Immunology and Immune Dysfunction

1. Innate immune system
2. Adaptive immune system
3. Hypersensitivity
4. Immune dysfunction
1. Innate immune system

- The innate immune system is non-specific and acts rapidly on extracellular pathogens
  - **Phagocytes** (neutrophils and macrophages) endocytose and degrade bacteria and cellular debris
    - Phagocytic cells express pathogen recognition receptors (PRRs)
    - PRRs bind to pathogen-associated molecular patterns (PAMPs)
  - **Macrophages** are long-lived, ubiquitous within tissues and secrete important cytokines
    - Secretion of IL-1 and IL-6 causes fever (see acute phase response below)
    - Secretion of IL-8 activates and recruits neutrophils to sites of infection
    - Secretion of IL-12 activates T cells and natural killer cells
  - **Neutrophils** are short-lived but powerful phagocytes and move to sites of infection via chemotaxis
    - Unlike macrophages make up the majority of circulating leukocytes in the blood and not APCs
    - Are killed as they destroy pathogens – contribute to pus formation in acute inflammation
  - **Natural killer cells** do not recognise specific antigens and circulate in the peripheral blood
    - Activated by surface IgG-antigen complexes or lack of MHC class I e.g. in tumours
    - Induce apoptosis in target cells by similar mechanisms to CD8 T cells without CD4 stimulation
  - **Mast cells** (found in tissues) and **basophils** (small amounts in circulation) are granulated cells
    - IgE induces degranulation via calcium influx releasing various inflammatory mediators
    - Capillary permeability increases, blood vessels vasodilatate, extracellular matrix degrades

- The acute phase response is an immediate systemic response to infection or tissue damage
  - **Macrophages** secrete cytokines IL-1, IL-6 and TNF-α
  - These cause the liver to produce a number of acute phase proteins e.g. C-reactive protein (CRP)
  - Production of fibrinogen causes rouleaux formation (RBC stacking) and a gradual increase in ESR
  - The APPs induce fever, leucocytosis, thrombocytosis and protein/fat catabolism
    - CRP levels are particularly elevated in acute bacterial infection
    - Chronic inflammation results in high CRP and ESR – prolonged catabolism leads to weight loss

- The complement system has three pathways all leading to formation of C3 convertase
  - Involves around 20 proteins all normally circulating in the bloodstream
  - The classical pathway is activated by an antigen-antibody complex acting on C1
    - C1 activates C2 and C4
    - C2 and C4 together activate C3
  - The lectin pathway involves mannan-binding lectin (MBL) and its serine proteases (MASP)
    - MBL in the serum binds to MASP forming a complex
    - Attachment of this complex to microbial surface carbohydrates activates MASP
    - MASP activates C2 and C4 which together also activate C3
  - The alternative pathway involves C3b (more stable form of C3) attached to microbial surfaces
    - Factors B and D activate C3 directly – spontaneous activation
  - In the common pathway C3 is activated to form C3 convertase which converts C3 into C3b
  - The membrane attack complex (MAC) causes cell lysis of gram-negative bacteria e.g. Neisseria
    - C3b activates C5 to form C5b
    - C5b activates C6-C9 – together these 5 proteins form MAC itself
  - A local inflammatory response is triggered through mast cell and basophil degranulation
    - C3b activates C3-C5 (the anaphylatoxins) which induce degranulation
    - C3a and C5a promote neutrophil chemotaxis
  - Antigens and microbes can be coated in C3b in the process of opsonisation facilitating phagocytosis
2. Adaptive immune system

- The adaptive immune system is organism-specific and responds slowly on first presentation
  - Cells based in lymphoid tissue require interaction with antigen presenting cells (APCs)
    - Macrophages, dendritic cells and B cells are all APCs
    - Dendritic cells bind antigen and move from peripheral to lymphoid tissues
  - APCs contain Toll-like receptors (TLRs) on their surfaces
    - 10 identified in humans to date – each binds to specific molecular patterns
    - TLR activation results in cytokine production to mount an adaptive immune response
  - Specialised lymphocytes (B and T cells) contain antigen-specific receptors
    - Both B and T cells are produced in the bone marrow and can secrete and respond to cytokines

- Major histocompatibility complex (MHC) molecules are antigen-presenting receptors
  - Human leucocyte antigen (HLA) is encoded on chromosome 6 and variable between individuals
  - MHC class I is synthesised in the ER and found on all nucleated cells
    - Endogenous antigen undergoes intracellular proteosome degradation into fragments
    - Resulting peptides complex with MHC class I which is then expressed on the cell surface
    - Activated CD8 (cytotoxic) T cells recognise the antigen-MHC complex and kill the cell
  - MHC class II is found on APCs, thymus cells and activated T cells
    - Exogenous antigen is phagocytosed and its fragments held in intracellular vesicles
    - MHC class II is transported into the vesicle and complexes with the fragments
    - Activated CD4 (helper) T cells recognise the antigen-MHC complex and release cytokines

