When Immunity fails

Course	Immunology
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Type	Lecture
Status	Completed
Reading	☐

Our immune system normally protects us against pathogens in our environment, and defects in the various components of the immune system can lead to life-threatening infections.

The type of infection seen can often give a clue as to what components are defective.

- Extracellular bacterial infections would suggest an antibody defect
- Viral, fungal, and intracellular bacterial infections would implicate the T cell system

Infections can be **opportunistic**, i.e. pathogens such as cytomegalovirus and *Toxoplasma gondii* that are normally dealt with effectively but are able to take hold in immunodeficient individuals.

Infections in these immunocompromised patients are most commonly respiratory or gastro-intestinal.

Genetic mutations cause primary immunodeficiency

- A single nucleotide change (mutationn) in a gene sequence can result in:
  1. No protein
  2. Abnormal protein
  3. Loss of function
  4. Gain of function

  The involved genes are normally expressed in immune cells which develop from bone marrow stem cells
- Types of genetic mutations causing disease

- Substitution
- Insertion
- Deletion
  - Latter two cause frameshift mutations
  - Silent mutations: alter nucleotide sequence and mRNA but encode same amino acid

POINT Mutation	Refers to an alteration of a single nucleotide in a gene	Involve single nucleotide alterations	Occur due to substitutions	Alter the structure of the gene	Example: Sickle Cell Disease
FRAMESHIFT Mutation	Refers to mutations that alter the open reading frame of a gene	Involve alterations in several nucleotides	Occur due to insertions or deletions of nucleotides	Alter the number of nucleotides in a gene	Example: Cystic Fibrosis

NONSENSE Mutation	A sense codon that corresponds to one of the 22 amino acids specified by the genetic code is changed to a chain-terminating codon	Introduces a stop codon to the codon sequence at the site of mutation	Results in a premature chain termination at the site of mutation	Results in an incomplete or truncated protein	Proteins produced are mostly non-functional
MISSENSE Mutation	A single base pair substitution, which alters the genetic code in a way that produces an amino acid that is different from the usual amino acid at that position	Introduces a distinct codon	Results in a distinct amino acid, which is conservative or non-conservative	Results in a conserved or non-conserved protein	Proteins produced are either functional, non-functional, or they have a distinct function from the original protein/

Primary immunodeficiency disorders

- **Occur due to a genetic defect in the immune system**
- Inborn errors if immunity (IEI) (approx. 1:10000)
- Susceptibility to infection
- Associated with autoimmunity, inflammation, immune dysregulation and an increased risk of malignancy
- ~430 different PID genes known
- Rapid advances with widespread sequencing
  - Targeted Chips, WGS, Clinical Exomes

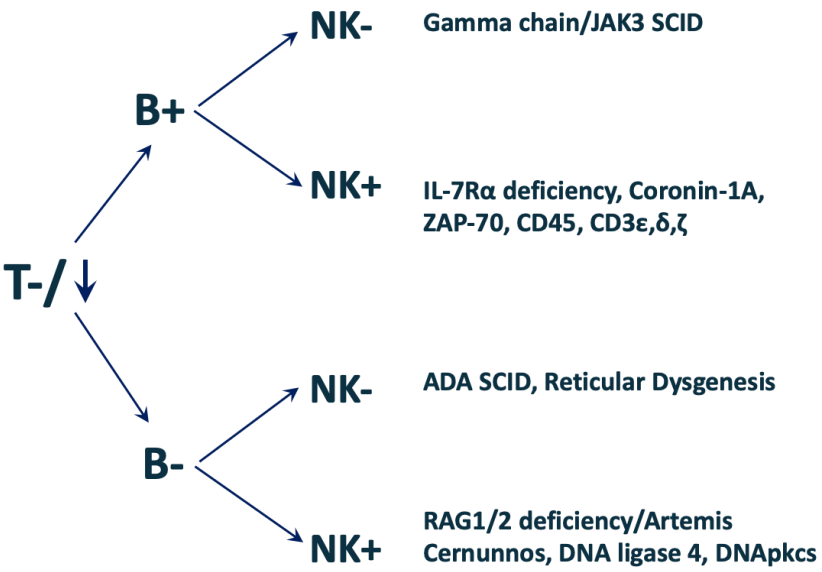
Primary deficiencies can result from defects in either innate or adaptive immunity and vary in severity depending upon the particular gene defect.

