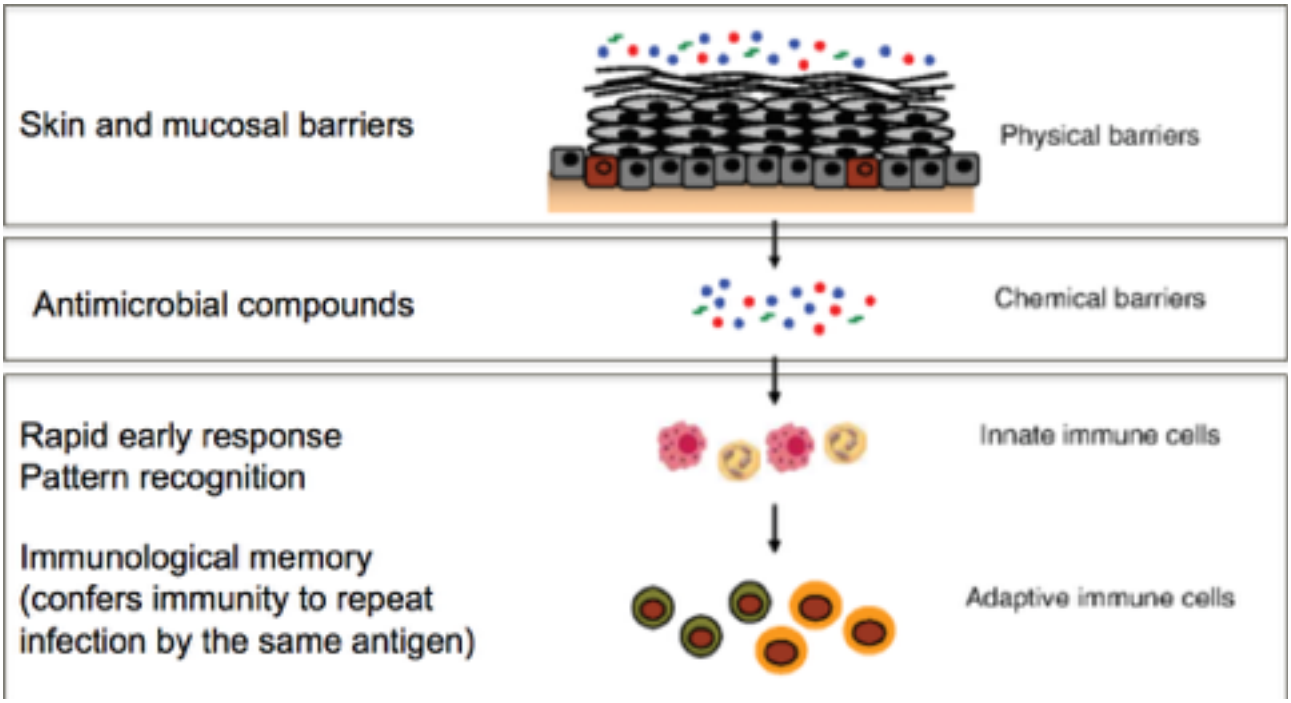
1 - Fundamentals of Human Immunology

- Immunology is the body's defence against bacteria, parasites and allergens
- The word **vaccination** is derived from the latin word for cow (vacca) and reflects the importance of the use of cow pox to protect humans from small pox
- Vaccination relies on the generation of **acquired immunity**, inducing an immune response to **antigenic products** contained in the vaccine (usually killed or live attenuated viruses)
- When the body is infected by a live pathogen, the **memory cells** recognise the same or very closely related **antigens** and generate an **immune response** against the pathogen
- The memory response is more rapid and potent than the **primary response** against the vaccine



- There is extensive cross-talk between different arms of the immune system
- Innate immune cells are also recruited to inflamed epithelia
- Epithelial cells secrete antimicrobial peptides
- Infection of skin and mucosal barriers releases pro-inflammatory molecules that recruit immune cells
- T-cells are recruited to sites of inflammation

	Primary Lymphoid Organs		Secondary Lymphoid Organs	
Epithelial barrier	**Bone marroe**	**Thymous**	**Lymph nodes**	**Spleen**
- Respiratory tract - Urogenital tract - Conjunctiva - Intestine - Skin	- Hematopoietic stem cells	- T-cell selection	- B-cell maturation - T-cell activation and differentiation	- Immune response against blood-borne antigens