- B cells express surface antigen receptors as membrane-bound immunoglobulins
  - B cell receptors comprise two basal heavy chains with two light chains attached on either side
   - The apical regions of both chain types are antigen capturing areas of variable structure
   - The basal regions are class determining of fixed structure for a particular class
   - These receptors can recognise and bind antigenic epitopes directly
  - The five recognised classes of B cell receptor are IgA, IgD, IgE, IgG and IgM
    - All B cells initially express surface IgM – powerful activator of complement
    - Under influence of cytokines some receptors may undergo isotype class switching
  - Free B cell receptors are antibodies (free immunoglobulins, Ig)s
    - IgA and IgG are effective for neutralising toxins
    - IgA lines mucosal surfaces particularly in the gut – found in saliva, tears, breast milk
    - IgG is a powerful promoter of opsonisation and uniquely can cross the placenta
    - IgE is involved in allergic responses and mast cell sensitisation
  - Antigen receptor diversity is achieved through genetic recombination of 2 or 3 gene segments
    - Heavy chains comprise combinations of variable (V), diversity (D) and joining (J) regions
    - Light chains comprise combinations of the V and J regions only
    - The joining of these segments is also subject to variation – junctional diversity
    - Random nucleotides can also be spliced into heavy chains to fine-tune specificity
  - B cells undergoing mitotic division uniquely may undergo some genetic mutation – affinity maturation
    - Affinity of the variable region (antigen-capturing) for the pathogen may change
    - B cells with reduced affinity undergo apoptosis – others undergo somatic hypermutation
  - B cells can differentiate into Ig-producing plasma cells or long-term memory cells
    - Combined APC and CD4 (helper) T cell stimulation promotes plasma cell formation
    - As antigen diminishes remaining CD4 (helper) T cells alone induce memory cell formation
• **T cells** mature in the *primary lymphoid tissue* of the **thymus** through **genetic recombination**
  o Immature T cells move from the bone marrow to the cortex of the thymus in the mediastinum
    ▪ T cell receptor genes undergo genetic recombination producing diverse specificities
    ▪ Subject to junctional diversity but cannot undergo somatic hypermutation or class switching
  o T cells expressing specificity for self-antigen (i.e. of normal proteins) subsequently undergo apoptosis
    ▪ T cells specific for self-MHC only enter the inner medulla for further maturation
    ▪ 1-5% of T cell progenitors emerge as antigen-specific, immunocompetent mature T cells
  o All mature T cells express the marker CD3 by definition along with several other important proteins
    ▪ CD4+ T cells are helpers and only recognise antigen associated with self-MHC class II
    ▪ CD8+ T cells are cytotoxic and only recognise antigen associated with self-MHC class I
    ▪ CD25+ T cells are regulatory and moderate immune responses to prevent autoimmunity
  o **Cytokines** may induce CD4 (helper) T cells as Th1 (cell-mediated immunity) or Th2 (humoral immunity)
    ▪ *Tuberculous leprosy* has low infectivity and normal T cell responses – Th1 reaction (IL-12, IFNy)
    ▪ *Lepromatous leprosy* has high infectivity and low T cell responses - Th2 reaction (IL-4)
  o T cell receptors comprise an α (analogous to B cell light) and β chain (heavy) associated with CD3
    ▪ These receptors have constant (basal) and variable (apical) regions like B cell receptors
    ▪ However they can only recognise and bind to MHC-associated antigen fragments

• **Humoral immunity utilises antibodies to eliminate extracellular pathogens**
  o An extracellular pathogen expressing the exogenous antigen X penetrates mucosal barriers
  o Antigen X expresses PAMPs which bind to PRRs on a dendritic cell inducing phagocytosis
  o Fragments of degraded pathogen complexed with MHC class II are expressed on the cell surface
  o The dendritic cell moves to lymphoid tissue and binds to an antigen X-specific CD4 (helper) T cell
  o The activated T cell now expresses the CD40L surface receptor and begins cytokine production
  o Antigen X stimulates B cells in the spleen and lymph nodes expressing X-specific receptors
  o **Somatic hypermutation** occurs within the germinal centres and the B cells begin to differentiate
  o A stimulated B cell interacts with the activated T cell: CD40 binds to CD40L; B7 binds to CD28
  o The activated T cell produces cytokines IL-2 and IL-4 to -6 which activate the stimulated B cell
  o The T cell may then become a memory T cell not requiring co-stimulation in subsequent infection
  o The activated B cell undergoes clonal expansion — it proliferates and differentiates
  o Antibody-producing plasma cells and long-term memory cells are formed

