K-RITH Immunology Lecture Series
An Intensive Course in Basic Immunology

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University of KwaZulu Natal, Durban
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Lecture 13: Failures in Host Defense Mechanisms
Questions to Consider

- What insights into the working of the immune system can we learn from patients?
- How does one elicit and utilize clinical history to diagnose the etiology of a congenital immunodeficiency?
- How can ignorance of immunology kill your patients?
“Bubble Boy” - Patient Without T and B Cell Immunity Needs Isolation to Protect From Infection
Etiology of Immunodeficiency

- B cell: 53%
- Phagocytic: 14%
- B and T cell: 23%
- Misc.: 10%
Evaluation of Immunodeficiency

- **Complaint**
  - increased frequency of infections
  - inability to clear infection
  - infection with opportunistic pathogens

- **Age of presentation**
  - < 6 months suggests cellular defect
  - > 6 months indicates antibody deficiency
Maternal IgG Crosses the Placenta Providing Newborns With IgG Levels Equivalent to Those Present in the Mother
Evaluation of Immunodeficiency

- **Complaint**
  - increased frequency of infections
  - inability to clear infection
  - infection with opportunistic pathogens
- **Age of presentation**
  - < 6 months suggests cellular defect
  - > 6 months indicates antibody deficiency
- **Infections**
  - Viruses/Fungi- T cell defect
  - Bacteria- Antibody deficiency
Hematopoietic Lineage

Bone marrow
- pluripotent hematopoietic stem cell

Blood
- Granulocytes (or polymorphonuclear leukocytes)
  - neutrophil
  - eosinophil
  - basophil
  - unknown precursor of mast cell
  - monocyte
- Immature dendritic cell
- Mature dendritic cell
- Platelets
- Erythrocyte

Lymph nodes
- B cell
- T cell
- NK cell

Tissues
- Immature dendritic cell
- Mast cell
- Macrophage

Effector cells
- Plasma cell
- Activated T cell
- Activated NK cell

Figure 1-3 Immunobiology, 7ed. (© Garland Science 2008)
Leukocytes Can be Identified by Flow Cytometric Analysis
Leukocytes Can be Identified by Flow Cytometric Analysis
Severe Combined Immunodeficiency

- **Cellular:** ↓ cells, to normal B cells
- **Humoral:** ↓ immunoglobulins
- **Presentation:** After birth
- **Pathogens:** Bacterial, viral, fungal
- **Etiology:** mutation
- **Therapy:** Bone marrow transplant, gene therapy
X-linked SCID is Associated With Defective Maturation of Lymphocytes
The Interleukin 2 Receptor Complex Includes a Gamma Chain Utilized for Signal Transduction
The Same γ-chain is Used by Multiple Cytokine Receptors For Signal Transduction

Nat Rev Immunol. 2005 Sep;5(9):688-98
Mutation of the Common $\gamma$-chain Causes Almost 50% of SCID Cases

- Deficiency of common $\gamma$ chain, 45.4% (n=64)
- Deficiency of interleukin-7 receptor $\alpha$ chain, 1.4% (n=2)
- Adenosine deaminase deficiency, 15.6% (n=22)
- Jak3 deficiency, 6.4% (n=9)
- Autosomal recessive, 20.6% (n=29)
- Unknown, 9.2% (n=13)
- Cartilage hair hypoplasia, 0.7% (n=1)
- Reticular dysgenesis, 0.7% (n=1)

NEJM 2000;343:1313
Severe Combined Immunodeficiency

- **Cellular:** T cells, to normal B cells
- **Humoral:** Immunoglobulins
- **Presentation:** Months to years after birth
- **Pathogens:** Bacterial, viral, fungal
- **Etiology:** Adenosine deaminase deficiency
- **Therapy:** Bone marrow transplant
- Rosen/Geha- Case 14
Absence of Adenosine Deaminase Prevents Elimination of Adenosine
Alternate Pathway for Metabolism of Adenosine

Adenosine
- Adenosine Kinase
  - Adenosine monophosphate
    - Adenylate Deaminase
      - Inosine monophosphate
        - Inosine Phosphatase
          - Inosine

Deoxyadenosine
- Deoxycytidine Kinase
  - Deoxyadenosine monophosphate
    - No Enzyme for Deamination of dAMP
      - STOP
Elevated Level of Deoxycytidine Kinase in Lymphocytes
Phosphorylates dATP Which Builds Up In the Cell

1. Inhibition of Ribonucleotide Reductase
   RESULT: Decreased pools of dNTP's
2. Inhibition of Endogenous DNA Repair
   RESULT: Build up of DNA nick$^-$ mRNA
3. Activation of poly-(ADP-ribose) polymerase
   RESULT: Decrease NAD and ATP
Severe Combined Immunodeficiency

- **Cellular:** \(\downarrow\) cells, \(\downarrow\) to normal B cells
- **Humoral:** \(\downarrow\) immunoglobulins
- **Presentation:** After birth
- **Pathogens:** Bacterial, viral, fungal
- **Etiology:** JAK/STAT defect
- **Therapy:** Bone marrow transplant
Signal Transduction by Heterodimeric Cytokine Receptors is Mediated by JAK/STAT Pathway

- Cytokine receptors consist of at least two chains, the cytoplasmic kinases (JAKs).
- Cytokine binding dimerizes the receptor, bringing together the cytoplasmic JAKs, which activate each other and phosphorylate the receptor.
- Transcription factors (STATs) bind to the phosphorylated receptors, and are in turn phosphorylated by the activated JAKs.
- Phosphorylated STATs form dimers that translocate into the nucleus to initiate new gene transcription.

