Introduction, Innate and Adaptive Immunity (W4)

Introduction to Immunology (L1)

Glossary

- **Immunity** – Resistance to infectious diseases
- **Immune system (IS)** – Collection of cells, tissues, molecules that mediate immunity
- **Immune response (IR)** – Co-ordinated reaction of the IS to microbes
- **Immunology** – Study of the IS, its responses to pathogens and damaged tissues and role in disease
- **Antigen** – A molecule that binds to an antibody or T-cell receptor
- **Antibody** – Type of glycoprotein produced by B-cells that binds antigens
- **Antigen-presenting cell (APC)** – Cell that displays peptide fragments of protein antigens on its surface and stimulates T-cells.
  - Also express co-stimulatory molecules
- **Cytokines** – Proteins produced by many different cell types that mediate inflammation and immune reactions – communicators between cells
- **Chemokines** – Chemoattractant cytokines

Role of Immune System	Implications
Defence against infection	Deficient immunity increases susceptibility to infections (e.g. AIDS) Vaccination boosts immune defences and protects against infections
Defence against tumours	Potential for immunotherapy for cancer
Control of tissue regeneration and scarring	Damaged tissue repair
Cell injury and induction of pathologic inflammation	Immune responses lead to allergic, autoimmune and other inflammatory diseases
Recognition and response to tissue grafts and newly induced proteins	Immune responses are barriers to transplantation and gene therapy

Physiologic function of the immune system

- To **prevent** or eradicate **infections**
- **Prevention** of some **tumours**
- Clearance of **dead cells**
- Tissue **repair**
- Some negative aspects:
  - Abnormal immune responses
    - Leading to **inflammatory diseases**
  - Barrier to organ **transplantation**

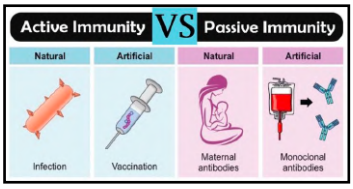
Immune response

- Thus – The immune system can respond to **microbial** and **non-microbial** substances and can cause disease under some circumstances
- What is the “Immune Response”?
  - A **reaction** to microbes and to other molecules that are **recognised as foreign**, regardless of the physiologic or pathologic consequences of the reaction

2 major immune responses in defence against infection

1. Innate immunity
   - The initial protection
   - non-specific
2. Adaptive immunity
   - Gradual development of
     - more **specialised** response
     - More **effective** response

Induction of immunity



1. **Active**
   - Due to **infection**
   - Due to **vaccination**
2. **Passive**
   - **Transfer** of antibodies or lymphocytes from actively immunised individuals
     - **Treatment** or **maternal**
   - Only lasts for the lifetime for the transferred antibodies or cells (short-lived)

Characteristics of innate immunity

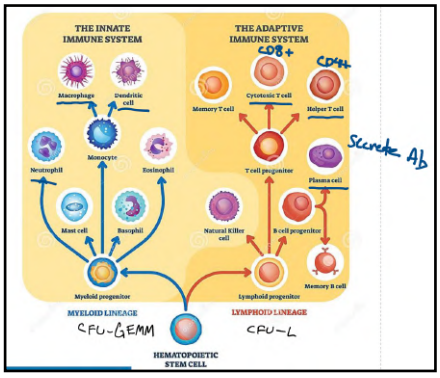
- Natural or native immunity
- **Physical** and **chemical barriers**
- Ready to block microbial entry

- Always present in healthy subjects
- React **rapidly** to eliminate microbes that manage to gain entry

Innate immunity
- **First line** of defence
  - **Epithelial** barriers
  - Cells and **natural antibiotics in epithelia**
- **Second line** of defence
  - **Phagocytes**
  - **Natural killer cells** - special type of lymphocytes
  - Several **plasma proteins** (complement system)