- Many of the genes associated with primary immunodeficiencies are on the X-chromosome and therefore found much more commonly in males.

> 💡 Signs of primary immunodeficiency: recurrent viral infections, chronic diarrhea and weight loss, an unusual number of bacterial and fungal infection (not cancer or autoreactive antibodies)

Severe combined immunodeficiency (SCID)

- Both T-cell immunity and humoral immunity is affected
  - Characterised by severe recurrent opportunistic infections with many different pathogens
    - E.g. Pneumonia, diarrhoea, candidiasis
  - Typical SCID <300 autologous T cells per 1ul blood
  - Function <10% lower limit of normal
  - Deleterious mutations
- BCG vaccination 卡介苗
  - Live attenuated vaccine
  - Can cause disseminated disease (BCGiosis) in undiagnosed SCID patients
- Immunophenotype

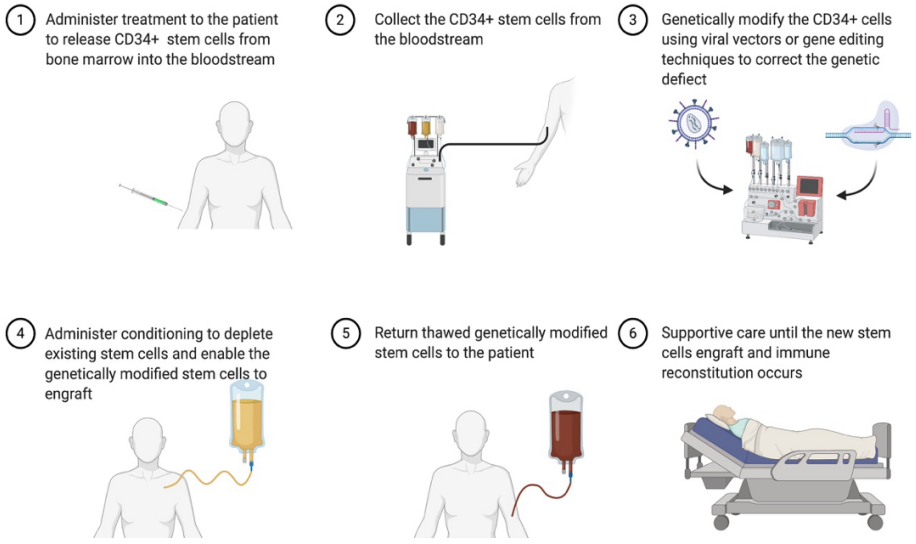


- There are several gene defects that can lead to SCID
  - Mutations in the X-linked **common gamma chain (gamma c)** used by several cytokine receptors
    - No T or NK cells, sparing B, IL-2 receptor gamma
    - Also the **JAK-3** signalling molecule
  - Mutations in autosomal genes including those encoding **adenosine deaminase (ADA)**
    - No T, B, or NK cells
  - the recombination-activating genes **RAG-1** and **RAG-2,** and the **Artemis** component of the **DNA-dependent protein kinase complex**.
    - No T and B, sparing NK
  - CD45, CD3 epsilon, delta, zeta deficiency
    - No T cells
- Treatment

Definitive therapies

Supportive Care	HSCT	Gene therapy
• Antimicrobial (including PCP) prophylaxis • CMV- irradiated blood products (to prevent GvHD and infections) • Avoid live vaccines • IVIg replacement	Results dependent on donor status Outcome also dependent on pre-HSCT state Improving outcomes with alternative donor sources Toxicity	For specific diseases Autologous cells Reduced toxicity Evolving

