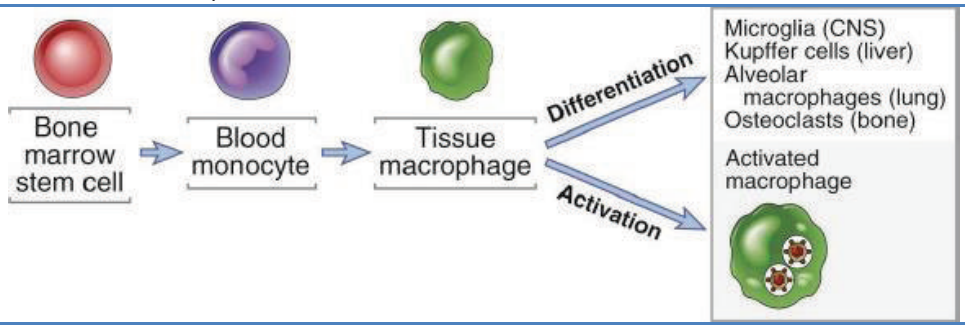
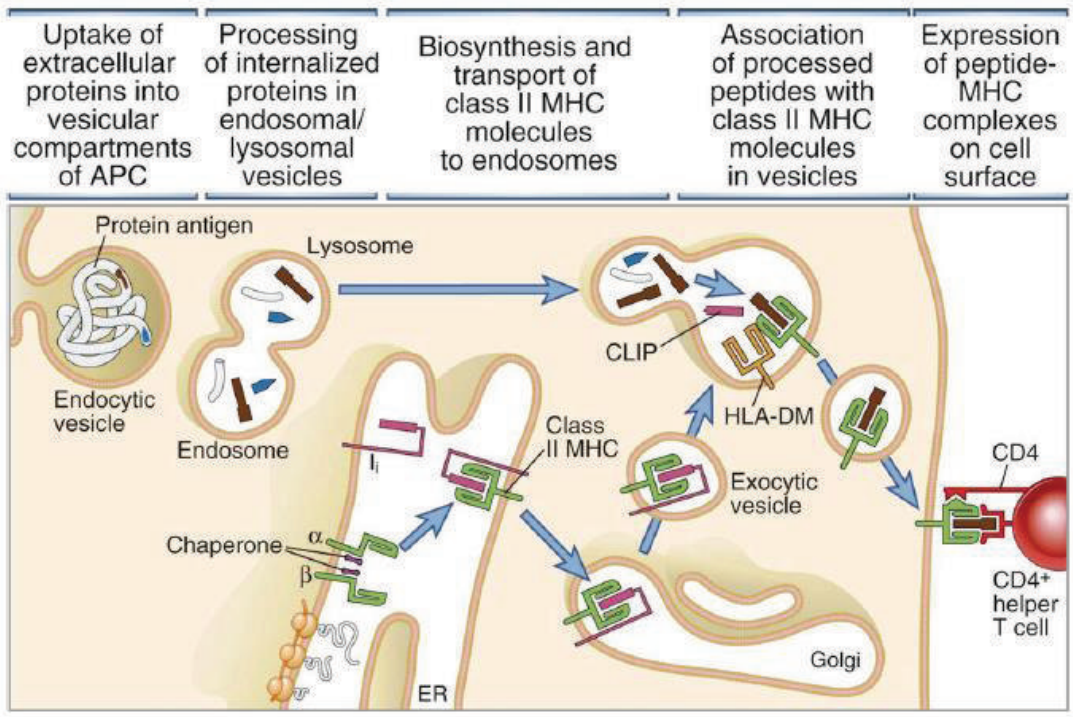
# IMMU2101 – INTRODUCTORY IMMUNOLOGY