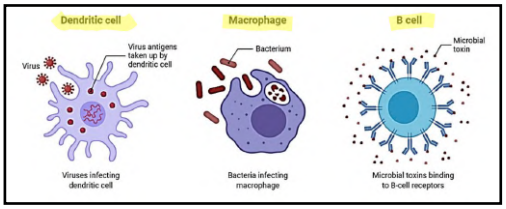
Characteristics of adaptive immunity
- More **specialised** than innate immunity
- **Specified or acquired immunity**
- **Adapts** to the presence of specific microbes
- Involves **differentiation** and **expansion** of lymphocytes
- Essential for defence against **pathogenic infectious microbes**

Adaptive immunity
- System consists of **lymphocytes (T/B cells)** and **their products** (eg. Antibodies)
- Lymphocytes express **surface receptors** that recognise a wide variety of **molecules or "antigens"** produced by microbes
- **Use cells and molecules** of **innate immune responses** to **eliminate microbes**
- Functions to **greatly enhance antimicrobial mechanisms of innate** immunity
- Demonstrate collaboration between innate and adaptive IR



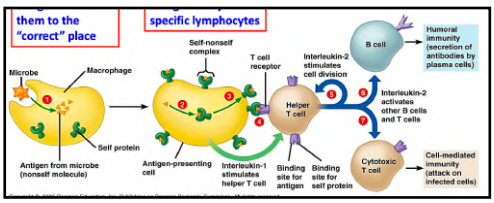
Cells of the immune system
- Located in different tissues
- Severe different roles in host defence
- Most derived from **bone marrow precursors** and **circulate** in blood
- Others are present in **tissues**, at all times (e.g. **dendritic cells, macrophages and mast cells**)

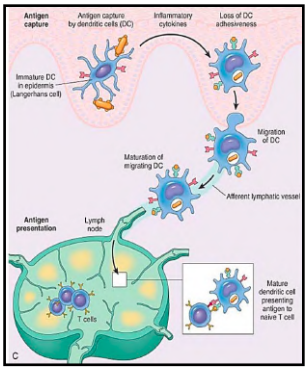
Cells of the adaptive immune system
- Antigen presenting cells (APC)
- Lymphocytes
- Effector cells



Antigen presenting cells (APC)
- Specialised cells located at **portals of entry for microbes**
  - **Skin, GI tract, respiratory tract**
- Include **dendritic cells, macrophages, B cells**

Actions of APCs
- Capture microbes, process into antigens and take them to the "correct" place
- Display antigens in a form that can be recognised by specific lymphocytes
- Provide "second signals" for T cell activation
- **IL-1**: stimulates **helper T cells**
- **IL-2**: **stimulate B cells/CD8+ T cells**; stimulates **CD4**+ T cell proliferation





Dendritic cells prime naive T cells

- **Dendritic cells** - most **effective** APCs for starting T-cell responses

1. Long **surface processes**
2. **Immature DCs capture protein antigens** and migrate to regional LNs
3. DCs **mature** along the way
4. Mature DCs **present portion** of **antigen to naive T cells** (epitopes)

Other antigen presenting cells (APCs)

- **Macrophages** line lymphatic channels - may capture antigens and display them to **B cells**
- **Follicular dendritic cells**
  1. Located in **germinal centre** of lymphoid follicles in peripheral lymph organs
  2. Display antigens that **stimulate B cell differentiation** in follicles
- These differ from dendritic cells that are APCs for T-cells

Lymphocytes

- 30% of while cells in blood
- Key mediators of adaptive immune responses
- Formed by
  - liver and thymus in foetus
  - **bone marrow and lymph nodes in adults**
- Produce receptors that are specific for variety of antigens
- Heterogeneous – lineage / function / phenotype
- Participate in complex biological activities and responses
- Distinguishable by **specific surface molecules designated** “CD” –
  - **Clusters of differentiation** –
    - eg **B-cells: CD19+ and CD20+**
    - **T-cells: CD3+** (pan-T-cell marker)
      - T-helper: CD3+/**CD4+**
      - T-cytotoxic: CD3+/**CD8+**