Autologous gene therapy for PID



SCID - Summary

- Most severe PID
- Immunophenotype
  - absent/reduced T cells
  - +/- absent/reduced B cells
  - +/- absent/reduced NK cells

- Dramatic presentation in infancy with life-threatening complications
- Newborn screening introduced in many countries including UK

> 💡 Initial tests for suspected immuneodefficiency: full blood counts, “immunodeficiency panel” by flow cytometry, vaccination and monitoring B cell response

- Requires definitive treatment inform of bone marrow transplant or gene therapy for patient to survive past infancy

Non-SCID

Antibody and cell-mediated deficiencies occur when B & T cells fail to develop or function normally.

T cells related (also SCID)

- Impaired T cells characterised by respiratory infections and chronic lung and skin inflammation

Di George syndrome

- A defect on the ***Tbx1*** gene where the thymus fails to develop during ontogeny, results in a lack of T cells.

Wiskott-Aldrich syndrome

- Mutation in the gene encoding ‘Wiskott-Aldrich syndrome protein’, **WASp on the X-chromosome**
- A defect in cytoskeletal organisation particularly in lymphocytes and NK cells, T cell activation response and Treg dysfunction

B cells and antibody related

Selective IgA deficiency

- The most common type of primary immunodeficiency
- Specific abnormality is MHC-linked

X-linked agamma-globulinaemia

- defect in the **Bruton's tyrosine kinase, BTK gene**, essential for development and maturation of B cells

- No mature antibody-secreting B cells are produced

X-linked hyper IgM syndrome

- Most commonly a mutation in either the gene for **CD40L** or the gene for **CD40**
- Due to a lack of T-cell help via CD40-CD40L interactions, B-cells are unable to undergo class switching from IgM to IgG and IgA and therefore have no secondary humoral immune response.

X-linked lympho-proliferative syndrome

- Involves mutation in either the SH2D1A (SAP) gene encoding an intracellular signalling molecule or the XIAP gene encoding an inhibitor of apoptosis.
  - Inability to control B cell growth
- These patients are particularly susceptible to infection with Epstein-Barr virus (EBV)
  - EBV derived tumour

Common variable immunodeficiency

- Mutation in ICOS, and TACI, CD19
- Defective IgA and IgG production

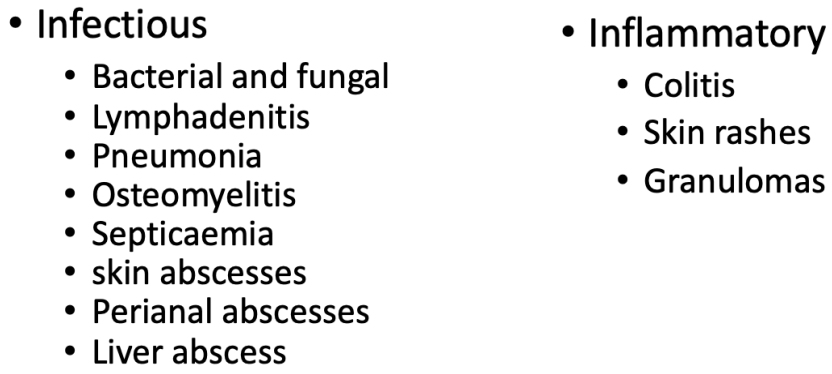
Leukocyte adhesion deficiency

- Due to a defect in the **beta 2 integrin** gene

Chronic granulomatous disease

- Defect in components of **NADPH oxidase**
  - NAPDH oxidase complex - critical for respiratory burst and normal neutrophil function
  - X-linked and autonomic recessive
    - Including several autosomal genes but most commonly the ***gp91phox* gene** on the X chromosome
  - 1:200000 - 1:400000
- Failure of **intracellular bacterial killing**
  - Recurrent and severe bacterial and fungal infections
  - Catalase and organisms (e.g. S. aureus)

- Non-infective granulomas
- Onset in majority < 2 years of age
- Clinical features