**CONTENTS**

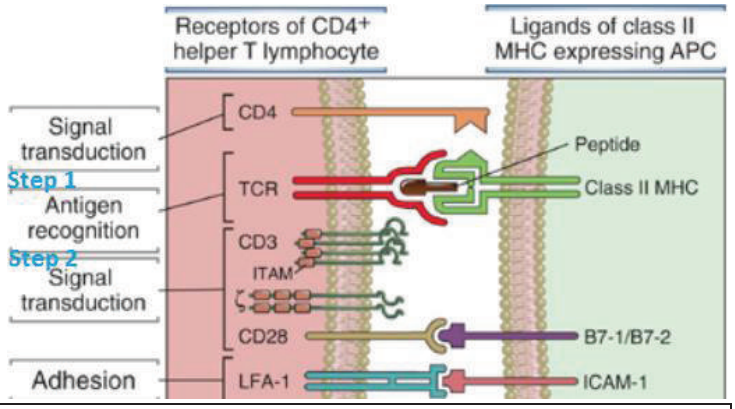
| Cells | Characteristics | Functions |
|---|---|---|
| **Mast cells** | • Enter tissues as immature mast cell progenitors where they mature<br>  ○ Progenitor not yet known<br>• Each type of mast cell has different functions depending on where they mature<br>• Mature mast cells are **resident** cells in peripheral tissues exposed to the environment (skin, lung, gut)<br>• Long lived | <u>Activation of immune response</u><br>• Secrete or **degranulate** to release **cytokines** (soluble mediators)<br>• Secrete **histamines** and other inflammatory mediators → can cause allergies<br>• Important antibacterial functions → recruitment of inflammatory cells to sites of infection (**danger signals**)<br><br><u>Regulate or suppress the immune response</u><br>• Contributing to tumour growth |
| **Neutrophil** | • Derived from common myeloid progenitors in bone marrow<br>• **Most abundant** leucocytes in blood<br>• Not normally found in tissues (only infiltrates inflamed peripheral sites)<br>• Very fast recruitment to peripheral sites (e.g. <u>swarms</u> and <u>homes</u> in on necrotic tissue or from a scratch)<br>• **Short-lived** (due to pro-inflammatory and antibacterial properties)<br>• Possesses a polymorphic nucleus | • Involved in inflammatory cascades<br>• Potent antibacterial functions<br>• Phagocytosis<br>• Secrete **cytokines** which promotes inflammation and phagocytosis<br>• Signal other cells<br>• Activation of adaptive immune system<br>• **Tumour-associated neutrophils** – may help tumours to grow – mechanism *not known* |
| **Monocytes Macrophages** | • Derived from common myeloid progenitors in bone marrow<br>• Monocytes in blood<br>• Macrophages may be activated in tissues, or be found as resident cells already in tissues (e.g. Kupffer cells in liver)<br>• **Long-lived** → may contribute to the symptoms of some disease (e.g. TB, chronic inflammation) | • Monocytes in blood migrate to inflamed tissues to become macrophages<br>• Potent antibacterial functions<br>• Secrete cytokines<br>• Recent evidence shows some macrophages may help tumours evade the immune system and grow<br>• Communicate with lymphocytes |
| |  | |
| **B lymphocytes** | • "B" because first discovered in "bursar of Fabricius"<br>• Derived from common lymphoid progenitors in bone marrow<br>• Undergo maturation in bone marrow | • Form part of **humoral immune response**<br>• Secrete **antibodies** |
| **T lymphocytes** | • Derived from common lymphoid progenitors in bone marrow<br>• "T" because they migrate to thymus where they mature<br>• Express only one type of antigen-specific receptor on their surface | • Form part of **cell-mediated immune (CMI) response** |