Effector Cells

- Cells that **eliminate microbes** - include:
  1. **Lymphocytes**
  2. Other WBCs - **macrophages** and **granulocytes**
- Macrophages and granulocytes may function as effector cells in both innate and adaptive immune responses

Primary and secondary lymphoid organs

- Cells, organs and tissue of the immune system are found throughout the body
- **Primary** or Central (Generative) **Lymphoid Organs** (green)
  - Where **T- and B-cells mature** and become competent to respond to antigens
  - Thymus/bone marrow
- **Secondary** or Peripheral
  - Lymphoid Organs (pink)
    - Where **adaptive immune responses to microbes** are initiated
  - Lymph nodes/spleen

Primary lymphoid organs

- Lymphocytes develop from **bone marrow stem cells**
- **Hematopoietic progenitors** or stem cells:
  - commit to the **B- or T-cell lineage**
  - proliferate
  - **rearrange** and **express antigen receptor genes**
  - undergo **selection** and **expansion** of cells that express potentially useful antigen receptors
    - **B**-lymphocytes **mature** in the **bone marrow**
    - **T**-lymphocytes **mature** in the **thymus**

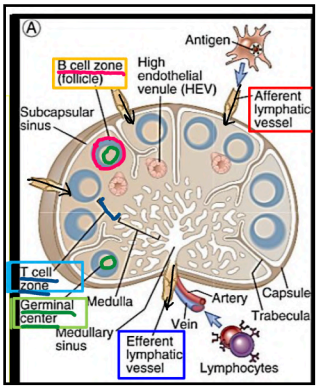
Secondary lymphoid organs

1. Lymph nodes
2. Spleen
3. Mucosal immune system
4. Cutaneous immune system

- Antigen presenting cells (**APCs**) **concentrate antigens** in these organs
- **Naïve lymphocytes** preferentially go to **specialised organs** and tissues where antigen is concentrated
- **Optimal interaction** of **antigen, APCs and lymphocytes**
- Lymphocytes respond to the antigens
- Effector cells go to sites of infection for microbe elimination

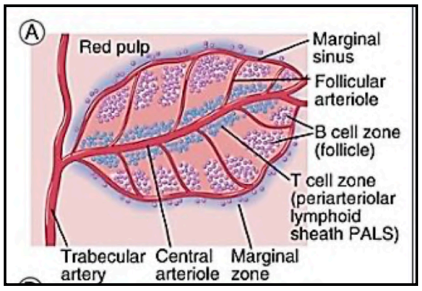
Lymph nodes

1. Encapsulated aggregates of lymphoid tissue
   - Primary lymphoid follicle - **B cell zone** (naive B cells are activated)
   - Secondary lymphoid follicle - **germinal centre** (somatic hypermutation and isotype switching, affinity maturation)
   - Parafollicular cortex - **T cell zone** (naive T cells are activated)
2. Located along lymphatic channels
3. Lymph - fluid leaking out of small blood vessels is drained by lymphatic vessels to lymph nodes (afferent) and back into circulation (efferent)
4. **Dendritic cells** transport **microbial antigens** from **epithelia** and other tissues to the **lymph nodes**
5. APCs in nodes sample microbe antigens that may enter through epithelial into tissues



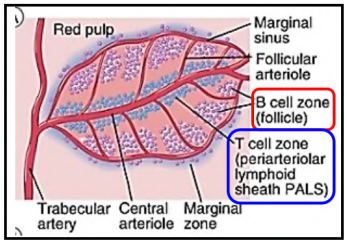
Spleen

1. Highly vascularised organ
2. Role in immune responses to **blood-borne antigens**
3. Blood enters spleen and flows through channels (sinusoids)
4. **Blood-borne antigens** are **trapped** and **concentrated by macrophages** and **dendritic cells in the spleen**
5. **Phagocytes** lining the sinusoids **ingest and destroy microbes in the blood**
6. **Phagocytes** also deal with **old red blood** cells