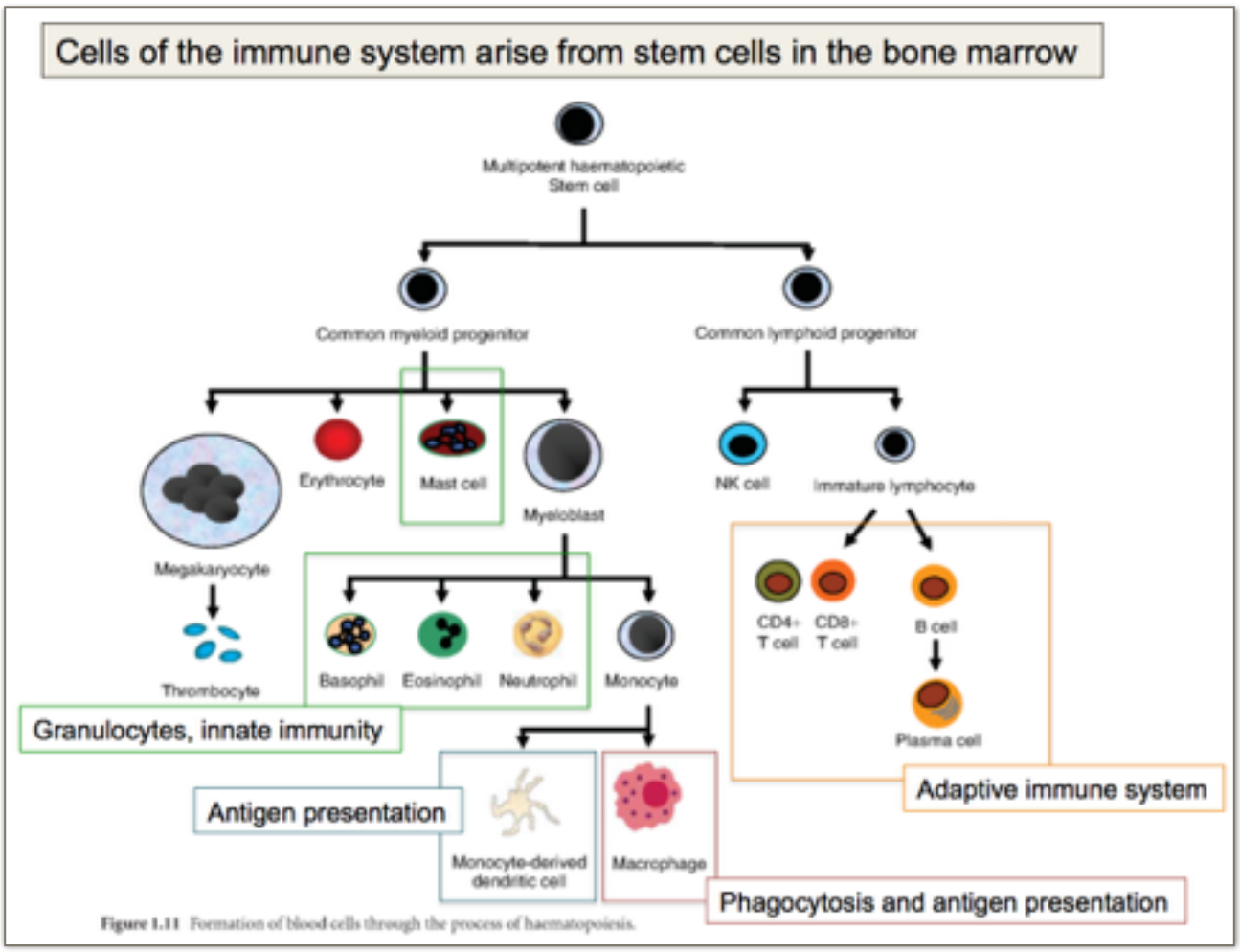


Figure 1.11 Formation of blood cells through the process of haematopoiesis.

- The innate immune system is activated rapidly in response to an infection
  - The innate immune system includes barrier defence at the mucosa of the airways, gut and urogenital tract as well as the skin
- The adaptive immune system response occurs later and is highly specific
  - The adaptive immune response involves humoral (antibody) and cellular responses

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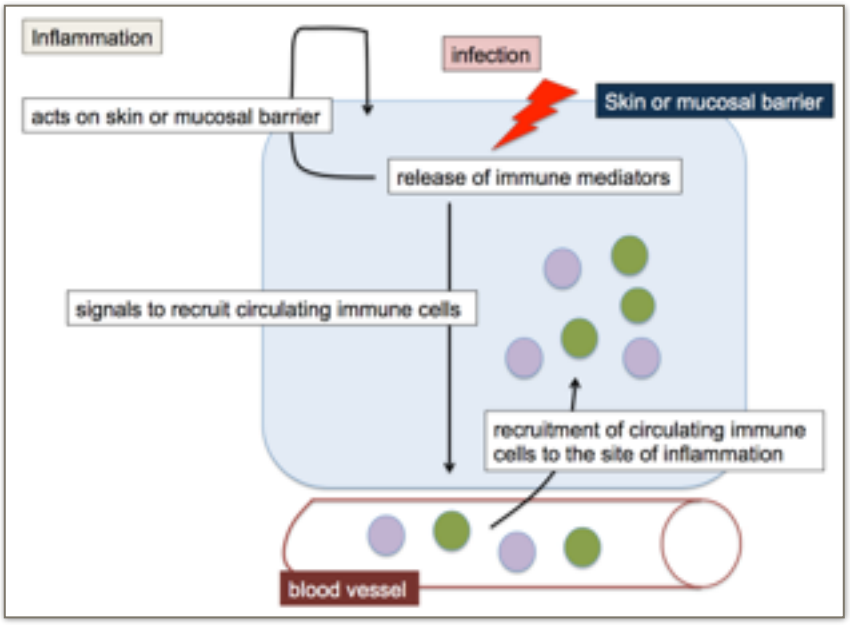
- The Innate immune system consists of cells that recognise specific features of viruses, bacteria and parasites
  - The recognition is pre-programmed and is fixed
- The Adaptive immune system can adapt to recognise new antigens
  - B-cells make antibodies that recognise specific antigens
- Cell-mediated immunity involves the innate and adaptive immune systems and does not involved antibodies
  - it's an adaptive immunity response in which antigen-specific T-cells have the main role
  - it also involves macrophages and neutrophils of the innate immune system

