Introduction

• Immunodeficiency results from the absence or failure of normal function of one or more elements of the immune system.

• Primary Immunodeficiency
• Secondary Immunodeficiency

Primary Immunodeficiency

B cell immunodeficiency

- X-linked agammaglobulinemia
- IgA deficiency
- Ig subclass deficiencies
- Common variable immunodeficiency
- BLNK deficiency

Severe Combined Immunodeficiency

- IL-2 receptor gamma chain deficiency
- Adenosine deaminase deficiency
- Purine nucleoside phosphate deficiency
- JAK3 deficiency
- Recombination activating gene (RAG) 1 and 2 deficiencies
- Omenn Syndrome
- Hyper IgM syndrome
- Zap 70 deficiencies
- CD3 sub unit deficiencies
- X linked lymphoproliferative disease
- Interferon gamma receptor deficiencies
- Major Histocompatibility complex class I and class II deficiencies

X-Linked agammaglobulinemia

XLA

- Congenital defect
- 1 in 100,000 male newborns.
- No B cells
- No IgA, IgM, IgD, IgE, small amount of IgG for 1st 6-12 months via maternal placenta.
- Recurrent pyogenic infections
- Have to be infused with large amounts of immunoglobulin to remain healthy.
- Btk gene missense mutation

Bruton’s Tyrosine Kinase

- Signalling molecule B-cell development into anti-body producing plasma cells
- 5 domains all of which can be affected by disease causing alterations.
**XLA - summary**

- *Btk* gene mutation
- Loss of functional tyrosine kinase
- Blocked B cell maturation
- No antibodies produced

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**X-Linked SCID**

- Most common form: 3:1 male:female
- Defect in IL2RG gene
- Defect in Cytokine receptor (γc) affecting:
  - Receptors of IL-2, IL-4, IL-7, IL-9, IL-15 & IL-21
  - Absent T-cells, normal / raised B-cells: IgM
  - IL-7 cytokine important for T-cell maturation

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**Severe Combined Immunodeficiencies (SCIDs)**

- ‘SCID – a heterogenous group of monogenic disorders’

  Characterised by:
  - Early on-set (1 in 75,000 births)
  - Severe infections by a full range of pathogens
  - 20 genetic defects identified

  Genetic defect:
  - Lies in T-cell differentiation
  - Indirect impairment of B-cell function & development

**SCIDs Types**

<table>
<thead>
<tr>
<th>SCID Defect in:</th>
<th>Genetic Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine signalling</td>
<td>IL2RG, IL2RA, IL7RA, JAK3</td>
</tr>
<tr>
<td>T-cell receptor signalling</td>
<td>PTPRC, CD3G, CD3E, ZAP70</td>
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<tr>
<td>Receptor gene recombination</td>
<td>RAG1, RAG2</td>
</tr>
<tr>
<td>Nucleotide salvage pathway</td>
<td>ADA, NTP</td>
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<tr>
<td>MHC-I expression</td>
<td>TAP1, TAP2</td>
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<tr>
<td>MHC-II expression</td>
<td>MHC2TA, RFXANK, RFXS, RFXAP</td>
</tr>
<tr>
<td>Other</td>
<td>WASP</td>
</tr>
</tbody>
</table>

Source: Barlow, S. A. & Geha, R. F., (2003), Primary Immunodeficiency Diseases / Allergy Clin Immunol Vol. 112(2) pp671-679

**γc dependent cytokines in T-cell Development**

- γc-dependent cytokines in T-cell Development

**SCID – ADAD**

- Adenosine Deaminase Deficiency
- Autosomal recessive – 15% of SCIDs
- Defect in salvage pathway
- Accumulation of toxic dATP and dGTP
- Inhibition of ribonucleotide reductase
- Impaired development and lifespan of:
  - T-cells & B-cells

**ADAD & PNPD Mechanism**

- Defect in nuclear translocation of nuclear factor of activated T-cells (NFAT)
- T-cell development normal
- Impaired proliferation in response to activation
- Defective Ca²⁺ influx via calcium regulated activated calcium (CRAC) channels
- Defect in ORAI1- essential CRAC component

**SCID – Impaired Ca²⁺ flux**

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**Mutations in genes required for T-cell development**

