Defects in MATURATION and/or ACTIVATION of the immune system

Immunodeficiency

Physiological
- Infancy
- Pregnancy
- Age

Primary
- Adaptive
- Innate
- Combined

Secondary
- Chemical
- Physical
- Malnutrition
- Chronic infections
Content

- Physiological Immunodeficiency
  - Infancy
  - Pregnancy
  - Age

- Primary Immunodeficiency including general aspects of the immune system, cases
  - Adaptive Immune system (CVID, ALPS, SCID)
  - Innate Immune system (CGD, LAD1, HAE, Factor I Deficiency)
Physiological Immunodeficiency: Neonate/Infancy

- Lack of immune memory
- Hyporesponsiveness
  - T cells can be less activated
  - Antibody production is weak and short-lived
  - Innate immunity impaired
- Treg and Th2 bias

Newborn are well protected against extracellular bacteria and fungi (TH17) but susceptible to intracellular infections
Physiological Immunodeficiency: Pregnancy

- IFN-γ, MCP-1, eotaxin ↓
- TNF-α, IL-10, G-CSF ↑
- Treg ↑
- Immunosuppression ➔ Tolerance of semiallogenic fetus?
  - good response to vaccination
- Rather Th2 bias, increase of innate immunity

No increased susceptibility but increase severity except Listeriosis, Malaria, (placental tropism)
Physiological Immunodeficiency: Age B cells

- Naïve B cells
- Transitional B cells
- Non-Switched memory B cells
- Switched B cells
- Plasma Blasts
Physiological Immunodeficiency: Age T cells

Overall numbers of T cells do hardly change
But
Composition of T cell population e.g. CD28neg CD8 T cells
Primary Immunodeficiency:
Classification according IUIS

1. Combined immunodeficiency
2. Well-defined syndromes with immunodeficiency
3. Predominantly antibody deficiency
4. Diseases of immune deregulation
5. Congenital defects of phagocyte number, function or both
6. Defects that involve innate immunity
7. Complement deficiencies
8. Autoinflammatory disorders

More than 130 different disorders have been described

IUIS: The international Union of Immunological Societies
Predominantly Antibody Deficiency: Common Variable Immunodeficiency (CVID)
Topics Bearing on CVID: B cell Maturation and Development

Bone Marrow

Stem cell → Pro B cell → Pre B cell → Transitional B cell → naive B cell → unswitched B cell → switched B cell → Plasma cell

Peripheral Blood

CD19
IgD
CD27
CD21
CD24
CD38
Topics Bearing on CVID: B cell Survival, Activation and Isotype Switching

Park et al. 2008 The Lancet
Common Variable Immunodeficiency Disorder (CVID)

- Diverse Aetiologies
- Age of onset is in the twenties or thirties
- Humoral deficiency > several blood B cell subpopulations may be affected
- Hypogammaglobulinaemia: decreased IgG and IgA with or without low IgM > defective isotype switch due to mutation in e.g. ICOS, TACI
- No T cell deficiency
- At least one of the following:
  - Autoimmune manifestation (e.g. Autoimmune haemolytic anaemia, autoimmune thrombocytopenia)
  - Increased susceptibility to infection
  - Granulomatous disease
  - Unexplained polyclonal lymphoproliferation (> lymphadenopathy)
- Diagnosis
  - Immunophenotyping of blood B cell subpopulations
  - Determination of levels of serum immunoglobulin
  - Determination whether there is a lack of functional antibodies
IgD

CD27

IgD

CD38

Healthy

Low unswitched

Low switched

Normal or low number of B cells
Paucity of unswitched (IgD+CD27+) or switched (IgD-CD27+) B cells
Increased CD21/CD38\textsubscript{low} B cells
Increased transitional (CD21+CD38+CD24+CD27-) B cells
Deficient in plasma blast

Healthy

High CD21/CD38\textsubscript{low}
Diseases of Immune Deregulation:
Autoimmune Lymphoproliferative Syndrome (ALPS)
**Topics Bearing on ALPS:**

**T cell Maturation**

TCRγδ:
- Mainly CD4/CD8 double negative
- Up to 5% of blood lymphocytes
- Recognize non-peptide phosphoantigens (e.g. Mycobacterium tuberculosis, anti-tumor)
Topics Bearing on ALPS: Apoptosis
Autoimmune Lymphoproliferative Syndrome (ALPS)

Defective T cell homeostasis due to mutations in Caspase-8, Caspase-10, CD95L or CD95 results in nonfunctional death-inducing signaling complex (DISC)

Impaired Apoptosis

Lymphoproliferation
Autoimmunity
Hypergammaglobulinaemia

Cunningham et al. 2005 Nat Rev Immunol

University Institute of Clinical Chemistry M. Fux
Immunophenotyping of T cells by FACS: Excessive Numbers of Double Negative TCR$\alpha\beta$ T cells

Healthy

ALPS

University Institute of Clinical Chemistry M. Fux
Case 1: Malignancy or ALPS?