Innate Immune System	Adaptive Immune System
Rapid response (hours)	Delayed response (days)
Non-specific response to conserved molecules	Highly specific response to antigen
Response fixed (not adaptive)	Response adaptive (changes over time)
No immunological memory	Immunological memory
Humoral and cell-mediated components	Humoral and cell-mediated components
Components found in all animals	Only found in jawed vertebrates

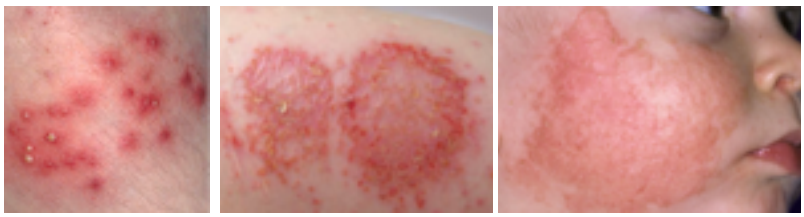
Inflammation

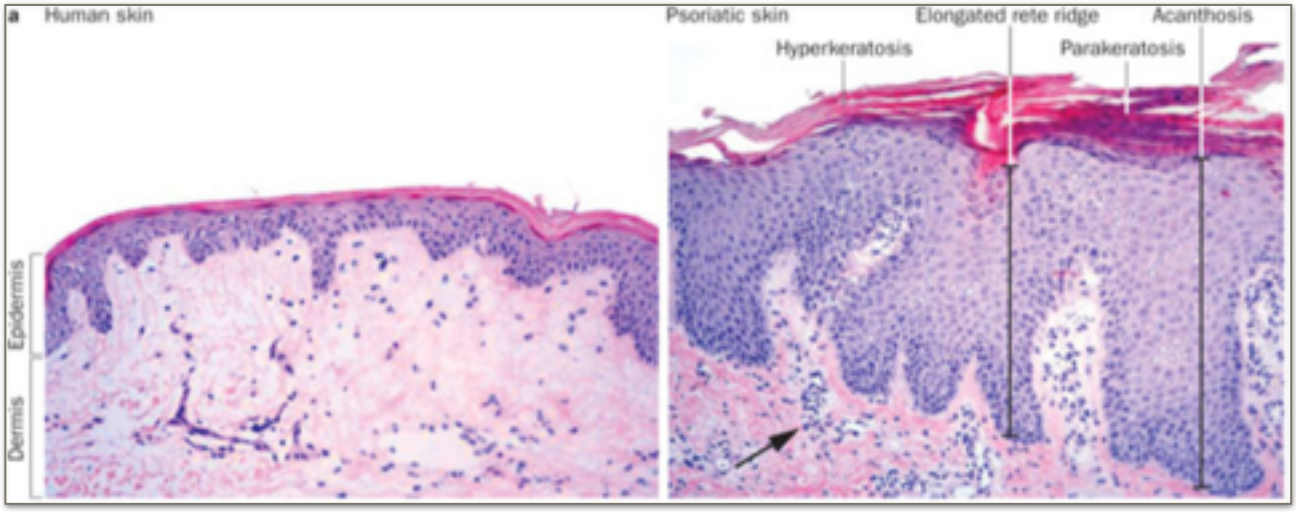
- Protective immune response triggered by infection and damage to tissues
- Inflammation is accompanied by redness, increased heat and swelling that are indicators of increased blood flow and the presence of immune mediators at the site of infection
- Acute inflammation protects and repairs damaged tissue
- Chronic inflammation is ongoing inflammation and is a disease state that is associated with heightened activity of the immune system and irreversible pathological changes to tissue architecture

- This shows the innate immune response:
- Infection penetrates/breaks into skin or mucosal barrier
- That causes host to release immune mediates to signal recruitment of circulating immune cells from the blood
- They're recruited to the site of inflammation

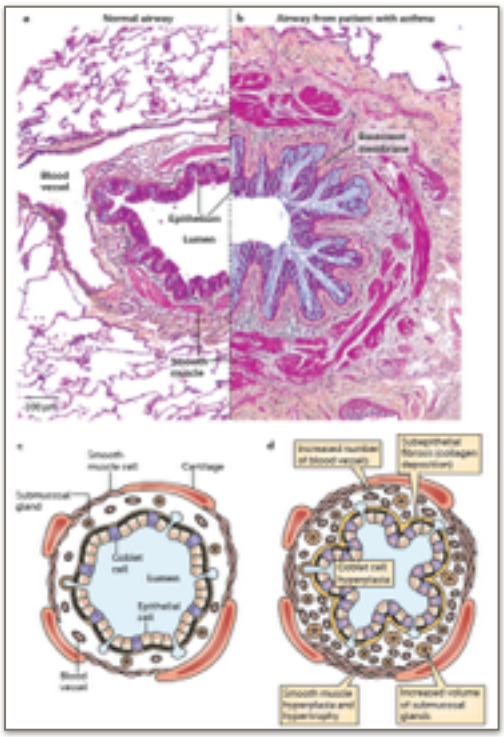


- Atopic dermatitis is an allergic inflammatory skin condition that is accompanied by an increased risk of viral and bacterial infection