**- MHC class II processing pathway (The *extracellular* pathway)**

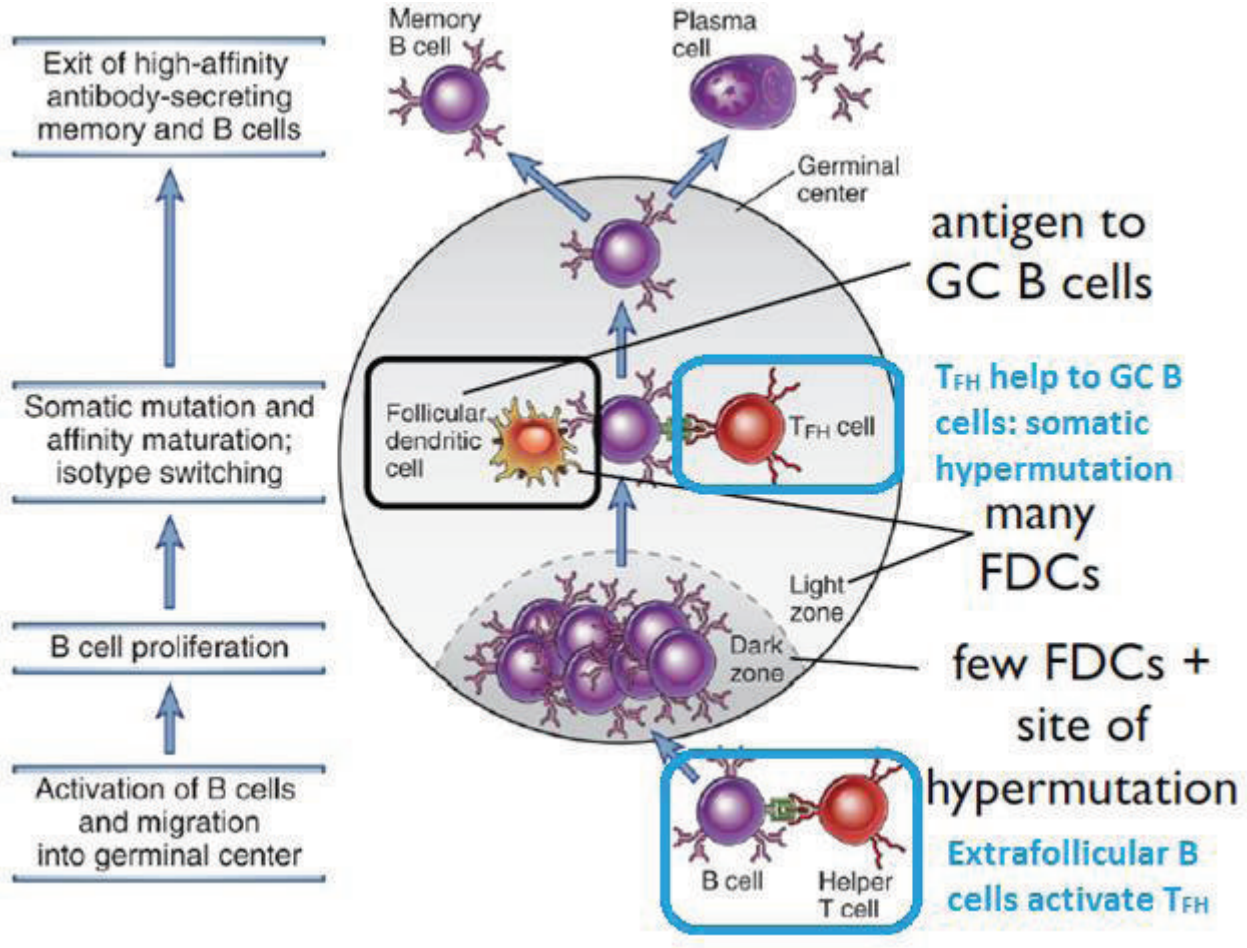



1. Extracellular antigens (bacteria, parasites, fungi) are recognised by pattern recognition receptors (macrophages and dendritic cells), or by B cell receptors (B cells), and are internalised by phagocytosis into phagosomes/endosomes
2. The endosome fuses with a lysosome to form a phagolysosome, which degrades proteins into peptides using proteolytic enzymes
3. At the same time, α and β chains of MHC II molecules are synthesised in the ER
    a. **Invariant chain ($I_i$)** with **CLIP** occupies the peptide binding cleft in newly synthesised class II molecules
    b. Invariant chain contains a sequence called the **class II invariant chain peptide (CLIP)**, which keeps the MHC molecule (with its open conformation) **stable**, while **blocking other peptides from binding** to the newly synthesised MHC molecule
4. Class II molecules are transported to the Golgi and then an exocytic vesicle, which then fuses with the phagolysosome, bringing MHC II molecules and degraded proteins together
5. **Enzymes** in the late endosomes/lysosomes **degrade the invariant chain**, leaving CLIP
6. **DM** (a MHC-like protein in the late endosome) exchanges CLIP for higher-affinity peptides in the endosome – involved in peptide loading of class II molecules
    a. Facilitates removal and **replacement of CLIP with antigen**
    b. Enzymes break down CLIP
7. Presentation to CD4+ MHC class II-restricted helper T cells