- 18-months of age, female
- Lymphadenopathy, Splenomegaly
- White blood count 12’500 cells/μl (normal 5’000-10’000 cells/μl)
- Lymphocyte count 9175 cell/μl (normal 3’000 cells/μl)
- B cells: 29% of lymphocytes (normal range 5-15%)
- IgG: 4’000mg/dl (normal 520-1’500), IgM 400mg/dl (normal 40-200), IgA 1’660mg/dl (normal 27-169)
- T cells: 65% of lymphocytes (normal range 61-84%)
- CD4positive T cells: 14% of T cells
- CD8positive T cells: 18% of T cells
- ?????????
Combined Immunodeficiency: Severe Combined Immunodeficiency (SCID)
Combined Immunodeficiency: May Affect the Innate and the Adaptive immunity

Darnoff et al. 2004 Nat Rev Cancer
Topics Bearing on SCID:
Antigen Receptor Gene Recombination

Nemazee et al. 2006 Nat Rev immunol
Topics Bearing on SCID:
T cell development in Thymus
Topics Bearing on SCID:
Function of T cell Help

[Diagram showing the process of B cell activation and differentiation, including recognition phase, activation phase, clonal expansion, isotype switching, affinity maturation, and antibody secretion.]
Severe Combined Immunodeficiency (SCID)

**T⁻B⁺NK⁻ SCID**: X-linked-recessive SCID (Common γ-chain deficiency)

**T⁻B⁺NK⁻ SCID**: Jak3-deficiency

**T⁻B⁺NK⁺ SCID**: IL-7Rα-deficiency

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Rochman et al. 2009 Nat Rev Immunol
Severe Combined Immunodeficiency (SCID)

$T^-B^+NK^-$ SCID: X-linked-recessive SCID (Common $\gamma$-chain deficiency)

$T^-B^+NK^-$ SCID: Jak3-deficiency

$T^-B^+NK^+$ SCID: IL-7R$\alpha$-deficiency

Rochman et al. 2009 Nat Rev Immunol

Non-functional B cells

No T cells

No NK cells

Non-functional B cells

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Severe Combined Immunodeficiency (SCID)

**T⁺B⁻NK⁻ SCID**: X-linked-recessive SCID (Common γ-chain deficiency)

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**Cytokine produced by:**

- **IL-2**: T cells and DCs
- **IL-4**: T cells, NK cells, eosinophils, and mast cells
- **IL-7**: stromal cells, epithelial cells, and fibroblasts
- **IL-9**: T cells
- **IL-15**: monocytes, DCs, and epithelial cells
- **IL-21**: CD4⁺ T cells and NKT cells
- **TSLP**: stromal cells, fibroblasts, mast cells, and basophils

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**Receptor expressed by:**

- T cells, B cells, NK cells, mast cells and basophils
- T cells, B cells, NK cells, mast cells, and DCs
- T cells, pre-B cells, and DCs
- T cells, mast cells, epithelial cells, and eosinophils
- T cells and NK cells
- T cells, NK cells, mast cells, and DCs
- T cells, B cells, DCs, NKT cells, mast cells, and basophils

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- Non-functional B cells
- No T cells
- No NK cells
- Non-functional B cells
Severe Combined Immunodeficiency (SCID)

\( T^+B^+NK^- \) SCID: X-linked-recessive SCID (Common \( \gamma \)-chain deficiency)

\( T^+B^+NK^- \) SCID: Jak3-deficiency

\( T^+B^+NK^+ \) SCID: IL-7R\( \alpha \)-deficiency

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Receptor expressed by:
- T cells, B cells, NK cells
- T cells, B cells, NK cells, mast cells and basophils
- T cells, pre-B cells, T cells, mast cells, epithelial cells and eosinophils
- T cells and NK cells
- T cells, B cells, NK cells and DCs
- T cells, B cells, DCs, NK cells and mast cells

Cytokine produced by:
- IL-2: T cells and DCs
- IL-4: T cells, NK cells, eosinophils and mast cells
- IL-7: stromal cells, epithelial cells and fibroblasts
- IL-9: T cells
- IL-15: monocytes, DCs and epithelial cells
- IL-21: CD4+ T cells and NKT cells

Rochman et al. 2009 Nat Rev Immunol

TSLP: stromal cells, epithelial cells, fibroblasts, mast cells and basophils

No T cells
Severe Combined Immunodeficiency (SCID)

T-B-NK⁺ SCID: RAG-deficiency

RAG: Recombination-activating gene 1 & 2
Encode recombination signal sequences (RSSs)
Catalyze V(D)J-rearrangement

Nemazee et al. 2006 Nat Rev immunol

University Institute of Clinical Chemistry M. Fux
Severe Combined Immunodeficiency (SCID)

T-B-NK- SCID: Adenosine-deaminase (ADA) deficiency

If in Excess> Inhibition of ribonucleotide reductase

Case Studies in Immunology 7th Edition

University Institute of Clinical Chemistry M. Fux
Severe Combined Immunodeficiency (SCID)

T^·^·B^·^·NK^·^· SCID: Adenosine-deaminase (ADA) deficiency

If in Excess> Inhibition of ribonucleotide reductase

Excretion

Case Studies in Immunology 7th Edition
Case 2: X-linked recessive SCID, Jak3-deficiency, RAG-deficiency or ADA-deficiency?

