing assays
- Therapy:
  - Immunosuppression with prednisone/cyclosporine
  - Bone marrow transplant

Defects in the interferon-gamma (IFN-\(\gamma\))/interleukin-12 (IL-12) pathway:
IL-12/IFN\(\gamma\) Pathway Defects

- IL-12R\(\beta_1\)
- IL-12p40
- IFN\(\gamma\)R1 and IFN\(\gamma\)R2
- STAT-1

- Pattern of infections: overwhelming infection with intracellular pathogens, esp. atypical mycobacteria

Numerous acid-fast organisms and poor granuloma development in the liver of a Tunisian child with BCG infection.
Phagocyte Deficiencies:

- Chronic granulomatous disease (CGD) (gp91-phox, p22-phox, p47-phox, p67-phox)
- Leukocyte adhesion defects
  - LAD I (integrin CD11/CD18)
  - LAD II (GDP-fucose transporter SLC35C1)
- Granule defects – defects in phagocyte, NK cell, platelet, neuron function (albinism, infection, bleeding, FHL)
  - Chediak-Higashi syndrome (Lysosomal trafficking regulator, LYST)
  - Griscelli syndrome (Ras-associated protein RAB27A)
  - Hermansky-Pudlak syndrome – adapter protein 3 (APS2)
- Chronic or cyclic neutropenia (neutrophil elastase)

Chronic Granulomatous Disease

- Inability of phagocytes to generate hydrogen peroxide due to mutations in one of four proteins comprising the NADPH oxidase
- Severe tissue infections with catalase positive organisms, esp. Staph aureus, Serratia marcescens, mycobacteria, and fungi such as Aspergillus
Chronic Granulomatous Disease: Diagnosis

- Nitroblue tetrazolium (NBT) test
- or, more recently, flow cytometric tests using fluorescent dyes such as dihydrorhodamine (DHR)
DHR Flow Cytometric Assay

Patient

Father

Mother

CGD patient with skin infections due to *Serratia marcescens*
Leukocyte Adhesion Deficiency I

- Severe tissue infections due to absence of adhesion molecules (β-integrins CD11/CD18) on leukocytes
- Inability to make pus due to entrapment of phagocytes within the vasculature
- Lethal within the first decade of life without bone marrow transplant

Omphalitis in LAD I patient
Chediak-Higashi Syndrome

- Abnormal large granules in a variety of cells leading to:
  - hypopigmentation/partial albinism
  - severe immunodeficiency
  - neurologic abnormalities
  - mild bleeding tendencies
- Defective gene: CHS1 located on 1q42-43, protein product involved in granule trafficking
Complement Deficiencies:

- **Rule I:** In any inherited deficiency of a component of the classical pathway, total hemolytic activity (CH50) will be close to zero.
- **Rule II:** In any inherited deficiency of a component of the alternate pathway, total hemolytic activity (AH50) will be close to zero.