INFECTION AND IMMUNITY

Lecture 52: The Immune System - Innate Immunity

The Principles of Immune Responses are as follows:

Recognition: the ability to discriminate between 'self' and 'non-self'; and 'danger' vs 'non-danger'

Response: appropriate and specific for the pathogen and present as soon as the exposure occurs; rapid

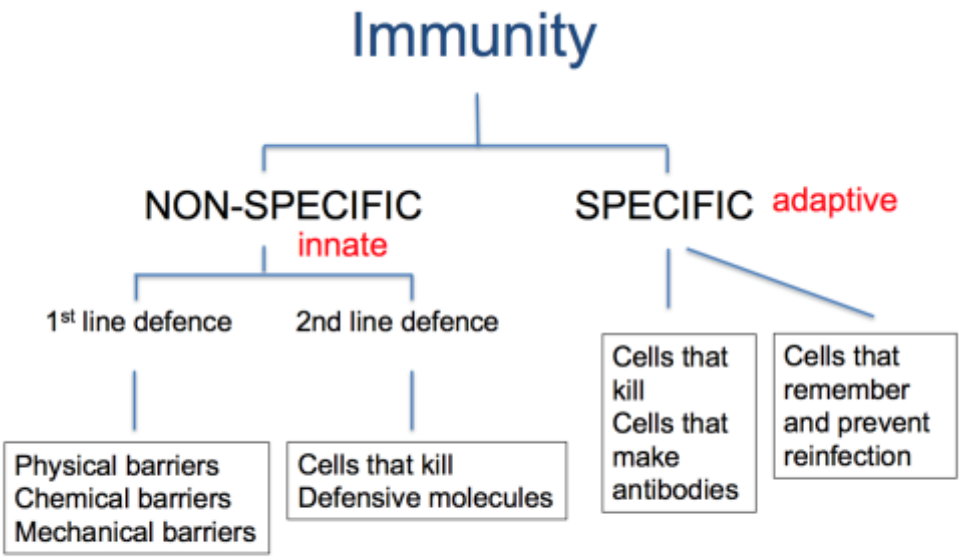
Memory: secondary infections are more rapid and give a stronger response; vaccines can be used to do this

Regulation: chronic inflammation, auto-immune disease; when a pathogen is eliminated from the body, the immune response must be down-regulated

Pathogens always have specific proteins on their surface that allow the immune system to distinguish and discriminate microbes from self components. Bacteria, for example, contain peptidoglycan and LPS which allow for immune cells to recognise them for destruction. Although these LPS molecules reveal to the individual that a 'non-self' cell is present, LPS are present on all Gram negative bacteria, and thus the individual will not be able to discriminate the type of pathogen. These indicators of pathogenicity are known as **PAMPs (pathogen associated molecule patterns)**.

However, there are other markers which are unique to a particular organism, and reveal the exact type of pathogen it is. These markers are known as **antigens** and always generate an antibody response which is highly specific for that particular antigen only. Because there are two types of patterns present - shared and unique, the immune system has two different types of receptors - **pattern recognition receptors (PRR)** and **antigen receptors**.

The **adaptive immune system** developed as a result of certain microbes being able to avoid the innate immune system:



Protection from and resistance to infection by microbes

	Innate	Adaptive
Characteristics		
Specificity	Molecules shared by microbes or damaged host cells	Microbial and non-microbial antigens
Diversity	Limited; germline encoded	Very large; somatic recombination of gene segments
Memory	None	Yes
Response	Rapid, constant magnitude	Slower, magnitude increases with multiple exposures
Components		
Cellular and chemical barriers	Skin, mucosal epithelia, antimicrobial molecules	Lymphocytes in epithelia, antibodies secreted at epithelial surfaces
Blood proteins	Complement, others	Antibodies
Cells	Phagocytes, NK cells	Lymphocytes

The Innate Immune System

- Is relatively non-specific and receptor molecules on cells and in serum recognise PAMPs
- More rapid as the components required are already present in the body
- Has a constant magnitude
- Is the first line of defence
- Interacts, facilitates and controls the activation of the adaptive immune system

There are multiple components and activation pathways of the innate immune system as well:

- Barriers: physical, chemical and cellular (epithelial); these are termed **fixed** defences as they are present with or without infection
- Specialised proteins (complement, chemokines, cytokines)
- Specialised cells (neutrophils, macrophages, NK cells, etc.)

Recognise 'non-self' by:

- Binding of PAMPs by pattern recognition receptors
- Ag-Ab complex attracts phagocytes
- Specialised receptors detect 'altered self' glycoproteins on the surface of infected/cancerous cells and cause NK cells to target these for killing

Non-specific Defence Systems

Many components of the human body make up this defence system, including the skin surface, which acts as a physical barrier that protects the individual from pathogenic infection. Many other features, such as low stomach pH (2) and mucus lining in respiratory organs, also protect the individual from infection. These defence systems lie on the exterior of the individual and prevent infection.