- Treatment
  - Prophylactic antibiotics (cotrimoxazole)
  - Prophylactic antifungals (itraconazole)
  - Steroids for inflammatory complications
  - Deep seated infection
    - Interferon gamma
    - White cell infusion
  - Definitive
    - Bone marrow transplant
    - Gene therapy
- Outcome
  - 50% mortality by 30 yrs with antibiotic prophylaxis
  - Poor quality of life un-transplanted
  - Small numbers in published studies of outcome post-HSCT
  - Generally good, 81% cure rate with MSD
  - 90% survival in mixed cohort of MSD, MUD
  - Fungal infection at time of HSCT associated with worse outcome

CTLA4 Insufficiency

- Heterozygous mutations in CTLA4 cause profound immune dysregulation
- Characterised by immune deficiency; uncontrolled lymphoproliferation; autoinflammation; severe, refractory autoimmunity and an increased risk of malignancy
- This results in progressive morbidity and premature mortality.
- Limited treatment options (I/S; abatacept).
- Only curative therapy is allogeneic HSCT, with high TRM.

CTLA-4

- CTLA4 is a co-inhibitory receptor.
- Constitutively expressed at high levels on Treg surface (and transiently expressed on activated conventional T cells).
- Binds co-stimulatory ligands CD80 and CD86.
- 'Strips' CD80 and CD86 from surface of APC and thus inhibits effector T cell response by removing signal 2.
- Removal of CD80 and CD86 occurs through a process referred to as transendocytosis (TE).

Genetic landscape

- Heterozygous mutations result in disease.
- Homozygous mutations incompatible with life in humans.
    - Unable to be born live
- Suggests requirement for tight regulation.
- >80% disease-causing mutations in exons 2,3.

Potential CRISPR Editing Strategies include:

1. Correction of patient specific mutations
2. Targeting exon 1
3. Targeting intron 1

Non-SCID Summary

- Variable phenotype.

- Frequently cause life-threatening complications necessitating definitive treatment.
- Individualised approach to treatment needed.

Disease	Functional Deficiencies	Mechanism of Defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutation in genes encoding proteins of the phagocyte oxidase complex;
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion to endothelial cells and migration into	Mutations in gene encoding the β chain (CD18)

	tissues linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	of β_2 integrins
Chédiak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, NK cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutation in LYST leading to defect in secretory granule exocytosis and lysosomal function
DiGeorge syndrome	Decreased T cells; normal B cells; normal or reduced serum Ig	22q11 deletion; T-box 1 (*TBX1*) transcription factor mutations
ADA deficiency	Progressive decrease in T cells, B cells, and NK cells; reduced serum Ig	Mutations in the ADA gene;
X-linked SCID	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γchain mutations; defective T cell development absence of IL-7–derived signals
Autosomal recessive SCID	Marked decrease in T cells; normal or increased B cells; reduced serum Ig	Mutations in IL2RA, IL7RA, JAK3
RAG1 or RAG2 deficiency (SCID)	Decreased T cells and B cells; reduced serum Ig; absence or deficiency of T and B cells	Mutations in *RAG1* or *RAG2* Cleavage defect during V(D)J recombination;
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Pre-B receptor checkpoint defect; BTK mutation
X-linked hyper IgM	Defects in T helper cell–mediated B cell,	Mutation in CD40L or CD40

	macrophage, and dendritic cell activation; defects in somatic mutation, class switching, and germinal center formation; defective cell-mediated immunity	
Common variable immunodeficiency	Hypogammaglobulinemia; normal or decreased B cell numbers	Mutations in ICOS and TACI in some patients

Fig. 13.1 Human immunodeficiency syndromes. The specific gene defect, the consequence for the immune system, and the resulting disease susceptibilities are listed for some common and some rare human immunodeficiency syndromes. Severe combined immunodeficiency (SCID) can be due to many different defects, as summarized in Fig. 13.2 and described in the text. AID, activation-induced cytidine deaminase; ATM, ataxia telangiectasia-mutated protein; EBV, Epstein–Barr virus; IKK, inhibitor of κ B kinase; STAT3, signal transducer and activator of transcription 3; TAP, transporters associated with antigen processing; UNG, uracil-DNA glycosylase.