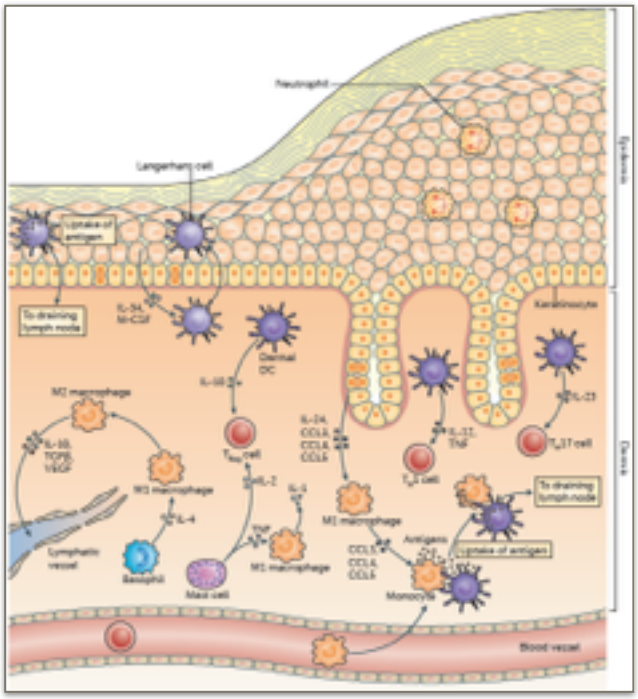
- Skin remodelling in **psoriasis**: thickening of the epidermis (tissue remodelling) and increased infiltration of inflammatory immune cells
  - Psoriasis is a chronic skin disease of scaling and inflammation
- Hyperkeratosis: thickening of the cornified layer (very most top part of the skin)
- Parakeratosis: presence of nuclei in cornified layer
- Acanthosis: thickening of the epidermis
- Arrow: increased infiltration of inflammatory immune cells

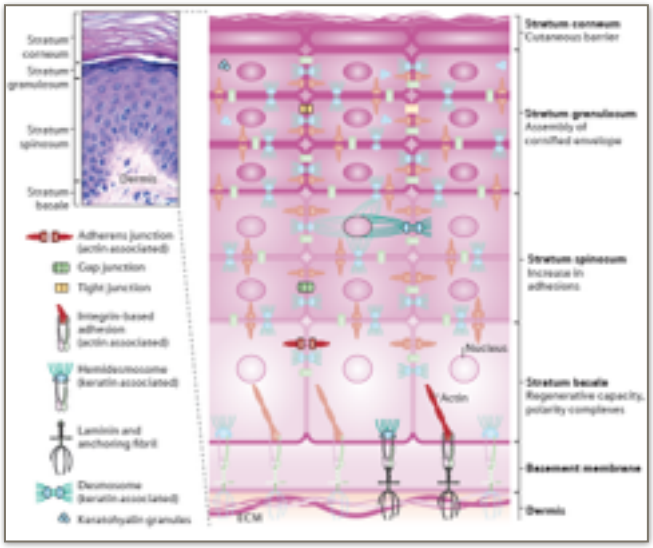


- Airway remodelling in severe asthma as a result of chronic inflammation

- The thinning of airways in patients with severe asthma represents an interaction between chronic inflammation and dysfunction of the smooth muscle of the airways
  - there's huge thickening of the smooth muscle cells and increase in the number of goblet cells, hence closing down the opening a bit

- The skin is classified as stratified epithelium. It provides a barrier against infection and damage to the underlying tissue and prevents water loss
- The different layers go from highly proliferating cells to highly differentiated cells





- **Skin macrophages** survey the skin and carry out early detection and response to foreign antigens that have breached the skin barrier.
- **Mast cells** contain preformed immune mediators and as such are the first cells that are activated and contribute to the innate immune response.
  - Mediators released from mast cells act on the infection itself as well as recruiting and activating additional immune cells

Monocytes and Macrophages

- Derived from the myeloid lineage and make up approximately 5% of circulating leukocytes in the blood
- In response to infection monocytes migrate into tissues where they mature into macrophages or monocyte-derived dendritic cells
- Within tissues macrophages are the primary phagocytosing cell of the immune system

Dendritic cells

- Have a particular morphology involving long cellular extensions known as dendrites
- There are several different classes of dendritic cell, reflecting differences in origin, location, and function
- Skin-resident dendritic cells are called Langerhans cells
- The primary function of dendritic cells is the presentation of antigen to T-cells
- and the initiation of an adaptive immune response