After a pathogen has bypassed barriers mentioned above, specialised plasma factors mediating innate immunity recognise pathogen associated molecular patterns (PAMPs). These include:

- **C-reactive protein:** binds capsule of several bacteria, aids phagocytosis, triggers the complement cascade; CRP levels reveal the level and extent of infection of an individual; the CRP is a PRR that binds to dying cells and some bacteria

- **Mannose binding lectin: MBL** binds to mannose residues on pathogens and triggers the *complement cascade*

- **Complement proteins:** pro-enzymes (C1 and C2) which are triggered after binding a pathogen to produce a cascade of reactions which generate effector molecules against the pathogen (acute phase proteins)

The Complement System

A large group of constitutively produced plasma proteins which interact with pathogens and mark them for killing. These proteins are activated in a sequential cascade and this cascade can be activated in several ways. There are 3 ways in which this cascade pathway can be activated, all of which result in the breakdown of C3 (into C3a and C3b). The outcomes of

this pathway are **migration of phagocytes to site of infection**, **phagocytosis of microorganisms** and **lysis of microorganisms**.

The 3 pathways that result in breakdown/cleavage of C3 are:

Classical Pathway: An antibody binds to antigen of microbe, resulting in the activation of C1, C2 and C4 molecules. These molecules trigger a signal cascade which eventually result in the cleavage of C3.

Lectin Pathway: A lectin molecule binds to mannose (on the surface of pathogens) and activates MASP, C2 and C4. These result in the cleavage of C3.

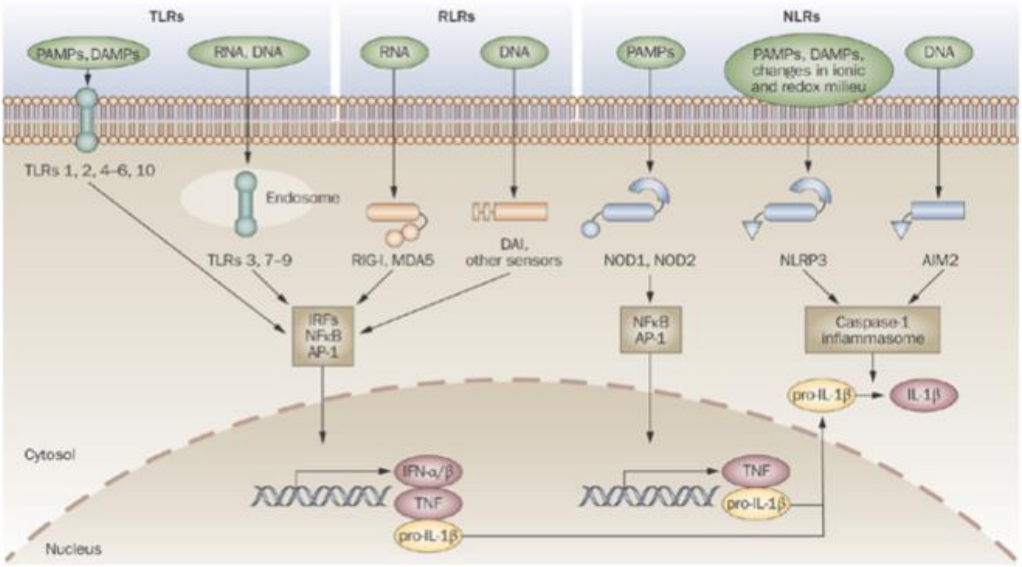
Alternative Pathway: Pathogenic surfaces are recognised (peptidoglycan, LTA and LPS) and are bound to by C3b which have spontaneously been hydrolysed. A signal cascade occurs that ultimately results in cleavage of more C3 into C3a and C3b.

Cleavage of C3

When C3 is cleaved, C3a (smaller) and C3b (larger) subunits are produced. The larger C3b protein binds to the surface of a microbe and induces phagocytosis by **opsonisation**. The C3a protein stimulates inflammation and recruits nearby macrophages and neutrophils to the location of infection (chemotaxis). The cleavage of C3 can also cause the formation of membrane attack complex (C5, C6, C7, C8 & C9), which gives rise to pore formation (imbalancing osmotic concentrations) and leads to lysis and cell death of microbe. Most cells of the innate immune system are generated in the bone marrow (neutrophil, monocyte, eosinophil, NK cell and basophil) and found circulating in the bloodstream.

Pattern Recognition Receptors

These attach to PAMPs and there are a few different types of PRRs with slightly different structures. **Toll-like receptors (TLRs)** recognise extracellular/endosomal PAMPs and typically trigger the synthesis and secretion of cytokines and chemokines. The ligation of **NLRs (NOD like receptors)** also results in production of chemokines and cytokines. **RIGs** are associated with anti-viral immunity



Cytokines

Cytokines are signalling proteins that are secreted and interact with and affect the behaviour of nearby cells bearing the appropriate cytokine receptor. The cytokines affect multiple functions and regulate innate immunity, adaptive immunity and haematopoiesis) They are many cytokines, such as *interleukins*, *interferons*, *colony stimulating factors*, *tumour necrosis factors*. Generally, the mode of action of cytokines is to reduce the likelihood of infection of neighbouring cells and to prevent and control the spread of infection.