Name of deficiency syndrome	Specific abnormality	Immune defect	Susceptibility
Severe combined immune deficiency	See text and Fig. 13.2		General
DiGeorge's syndrome	Thymic aplasia	Variable numbers of T cells	General
MHC class I deficiency	Mutations in TAP1, TAP2, and tapasin	No CD8 T cells	Chronic lung and skin inflammation
MHC class II deficiency	Lack of expression of MHC class II	No CD4 T cells	General
Wiskott–Aldrich syndrome	X-linked; defective WASp gene	Defective anti-polysaccharide antibody, impaired T-cell activation responses, and T_{reg} dysfunction	Encapsulated extracellular bacteria Herpesvirus infections (e.g., HSV, EBV)
X-linked agamma-globulinemia	Loss of BTK tyrosine kinase	No B cells	Extracellular bacteria, enteroviruses
Hyper-IgM syndrome	CD40 ligand deficiency CD40 deficiency NEMO (IKK) deficiency	No isotype switching and/or no somatic hypermutation plus T-cell defects	Extracellular bacteria *Pneumocystis jirovecii* *Cryptosporidium parvum*
Hyper-IgM syndrome—B-cell intrinsic	AID deficiency UNG deficiency	No isotype switching +/– normal somatic hypermutation	Extracellular bacteria
Hyper-IgE syndrome (Job's syndrome)	Defective STAT3	Block in T_H17 cell differentiation Elevated IgE	Extracellular bacteria and fungi
Common variable immunodeficiency	Mutations in TACI, ICOS, CD19, etc.	Defective IgA and IgG production	Extracellular bacteria
Selective IgA	Unknown; MHC-linked	No IgA synthesis	Respiratory infections
Phagocyte deficiencies	Many different	Loss of phagocyte function	Extracellular bacteria and fungi
Complement deficiencies	Many different	Loss of specific complement components	Extracellular bacteria especially *Neisseria* spp.
X-linked lympho-proliferative syndrome	Mutations in SAP or XIAP	Inability to control B-cell growth	EBV-driven B-cell tumors Fatal infectious mononucleosis
Ataxia telangiectasia	Mutations in ATM	T cells reduced	Respiratory infections
Bloom's syndrome	Defective DNA helicase	T cells reduced Reduced antibody levels	Respiratory infections

Secondary immunodeficiency

- **Result from the effects of external agents or breakdown in other body systems which then affect the immune system.**
- Secondary immunodeficiency is much more common than primary immunodeficiency.

Factors leading to secondary immunodeficiency include:

Malnutrition

- Protein-calorie malnutrition and lack of dietary elements (eg. iron, zinc) is worldwide a major predisposing factor for secondary immunodeficiency

Loss of cellular/humoral components

- Lymphocytes passively lost into the intestine in intestinal lymphangiectasia; proteins, especially antibodies, lost into the urine in nephrotic syndrome.

Tumours

- The direct effect of tumours of the immune system or other cells.

Drugs

- Chemotherapy
- Radiotherapy
- Monoclonal antibodies
- Direct Immunosuppression
- These are widely used for inhibiting tumour cell growth but simultaneously damage immune cells.

Diseases

- **Diabetes** are associated with infections

Infections

- Malaria inhibit the development of adequate immune responses;
- Human immunodeficiency virus (HIV) has caused a global catastrophe, causing a particularly severe form of immunodeficiency (AIDS)
    - This virus affects the pivotal CD4+ T cell

HIV

- Lentivirus that infects humans.

- Spread by sexual transmission/contact with infected bodily fluids.
- Leads to low levels of CD4+ T cells (due to pyroptosis, apoptosis, killing of infected cells.
- Cell mediated immunity is lost when CD4+ T cells decline below a critical level. Results in acquired immunodeficiency syndrome (AIDS).
- 40 million deaths, 38 million people living with HIV worldwide.