Pattern recognition receptors

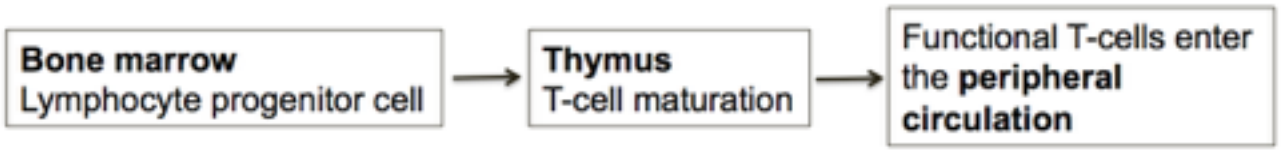
- Unlike the adaptive immune system, the innate immune system is not tailored to respond to specific antigens
- Cells of the innate immune system, as well as dendritic cells (which bridge the innate and adaptive immune systems) recognise infectious agents through receptors known as **pattern recognition receptors (PRR)**
- PRRs recognise evolutionarily conserved motifs on the surface of bacteria, viruses, fungi and parasites called **pathogen activated molecular patterns** (PAMPs)
- Antigens and infectious agents that are recognised by cells of the immune system and activate an immune response are often referred to as **danger signals**

Antigen

- A substance that is capable of stimulating an immune response
- An immune response involves the **specific activation of lymphocytes**
- Foreign antigens originate from outside the body
- Auto-antigens (or self-antigens) is the recognition of our own tissues by our immune system

Thymus

- T-cells originate in the bone marrow and complete their development in the thymus, they then leave the thymus and enter the peripheral circulation and take residence in our lymph nodes
- **Positive selection** allows only functional T-cells to leave the thymus (only the mature ones that can recognise antigen)
- **Negative selection** prevents **self-reactive T-cells** from leaving the thymus (the ones that attack us/self)
  - it ensures T-cells are tolerant to self-antigens
  - failure of negative selection leads to **autoimmunity**
- Most T-cell maturation and differentiation takes place in the embryo and neonatal period and the peripheral T-cell repertoire is complete by early adulthood
- After leaving the thymus, T-cells enter the circulation to take up residence in the secondary lymphoid organs



T-cells

- APC (Antigen Presenting Cell)
- $CD4^+$ and $CD8^+$ T-cells are identified by the expression of different co-receptors for the T-cell receptor (TCR).
- The function of $CD4^+$ T-cells is to assist in the activation of other immune cells. For this reason they are called T-helper (Th) T-cells
- $CD8^+$ T-cells are cytotoxic T-cells due to their cytolytic activity against virally infected cells and tumour cells
- Both cell types recognise MHC, CD4 recognising MHC II, whereas CD8 recognises MHC I

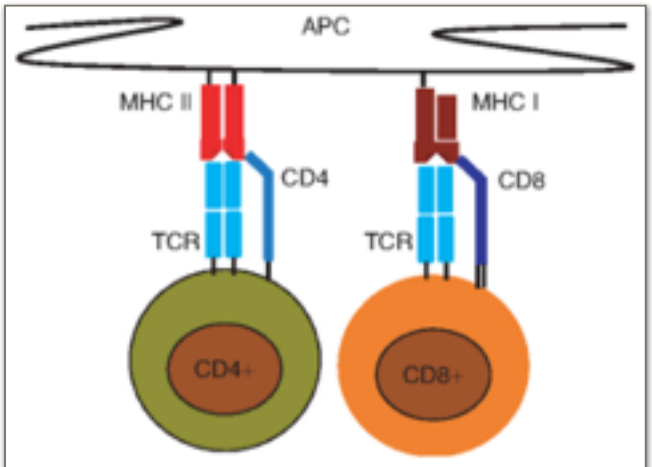


Figure 1.13 CD4+ T helper cells express TCRs that recognize MHC class II molecules, while CD8+ cytotoxic T cells recognise MHC class I molecules. Receptor binding is stabilised by the co-receptors CD4 and CD8.

- Newly generated T-cells exit the thymus to form the long-lived pool of **naïve T-cells** that recirculate within the confines of the peripheral lymphoid tissues.
- The generation of antigen-specific T-cells occurs in the lymph nodes when T-cells recognise antigen presented by dendritic cells
- This generates pools of **memory T-cells**
- CD4+ T-cells can differentiate into one of several different T-helper cell subsets based on differences in cytokine secretion (see online lectures)
- Mature differentiated T-cells can leave the lymphoid tissue and migrate to sites of inflammation as **effector T-cells** (because it effects an immune response)

B-cells

- **B-lymphocytes** are part of the adaptive **immune system** and are responsible for the production of antibodies.
- The term antibody is interchangeable with immunoglobulin, which when bound to the surface membrane is known as the **B-cell receptor (BCR)**
- Each B-cell produces an antibody that selectively binds a specific antigen and is known as a B-cell clone
- B-cell clonal selection takes place within the lymphoid organ, ensuring the selection of clones that produce the highest affinity to an antigen
- Mature B-cells are known as **plasma cells**