• **Cell-mediated immunity utilises T cells to eliminate intracellular pathogens**
  o **CD8** (cytotoxic) T cells are powerful killer cells effective against intracellular pathogens
    ▪ Recognise and bind to class I MHC-antigen complexes on infected cell surfaces
    ▪ Generally require co-stimulation from an activated CD4 (helper) T cell for activation
    ▪ CD4 (helper) T cells activate APCs expressing relevant class II MHC-antigen complexes
    ▪ The activated APC now expresses the CD40 surface receptor
    ▪ The naïve CD8 (cytotoxic) T cell can now be activated by the infected APC
  o **Dendritic cells** express large quantities of the B7 surface receptor
    ▪ If subject to intracellular infection they can directly activate CD8 (cytotoxic) T cells
    ▪ The activated CD8 (cytotoxic) T cell produces IL-2 which induces self-proliferation
  o Activated CD8 (cytotoxic) T cells also produce several cytokines
    ▪ IFNy (interferon) inhibits viral replication and activates macrophages
    ▪ TNFα is involved in promoting the acute phase response and induces vasodilatation
    ▪ TNFβ activates macrophages
3. **Hypersensitivity**

- **Hypersensitivity** is an *inappropriate, excessive* immune response to an antigen
  
  o **Type I** (*allergic*) hypersensitivity involves a rapid, localised *IgE-mediated* inflammatory response
    - 10-30% of individuals have a *genetic predisposition* to IgE production – *atopy*
    - Initial exposure to antigen *sensitises* the immune system to produce large amounts of *IgE*
    - **Mast cells** become coated in IgE and *degranulate* on subsequent re-exposure to the antigen
    - Symptoms arise locally within minutes following exposure – *urticaria, rhinitis, asthma*
    - Deterioration occurs hours later when *eosinophils* are recruited from the *bone marrow*
  
  o **Type II** (*antibody-mediated*) hypersensitivity involves *antibodies* mounted against particular *cells*
    - Cells may be *self* (e.g. in Graves’ disease) or *foreign* (e.g. blood transfusions) – usually *IgG, IgM*
    - Antigen-antibody complexes activate *complement* via the classical pathway causing lysis (*MAC*)
    - **Natural killer cells** are stimulated to engage in *antibody-dependent cell-mediated cytotoxicity*
    - The antibodies act as *opsonins* facilitating *phagocytosis* and subsequent degradation
  
  o **Type III** (*immune complex*) hypersensitivity involves complexes of *antigen, antibody and complement*
    - *Immune complexes* are normally transported by RBCs to the *spleen* for degradation
    - A sudden influx of complexes results in inappropriate deposition in *tissues* and *blood vessels*
    - **Neutrophil** interaction combined with *complement* action results in *necrosis* and *vasculitis*
  
  o **Type IV** (*delayed*) hypersensitivity involves sensitised *T helper cells* activating numerous *macrophages*
    - CD4 (helper) T cells recognise an antigen and undergo *clonal expansion* of 1-2 weeks’ duration
    - Subsequent re-exposure triggers *cytokine* release and mass-activation of *macrophages*
    - Persisting macrophage by-products may be damaging to tissues and lead to *granuloma*

- **Anaphylaxis** is a *severe, rapid onset systemic* hypersensitivity reaction that can be fatal
  
  o Essentially involves an extreme systemic *type I* (*IgE-mediated*) hypersensitivity response
    - Common causes are peanuts, fish, drugs (particularly *antibiotics*), *latex*, wasp stings
    - More common in adults and usually due to *ingestion* producing less severe reactions
  
  o Symptoms arise within minutes following *injection* of antigen or within hours following *ingestion*
    - **Angioedema** (sudden severe skin swelling), *wheezing, shock* and *abdominal pain* are common
    - More rarely some people may experience rhinitis, headache or seizure
    - Death can occur from *respiratory obstruction or cardiovascular collapse*
  
  o Treatment begins with *immediate* administration of *intramuscular adrenaline*
    - Adrenaline acts on α1 receptors to induce *vasoconstriction*
    - Patient should be supine and given high-flow *oxygen*
    - In severe shock adrenaline and fluids should be administered *intravenously*
    - H1 *antagonists* (e.g. *chlorpheniramine*) may be administered as an adjunct
4. Immune dysfunction