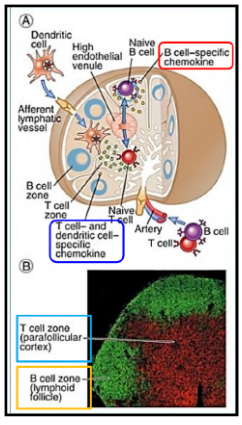
T and B cells occupy separate locations

1. Lymph nodes
   - **B cells** - located within **follicles in periphery or cortex**
   - Follicular dendritic cells (**FDCs**) **activate B cells**
   - Activated B cells responding to antigens form a **germinal centre** within follicles - this is the site of **antibody production**
   - **T cells** — outside but adjacent to follicle in **paracortex**
   - **Dendritic cells present antigen to T cells and activate them**
2. Spleen
   - **B cells** - within **follicles**
   - **T cells** - in **periarteriolar lymphoid sheaths (PALS)**
     - Surrounding small arterioles



T and B cells occupy separate locations

- **Localisation** - tightly regulated by **chemokines** – chemo-attractant cytokines
- **Naive B cells** have receptor - **CXCR5**
  - **FDCs** secrete a **chemokine bound by CXCR5**, which **attracts B-cells** from blood to **follicles**
- **Naïve T-cells** have receptor - **CCR7**
  - Naïve T-cells leave the **thymus** into circulation and enter **T-cell zone of LNs** via specialised venules: - **high endothelial venules (HEVs)**
- Chemokine bound by **CCR7**:



- produced in **paracortex** (LN) and **periarteriolar lymphoid sheath** (spleen)
- Displayed by HEVs

T and B cells are not static

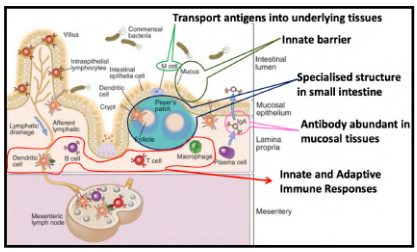
- **Naïve lymphocytes recirculate** between blood and peripheral lymphoid organs.
  - On activation by antigen, they become **effector cells**
- Lymphocyte activation alters **chemokine receptor expression** and **T- and B-cells migrate** towards each other and **interact at the edge of follicles**
- Effector or memory T-cells leave LN via **efferent lymphatic vessels** and migrate to sites of **tissue infection** to eliminate microbes
- **Effector B-cells = plasma cells** - do **not** migrate to site of infection.
  - **Secrete antibodies** which then enter the circulation where they may act or may be carried to infection sites in tissues

Mucosal and cutaneous immune systems

- Specialised collections of **lymphoid tissue (Peyer's patch),** APCs and effector molecules in and **under epithelia** of **gastrointestinal** and **respiratory tracts** and **skin**
- Contain scattered immune cells and discrete collections of lymphocytes and APCs similar to lymph nodes
- Sites of immune responses to antigens breaching epithelia

Mucosal immune systems

- Transport of antigens into underlying tissues
- Innate barrier
- Specialised structure in small intestine
- Antibody abundant in mucosal tissues
- Innate and adaptive immune responses



Lymphocyte types (+NK Cells)

- **B-cells** recognise **soluble or cell surface antigens** and differentiate into **antibody-secreting cells (plasma cells)**.
- **Helper T-cells** recognise **antigens** on the surfaces of **APCs** and **secrete cytokines**, which stimulate different mechanisms of immunity and inflammation.
- **Cytotoxic T-cells** recognise **antigens** in **infected cells and kill these cells**.
- **Regulatory T-cells limit activation** of other lymphocytes, especially of T cells, and **prevent autoimmunity**.
- **Natural killer cells** recognise **changes on the surface** of infected cells and **kill these cells**.
  - NK cells are cells of innate immunity, and all the other lymphocytes are cells of the adaptive immune system