**Secondary Immunodeficiency**

- Acquired immune deficiency caused by:
  - Malnutrition
  - Malignancy
  - Drugs
  - Trauma
  - Infections
  - Ageing: thymus deterioration → no new T cells → also affects antibody production

**Mechanism of impaired NFAT**

**Malnutrition**

- Most common cause of 2° immune deficiency
- Protein-Calorie malnutrition can lead to abnormalities of T cells, B cells and phagocytes
- Atrophic and fibrotic thymus
- Reduced lymphocyte proliferation in response to antigens
Malignancy

- Immunodeficiency caused by lymphoid tumours e.g. leukaemia, lymphoma, plasma cell dyscrasias
- Hodgkin’s lymphoma: causes classic example of T-cell deficiency
- Chronic lymphocytic leukaemia: causes classic example of B-cell deficiency

Infections

- Bacterial – e.g. Mycobacterium leprae
  - Tuberculoid leprosy: antibody deficiency
  - Lepromatous leprosy: severe T-cell deficiency
- Viral
  - Measles – transient suppression of NK, T & B cells
  - Herpes (Epstein Barr, HSV, cytomegalovirus)
  - Influenza
  - HIV

HUMAN IMMUNODEFICIENCY VIRUS (HIV)

- Human retrovirus
- RNA genome
- Enveloped (gp41, gp120)
- Strains M, O, N
- Targets host cell immune system itself... “abnormalities in every arm of the immune system”

Drugs and Trauma

- Cytotoxic drugs
  - e.g. azathioprine and cyclophosphamide
  - kill tumour cells but also lymphocytes
- Corticosteroids
  - Downregulate lymphocytic genes
  - Mimic action of glucocorticoids
- Glucocorticoids released naturally in response to trauma (burns/surgery) – induce immunodeficiency

REPLICATION OVERVIEW

- Enters lymphocytes and monocytes.
- Gp120 recognises CD4 and chemokine receptor (CXR4 or CCR5)
  → Gp 41 binds to heparan sulphate on cell surface, triggering envelope fusion
  → capsid released into cytoplasm
- 2 types of cell tropism:
  - M-tropic- “R5 viruses” → CCR5 coreceptor
  - T-tropic- “X4 viruses” → CXCR4 coreceptor
- Viral cDNA randomly integrates with host genome.
- Viral proteins are expressed
**IMMUNOLOGICAL CONSEQUENCES**

HIV infection induces:
- Dysfunction and deficiency of **B cells**
- Dysfunction and deficiency of **T cells**
- **Decreased phagocytosis** and intracellular killing by monocytes and neutrophils
- **Decreased cell-mediated cytotoxicity** by natural killer cells

...ultimately leading to severe secondary **IMMUNODEFICIENCY**

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**HUMORAL IMMUNE RESPONSE**

**B-CELL DYSFUNCTION...**

- B-cell hyperplasia → depletion
- Polyclonal hypergammaglobulinemia
  - Autoantibodies
  - Specific antibody response

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**CELLULAR IMMUNE RESPONSE**

- **IMMUNE EVASION:**
  - Provirus latency, reservoirs, strain switch, MHC downregulation, viral epitope mutation
  - Lymphopenia
  - CD4+ & CD8+ T cells
  - Cytokines

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**CYTOKINES**

- Switch $T_{h}1 \rightarrow T_{h}2$ cytokine response... enables efficient evolution of HIV tropism phenotype $R5 \rightarrow X4$
- $T_{h}1 \rightarrow$ more $CCR5 \rightarrow R5$ strain proliferates
- $T_{h}2 \rightarrow$ more $CXCR4 \rightarrow X4$ strain proliferates

- Alters cytokine secretion (IL1/2/6/7/10/12, IFNs)
- E.g. IL-7 favours HIV persistence

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**Summary of Immunodeficiency**

- Immunodeficiency is split into two main categories: primary and secondary. Each has a variety of causes and immunological effects
- **XLA (Primary) – Blocked B-cell development:** antibody deficiencies.
- **SCIDs (Primary)** directly compromises the normal development and function of T-cells and therefore indirectly, B-cells.
- **HIV** is an excellent example of a secondary immunodeficiency, affecting every aspect of the human immune system to devastating effect.

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**References**