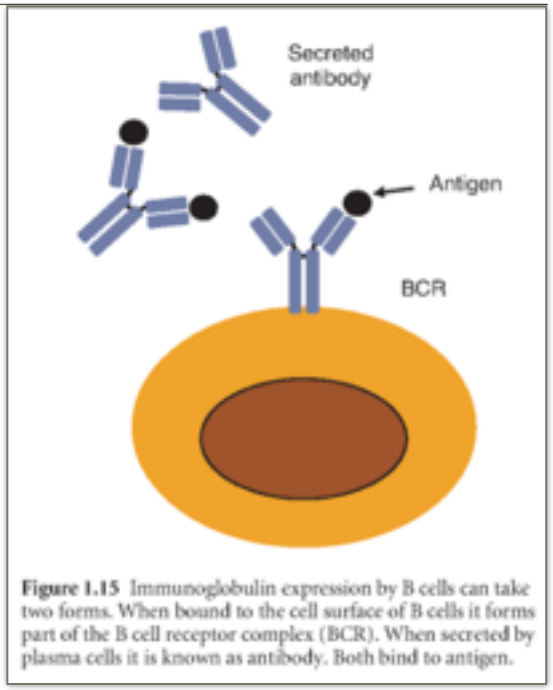
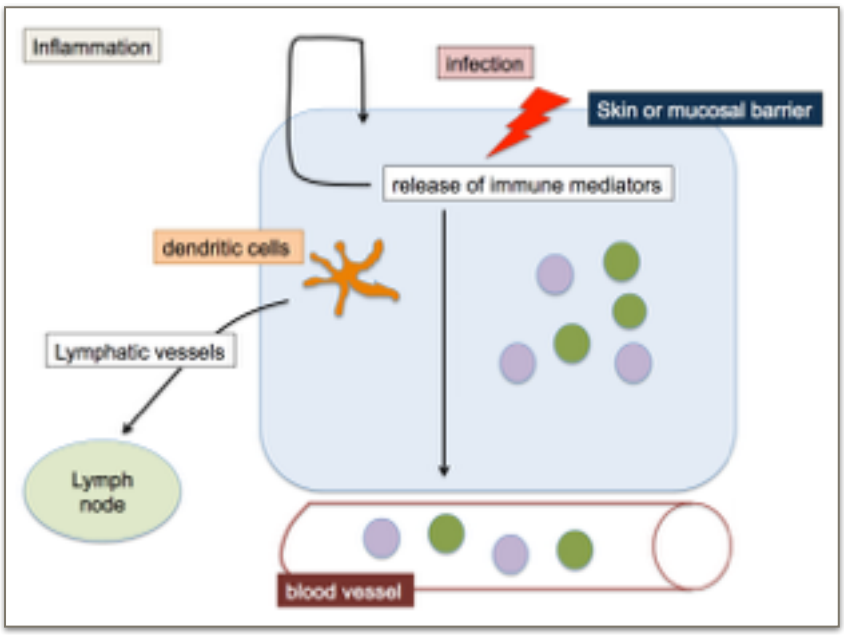


Figure 1.15 Immunoglobulin expression by B cells can take two forms. When bound to the cell surface of B cells it forms part of the B cell receptor complex (BCR). When secreted by plasma cells it is known as antibody. Both bind to antigen.

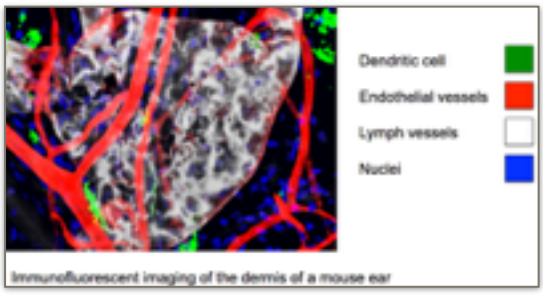
- The infection causes release of immune mediators
- The Dendritic cell is able to take up antigen and express it on its cell surface
  - moves via the Lymphatic vessels to the Lymph nodes where it encounters a T-cell (of the adaptive immune system)

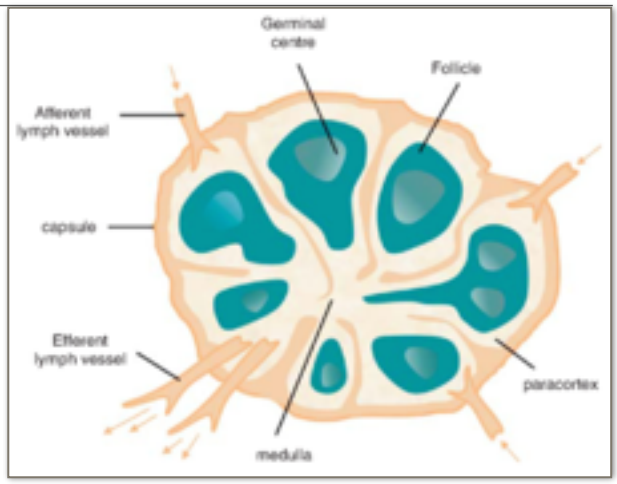
  ^ link between the innate and adaptive immune system



Lymph nodes

- Non-specific filtration and accumulation of particulate antigens and microorganisms
- Lymphatic fluid drains from the peripheral tissues and enters a lymph node via the afferent lymphatic vessels
- Microorganisms and particulate antigens are removed by the phagocytic activity of macrophages
- An important function of the lymph nodes is the presentation of antigen to lymphocytes, leading to T- and B-cell activation and proliferation