Fig 6.22 © 2001 Garland Science
SCID Can be Caused by Mutation of the Cytokine Receptor Transduction Molecule, Jak3

NEJM 2000;343:1313
Use of Gene Therapy for SCID

- In 1990-1st gene therapy trial the NIH in a four year old girl with adenosine deaminase (ADA) deficiency. Of two patients treated, the peripheral blood T cell counts in patient 1 rapidly increased until they reached the normal range where they have remained and patient 2 also showed an increase in the number of T cells.

- In 2002-3, nine of eleven children with SCID due to γ-chain receptor mutation have been successfully treated with hematopoietic stem cell therapy.

- However, four have developed leukemia due to insertional mutagenesis.
DiGeorge Syndrome

- **Cellular**: Decreased T cells, normal B cells
- **Humoral**: Decreased IgG
- **Presentation**: Hypocalcemia, seizures
- **Pathogens**: Bacterial, viral, fungal
- **Etiology**:
  - **Genetic**: A large deletion from chromosome 22q11, produced by an error in recombination at meiosis, variation in symptoms is related to the amount of genetic material lost in the chromosomal deletion.
  - **Anatomic**: Anomalous development of the 3rd and 4th brachial pouches
- **Therapy**: Thymic transplant
Lateral Chest X-ray in DiGeorge Syndrome

Normal

DiGeorge Syndrome
DiGEORGE SYNDROME
Absent T cells Cause Functional Antibody Deficiency Because T Cell Help is Required for IgG Production
X-linked agammaglobulinemia

- **Cellular**: Decreased B cells and normal T cell numbers
- **Humoral**: Absent Ig
- **Presentation**: After 6 months old
- **Pathogens**: Bacterial
- **Etiology**: Defective Btk (Bruton’s tyrosine kinase)
- **Therapy**: IV gammaglobulin
- **Rosen/Geha**: Case 10
Hyper-IgM Syndrome

- **Cellular:** Normal T cells and B cells
- **Humoral:** IgM, IgG, and IgA
- **Presentation:** After 6 months
- **Pathogens:** Bacterial
- **Etiology:** Absence of CD40 ligand or AID cytidine deaminase
- **Therapy:** Intravenous gammaglobulin
- **Rosen/Geha- Case 11 and 12**
CD40 Ligand-CD40 Interaction is Required for Isotype Switching

[Diagram showing the process of isotype switching involving CD40 ligand-CD40 interaction.]
IgG Subclass Deficiencies

- **Cellular** - Normal B and T cell numbers
- **Humoral** - Decreased IgG subclass (sometimes IgA also)
- **Presentation** - After 6 months old
- **Pathogens** - Bacterial
- **Etiology** - unknown
- **Therapy** - IV gammaglobulin
IgA Deficiency

- **Cellular:** Normal T cells and B cells
- **Humoral:** Decreased IgA
- **Presentation:** Sinopulmonary infections, allergic
- **Pathogens:** Bacterial
- **Etiology:** Failure of isotope switch
- **Therapy:** None
Bare Lymphocyte Syndrome

- **Cellular:** Cells, normal B cells
- **Humoral:** IgG deficiency
- **Presentation:** After birth
- **Pathogens:** Bacterial, viral, fungal
- **Etiology:** Mutation in MHCII promoter
- **Therapy:** Bone marrow transplant
- **Rosen/Geha- Case 17 and 18**
Genetic Mutations of Different Transduction Molecules are Associated with Various Immunodeficiencies

NEJM 2000;343:1313
Job’s Syndrome

- **Cellular:** phagocytic chemotaxis
- **Humoral:** IgE
- **Presentation:** Childhood with cold abscesses, eczema
- **Pathogens:** Staph, strep, candida
- **Etiology:** STAT3 dominant negative mutation
- **Therapy:** Antibiotic suppression
Chronic Granulomatous Disease

- **Cellular:** Ineffective phagocytosis
- **Humoral:** Normal to increased IgG
- **Presentation:** Hot abscesses
- **Pathogens:** Staph, Candida
- **Etiology:** Defective NADPH oxidase gp91phox gene mutation.
- **Therapy:** Antibiotics, γ interferon, gene therapy
- Rosen/Geha- Case 2
Blockage at Discrete Differentiation Steps Prevents Downstream Maturation

from Abbas et al. Abbas - Cellular and Molecular Immunology

- Btk deficiency (X-linked agammaglobulinemia)
- ADA, PNP deficiency (autosomal SCID)
- RAG deficiency (autosomal SCID)
- γc deficiency (X-linked SCID)
- Lack of thymus (DiGeorge syndrome)
- Class II MHC deficiency TAP-1 or TAP-2 deficiency

B cell maturation
- Stem cell → Pro-B → Pre-B → Immature B → Mature B

T cell maturation
- Stem cell → Pro-T → Pre-T → Double positive → Single positive (immature) T cell → Naïve mature T cell
Blockage at Discrete Differentiation Steps Prevents Downstream Maturation

from Abbas et al. Abbas- Cellular and Molecular Immunology
Conclusions

- Patients provide many insights into the working of the immune system
- Clinical history helps diagnose the etiology of congenital immunodeficiency
- Ignorance of immunology can kill your patients