Immune response decline and immunologic memory

- Initial lymphocyte activation produces
  - Effector cells
  - Memory cells

1. **Effector cells** - are **short lived**
   - Microbes provide essential stimuli for lymphocyte survival and activation. These **stimuli are lost** following microbial elimination
   - Therefore, **most effector lymphocytes** induced by the microbe die by a process of programmed cell death – **Apoptosis**
   - The immune system returns to basal resting state or homeostasis
2. **Memory cells** - are **long-lived**
   - May survive for **years** after infection, with **rapid and robust response** on **repeat exposure** to the antigen that led to their production

Innate and Adaptive Immunity - Responses and Effector Mechanisms (L2)

The innate immune response

- A series of reactions that provide defence
  - At the **portals of entry** for microbes: the **skin epithelia** and **gastrointestinal** and **respiratory systems** - physical barriers, antimicrobial molecules and lymphoid cells.
  - In the tissues: Microbes and dead cells are detected by **resident macrophages**, **dendritic cells**, and other sentinel cells. Some of these secrete **cytokines**, others **phagocytose** and destroy microbes and eliminate damaged cells.
  - In the **blood**: **Plasma proteins** react against microbes and promote their destruction
  - **Viruses** elicit special reactions – produce **interferons** from **infected cells** that (interfere with) inhibit infection of other cells

What initiates an immune response?

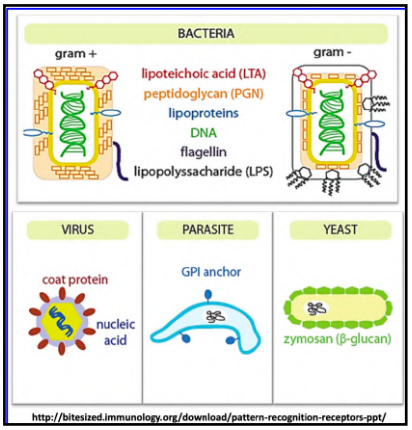
- **Recognition** of the presence of foreign substances or organisms
  - From **damaged or necrotic cells**; or
  - From **pathogens**

Molecules from damaged or necrotic cells

- **Damaged** or **necrotic** host cells release a limited number of molecules:
  - **Damage-Associated Molecular Patterns (DAMPs)**
- DAMPs Include:
  - A **histone protein** from cells with **damaged nuclei**
  - **Extracellular ATP** - from **damaged mitochondria**
  - **Uric acid**
- DAMPs are **recognised** by the **innate immune system**
  - Responses to DAMPs: Eliminate damaged cells
  - Initiate tissue repair

Molecules from pathogens

- Pathogens express molecules that are not shared with the host:
  - **Pathogen-Associated Molecular Patterns (PAMPs)**
- PAMPs are:
  - **Shared by pathogens** of the same type and are invariant
  - Specific to each pathogen
  - **Essential** for **pathogen survival** and **infectivity**
    - ie. Microbes without functional PAMPs are unable to infect or colonise host
- PAMPs include:
  - **Lipopolysaccharide** (LPS)
  - **Flagellin**
  - **dsRNA** produced during **viral replication**
  - **Unmethylated CG-rich (CpG) oligonucleotides**



Recognition of molecules from damaged or necrotic cells and pathogens

- Pattern Recognition Receptors (PRRs)
  - A key element of innate immunity
  - Belong to several protein families
  - Mainly on **antigen presenting cells (APCs) – Macrophages, dendritic cells**
  - Also on other immune cells (**lymphocytes**) and **non-immune cells** (epithelial and endothelial cells)
  - Expressed in **cellular compartments** where microbes may be located
    - On **cell surface** - recognise **extracellular** pathogens – bacteria and fungi
    - In **endosomes** - recognise **intracellular** pathogens – viruses
    - In **cytoplasm**
  - Recognise **conserved structures** PAMPs and DAMPs