- **Paracortex**: T-cell areas
- **Follices**: are surrounded by the paracortex and are B-cell areas
- **Germinal centre**: site of B-cell maturation

Primary and Secondary Immune responses

- It can take up to one week to generate an antigen-specific T-cell response and between 10 and 14 days to generate an antigen-specific B-cell response that results in significant amounts of antibody in the bloodstream
- Once naïve cells have encountered antigen and proliferated, any subsequent encounter with the same antigen provokes a more robust immune response

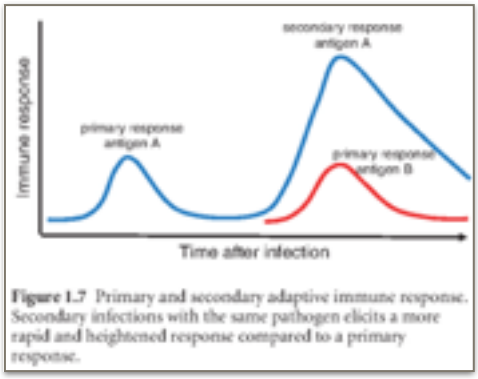
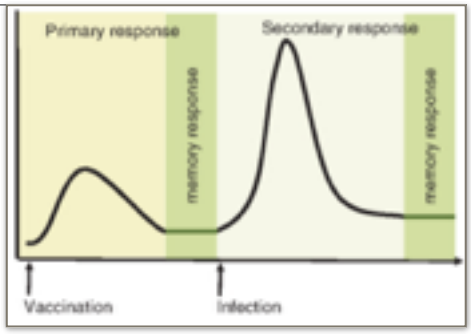


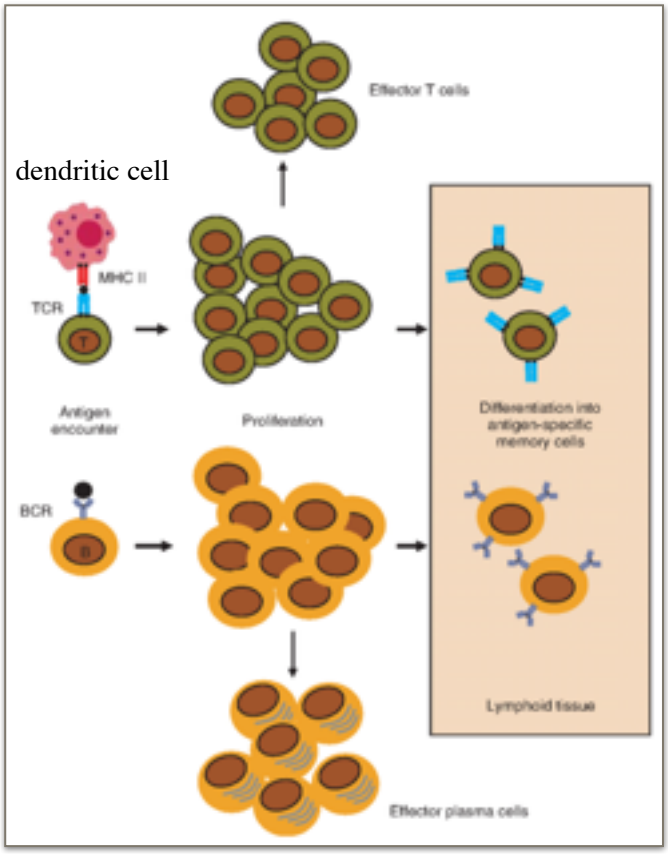
Figure 1.7 Primary and secondary adaptive immune response. Secondary infections with the same pathogen elicits a more rapid and heightened response compared to a primary response.

Vaccination

Vaccination induces immune memory, to when the real pathogen attacks, the body can have a much more robust defence system against it



Immunological Memory

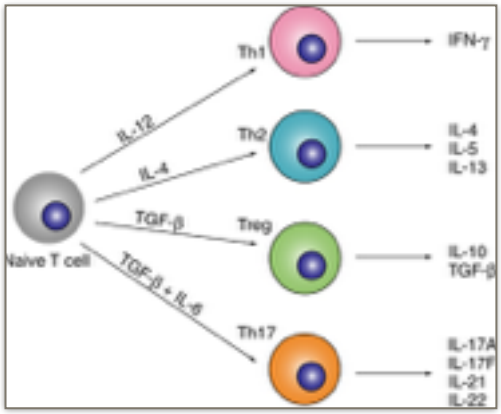


- The Dendritic cell has seen the antigen and is presenting that antigen on its cell surface via the MHC molecule
  - recognition of antigen involves: T-cell receptor (TCR), antigen, MHC II complex (and that combination is specific for that antigen, because we have many different combination of TCRs & our MHC has lots of genetic variants)
- A naïve T- or B-cell that encounters antigen for the first time will proliferate and mature into antigen-specific memory cells, ensuring an immune response upon re-exposure to antigen
- After the immune response has subsided the effector T-cells die (apoptosis)
- The remaining effector T-cells then become either **central memory** T-cells or **effector memory** T-cells

- When an antigen is re- encountered, central memory T- cells remain in the lymphoid organ and respond to the antigen while central effector T-cells are recruited to the site of infection