• 3 months of age, male:
  – recurrent infection
  – persistent cough > pneumonia
  – not gaining weight
  – Suffers from Candida ablicans in the mouth
• older sister, father, mother > no symptoms
• Hospitalization:
  – Very small tonsils
  – Detection of Pseudomonas aeruginosa in nasal fluid
  – White blood count 4’800 cells/μl (normal 5’000-10’000 cells/μl)
  – Lymphocyte count 760 cell/μl (normal 3’000 cells/μl)
  – IgG: 30mg/dl (normal 520-1’500), IgM 12mg/dl (normal 40-200), IgA non-detectable
  – Functional analysis: lymphocytes did not react upon stimulation (phytohemagglutinin, vaccine antigens)
  – 95% of lymphocytes were B cells (normal range 5-15%)
Congenital Defects of Phagocyte Number and/or Function:
Chronic Granulomatous Disease (CGD)
Leukocyte Adhesions Deficiency Type I (LAD1)
20% of reported primary immunodeficiency involve abnormalities in neutrophil numbers, functions or both.
Topics Bearing on Neutrophils:
The NAPDH oxidase complex

\[
\text{NADPH} + 2\text{O}_2 = \text{NADP}^+ + 2\text{O}_2^- + \text{H}^+ > \text{H}_2\text{O}_2 + \text{O}_2
\]

Lambeth et al. 2004, Nat Rev Immunol
Defects in Function: Chronic Granulomatous Disease (CGD)

- Microbicidal mechanisms are defect
- Infection can not be cleared
- Sustained activation of CD4+ T cells
- Chronic local Inflammation

Formation of Granuloma
Chronic Granulomatous Disease (CGD)

Defects in NADPH-Oxidase-Complex NOX2: no formation of superoxide

Lambeth et al. 2004, Nat Rev Immunol

25% (autosomal recessive)

70% (X-linked)

5% (autosomal recessive)
Defects of Motility: Leukocyte Adhesions Deficiency Type I

- Autosomal recessive genetic defect in CD18
- CD18: common β-chain of integrin receptors: LFA-1, Mac-1 and p150,95
- Defect in adhesion, chemotaxis and complement binding
Complement Deficiencies: Hereditary Angioedema (HAE) Factor I Deficiency
Topics Bearing Complement Deficiencies: Complement Pathways

Surfaces

Immune complexes

Polysaccharides

Opsonization

C3a, C5a

Chemotaxis

Inflammation

Lysis

Adapted from medscape.com
Consequences of Complement Deficiencies

Deficiency in:

– **Early C Components (C1q, C1r/s, C2, C4):** failure of clearance of immune complexes, apoptotic cells > autoimmune manifestation

– **MBL:** increased risk of infection with encapsulated bacteria

– **C3:** defect in opsonization, deficient chemotaxis of leukocytes, decreased MAC formation > increased risk of infection with encapsulated bacteria

– **MAC:** increased risk of infection, especially Meningococcal meningitis
Hereditary Angioedema (HAE): Deficiency in C1INH

C1q inhibitor C1INH

C1q inhibitor C1INH

C1q

C1r → C1s

C4b

C2b

C2 kinin

Vasodilation
Increased permeability

bradykinin

Injury blood vessels

Injury blood vessels

Plasmin

Clotting system

Classical Pathway
Hereditary Angioedema (HAE): Deficiency in C1INH

- C4, C2 decreased, late C components normal
- No increased susceptibility to infections
- Swelling of the skin, intestine and airway
- Edema fluid is free of cellular component (≠ anaphylactic edema)
- Normally no itching and hives (≠ allergy)
Alternative Pathway: Factor I Deficiency

- C3 decreased, nonproduction of iC3b > defective opsonization
- Late C components decreased
- Sustained itching and hives
- Increased susceptibility to infections, especially Neisseria
Case 3: HAE or Factor I Deficiency?

- 25-year old man
- Hives after drinking alcohol or taking a shower
- Hematocrit, white cell count and platelet count normal
- Red blood cells >positive agglutination reaction with anti-C3 Ab
- IgG, IgM and IgA serum levels normal
- Normal response to tetanus toxoid
- Serum levels of C3 27mg/dl (normal 97-104mg/dl) of this 8mg/ml was C3 and 19mg/ml was C3b
- His serum failed to kill Salmonella enterica, even after addition of C3
- Synthesis of C3 was normal but C3 was being broken down 4-times faster than normal
Thank You