Chemokines

A secreted protein that attracts cells bearing the appropriate receptor. This induces chemotaxis of nearby responsive cells and can recruit cells of the immune system to come to the infective site to combat the pathogen.

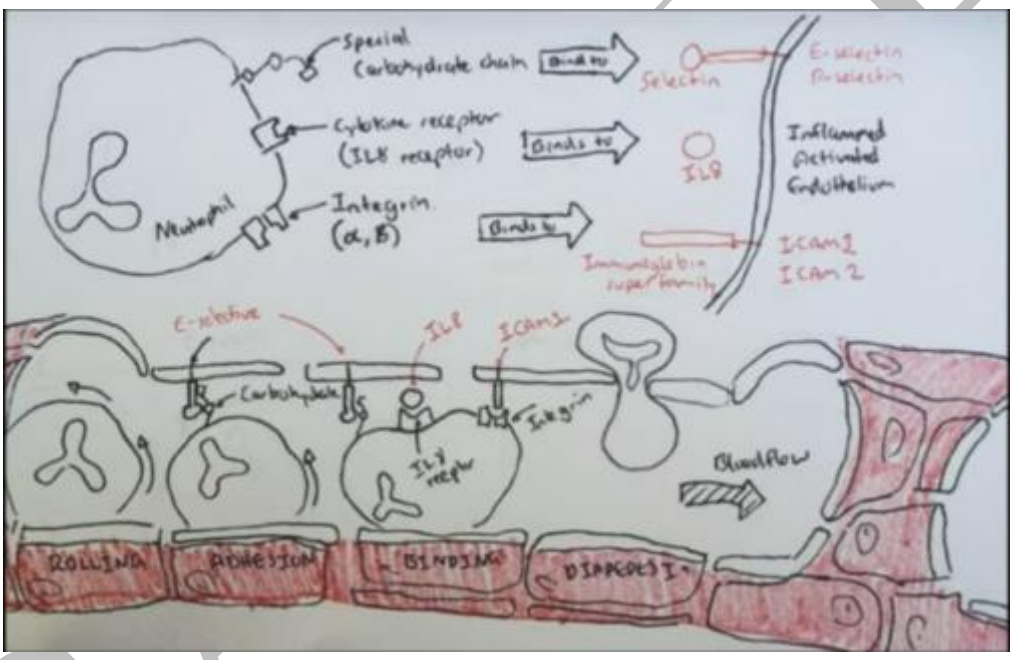
Phagocytes

Neutrophils originate from the bone marrow and are the most numerous, but short-lived, found in the circulation. **Phagocytes** such as macrophages and monocytes recognise PRRs and are long lived cells found in the circulation and tissues. They enter an infected site from the circulatory system where they bind to microbes, phagocytosing them and killing them. All cells of the innate immune system can produce signals (cytokines and chemokines)

which regulate the immune response. Of the various signals produced a few important signals to consider:

1. **Inflammatory Cytokines:** *Interleukin 1*, *Tumour Necrosis Factors* and *Interleukin 6* facilitates neutrophils to access the location of infection.
2. **Antiviral Cytokines:** *Interferon-alpha* are produced that specifically target viruses for destruction
3. **Stimulatory Cytokines:** *Interleukin-12* and *GM-CSF*
4. **Suppressive Cytokines:** *Interleukin-10* and *TGFBeta* ensures inflammation isn't sustained
5. **Chemokines:** *CXCL8 (Interleukin-8)* recruits neutrophils

Neutrophil Migration (Diapedesis)



Neutrophils roll in the bloodstream and bind to **E-selectin** on blood vessels that have become activated due to infection. Tissue macrophages that have lysed microbes produce cytokines and chemokines (*CXCL8 or IL-8)* that signal to neutrophils and tell them to go to the site of infection. Neutrophils have *CXCL8 Receptors (CXCLR)* and *LFA1*, which allow neutrophils to adhere to the blood vessel (by attachment to *ICAM-1* and *IL-8*). Once attached, the neutrophils undergo **diapedesis** and migrate through the blood vessel to the site of infection. Once at the site of infection, neutrophils are able to phagocytose the microbes, release soluble anti-microbials (degranulation) and generate neutrophil extracellular traps. The phagocytic action of neutrophils is largely dependant on whether the microbes are opsonised and whether they have antibodies attached. Phagocytes destroy microbes using low pH (pH 3.5-4.0), using antimicrobial peptides (defensins and cationic proteins), using enzymes such as lysozymes and acid hydrolases, lactoferrin (binds and inhibits growth of microorganism), nitric oxide and toxic oxygen intermediates.