- Naïve T-cells can differentiate into several different T-helper cell subsets

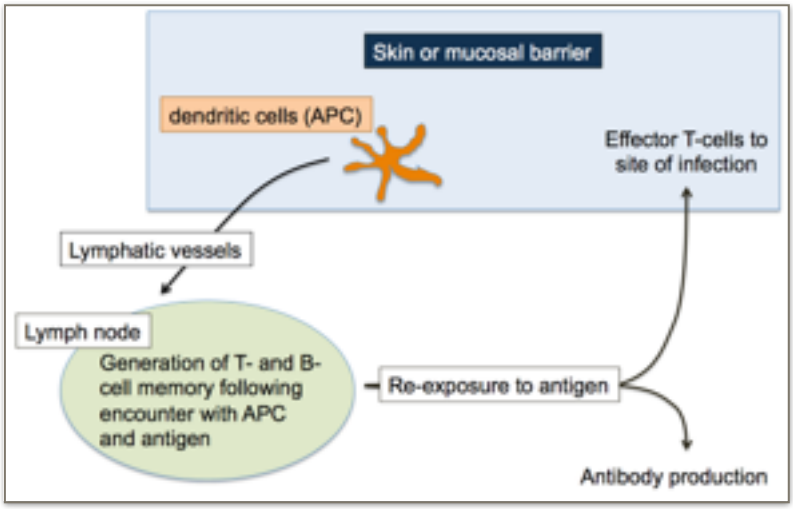
Th1, Th2 and Th17 turn things ON



T-regulatory cells (Treg) are the suppressor cells of our immune system

(turn things OFF)

- Immunological memory and the adaptive immune response
- Dendritic cells taking antigen to lymph nodes via lymphatic vessels
- T and B cells are generated and get in contact with the APC and antigen
  - there is antibody production form the B-cells
  - memory T-cells go to the site of infection as effector T-cells
  - central T-cells help the B-cells in their antibody production



- The immune response need to be tightly controlled so it's under control, or else we end up with chronic diseases, our own tissues being attacked, tissue remodelling

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Psoriasis is associated with elevated levels of interleukin-17

An imbalance in the differentiation of naïve T-cells that results in elevated numbers of one T-helper subset causes chronic inflammatory diseases Understanding the mechanisms that control the activation of our immune system is essential for the diagnosis and treatment of many immune-mediated diseases

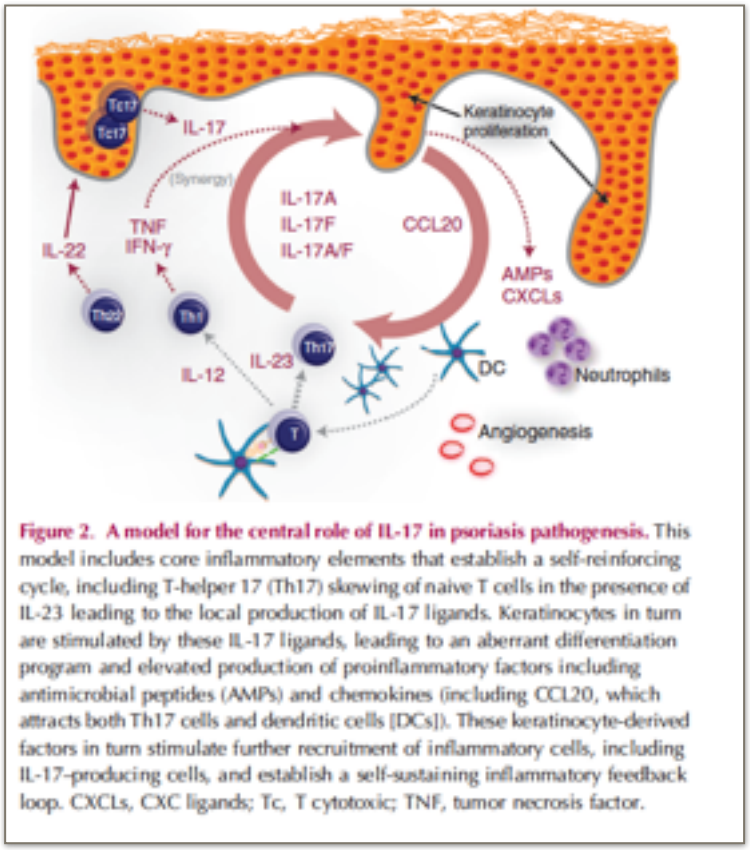

Figure 2. A model for the central role of IL-17 in psoriasis pathogenesis. This model includes core inflammatory elements that establish a self-reinforcing cycle, including T-helper 17 (Th17) skewing of naive T cells in the presence of IL-23 leading to the local production of IL-17 ligands. Keratinocytes in turn are stimulated by these IL-17 ligands, leading to an aberrant differentiation program and elevated production of proinflammatory factors including antimicrobial peptides (AMPs) and chemokines (including CCL20, which attracts both Th17 cells and dendritic cells [DCs]). These keratinocyte-derived factors in turn stimulate further recruitment of inflammatory cells, including IL-17–producing cells, and establish a self-sustaining inflammatory feedback loop. CXCLs, CXC ligands; Tc, T cytotoxic; TNF, tumor necrosis factor.