- The **immune system** is prevented from attacking the **self** by mechanisms of **self-tolerance**
  - **Central tolerance** eliminates B and T cells that develop **high-affinity receptors** against **self-antigen**
    - Self-reactive **B cells** are detected in the **bone marrow**
    - Self-reactive **T cells** are detected in the **thymus**
  - **Peripheral tolerance** prevents peripheral self-antigens from triggering an immune response
    - Cells lack crucial **co-stimulatory molecules** (e.g. CD40) and express low levels of **MHC**
    - T cells entering the **brain, testes or anterior chamber of the eye** undergo apoptosis (Fas ligand)
    - **CD25** (regulatory) T cells secrete **IL-10** and **TGFβ** which inhibit other **self-reactive T cells**
  - These mechanisms can **fail** due to a combination of **genetic predispositions** and **environmental factors**
    - Defective HLA genes mean that self-reactive T cells are not detected in the thymus
    - Some **bacteria** and **viruses** express antigens that mimic self-antigen though this is usually minor
    - Infections can also cause non-specific mass B and T cell activation or excessive **MHC** expression

- **Failure of self-tolerance results in either systemic or organ-specific autoimmune disease**
  - **Systemic lupus erythematosus** (SLE) involves **auto-antibodies** against **DNA** and blood cell elements
    - Nine times more common in **women** compared to men
    - Defective **MHC** (HLA-DR2/DR3) and **complement-associated genes** implicated in aetiology
    - Self-reactive **B cells** generate IgG **auto-antibodies** which form numerous **immune complexes**
    - Inappropriate deposition of immune complexes leads to **arthritis** and **glomerulonephritis**
    - **Vascular damage** results in characteristic rashes e.g. on the **hands and cheeks** (**malar rash**)
    - Treatment includes **immunosuppression** and anti-inflammatory drugs
  - **Rheumatoid arthritis** is a **systemic** autoimmune disease that particularly affects the **joints**
    - Non-specific inflammation of the **synovial joints** activates **CD4** (helper) T cells
    - TNF-α and other cytokines trigger the **acute phase response** leading to **bone erosion**
    - Activated B cells secrete **rheumatoid factor** (anti-IgG IgM) exacerbating inflammation
  - **Graves’ disease** is specific to the **thyroid gland** and the commonest cause of **hyperthyroidism**
    - Self-reactive **B cells** generate IgG **auto-antibodies** against the **TSH receptor** which stimulate it
    - Negative feedback to the **hypothalamus and pituitary** to reduce TSH secretion is ineffective
    - Clinical features include **weight loss, tremor, sweating, tachycardia, exophthalmos, anxiety**
  - **Hashimoto’s thyroiditis** is an **inflammatory** thyroid disease and a common cause of **hypothyroidism**
    - Self-reactive **CD8** (cytotoxic) T cells destroy the epithelial cells reducing hormone production
    - Significant **lymphocytic infiltration** leads to **anti-thyroid peroxidase auto-antibody** production
    - Clinical features include **goitre, dry skin, facial oedema, fatigue, anovulation**
  - **Autoimmune haemolytic anaemia** involves **auto-antibody-mediated erythrocyte destruction**
    - May be **idiopathic** or secondary to SLE or chronic lymphocytic leukaemia
    - IgM auto-antibodies cause agglutination, **complement activation** and MAC-mediated lysis
    - IgG auto-antibodies act as **opsonins** and induce **phagocytic destruction** in the spleen

- **Primary immunodeficiency results from congenital defects of immune function**
  - **X-linked agammaglobulinaemia** is a rare disease in which progenitor B cells fail to mature
    - Antibodies cannot be produced resulting in failure of the **humoral immune response**
    - **Bacterial infections** become frequent but cell-mediated immunity is largely unaffected
    - Symptoms arise within the first year of life with recurrent severe **respiratory infections**
    - Treated with **intravenous immunoglobulin** and antibiotic therapy
  - **Wiskott-Aldrich syndrome** is another X-linked disorder involving eczema and **haemorrhagic diathesis**
    - Defective WASP protein results in defective antibodies, T cell responses and platelets
- Presents with recurrent bacterial infections particularly of the respiratory tract
- Secondary autoimmune disease may follow such as haemolytic anaemia

**Chronic granulomatous disease** (CGD) involves phagocytes being unable to kill ingested microbes
- Enzymatic defect results in inability to produce lethal oxidative burst
- Very rare but mostly X-linked with some autosomal recessive types
- Presents early in life often with skin infections, pneumonia and suppurative lymphadenitis
- Treated with interferon and cotrimoxazole though often fatal in infancy

**Di George syndrome** is a congenital absence of the thymus causing a severe T cell deficiency
- Spontaneous deletion on chromosome 22 occurring in 1 in 4000 births
- Third and fourth pharyngeal pouches become malformed preventing thymus development
- Cell-mediated immunity fails resulting in persistent viral infection
- Parathyroid glands fail to develop and there are often cardiac defects

**Severe combined immunodeficiency** (SCID) is a group of rare congenital diseases that are usually fatal
- Inherited as X-linked or autosomal recessive trait
- Combined failure of B and T cell function results in persistent infections and failure to thrive