**To be able to recall the name and function of the key molecules involved in each of the 4 steps that lead to T cell activation:**
**Step 1: Antigen Recognition**
**Step 2: Co-receptors and adhesion molecules**
**Step 3: TCR complex Signalling**
**Step 4: Co-stimulation**

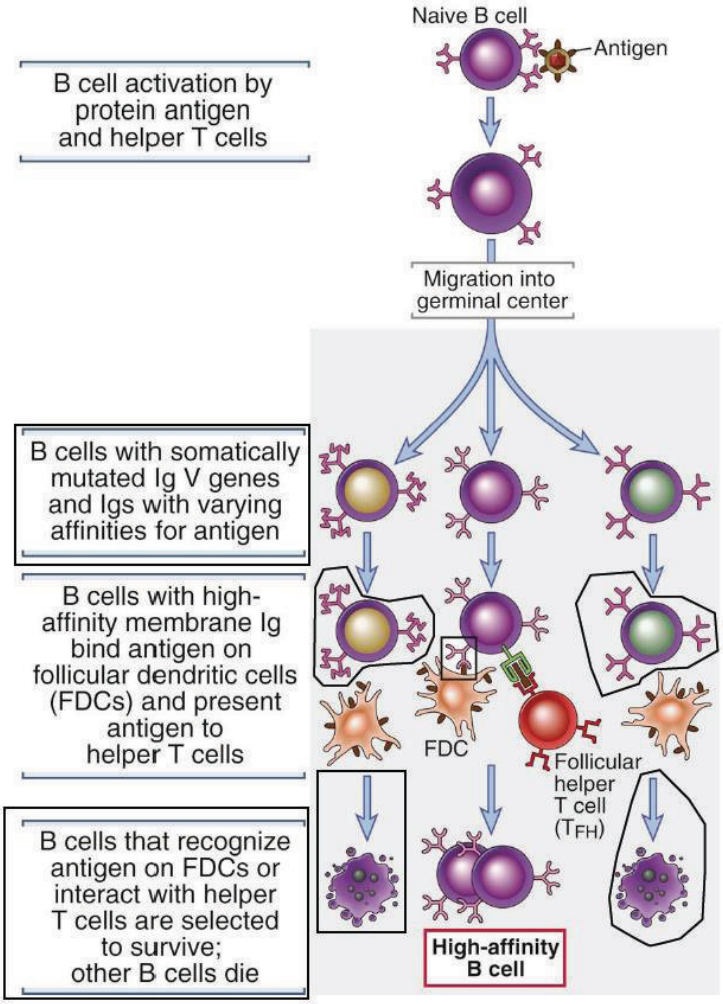



| | |
|---|---|
| Step 1 | Recognition of peptide + MHC<br>• TCR recognises peptide-MHC → antigen specificity<br>• TCR recognition is **MHC-restricted**<br>• TCR binding to peptide-MHC is *low affinity*<br>• Two or more TCR must be engaged, for several minutes to commence activation<br>• The number of MHC-TCR that needs to be engage varies depending on the peptide. It was previously estimated to be 100-400/cell but is now estimated to be fewer than 10 |
| Step 2a | Co-receptors<br>• **CD4 co-receptor** on T helper cells binds conserved **β2 chain** on MHC class II<br>• **CD8 co-receptor** on cytotoxic T cells binds conserved **α3 chain** on MHC class I<br>• **Stabilises** ***low affinity binding*** of TCR to peptide-MHC<br>• Ensures appropriate T cell type is activated<br>• Activation via signalling through TCR complex (CD3 molecules and zeta chain provide activation signal transduction via ITAM sequences) |
| Step 2b | Adhesion molecules<br>• **LFA-1** (leukocyte function-associated antigen-1, CD11a) is an integrin molecule expressed in the T cell membrane<br>• LFA-1 binds **ICAM-1** (intercellular adhesion molecule-1, CD54) adhesion molecules on APC<br>• Adhesion molecules ↑↑↑ **binding affinity** of TCR to peptide-MHC complex |
| Step 3 | TCR complex signalling<br>• CD3 and zeta chains trigger signal transduction via ITAM motifs leading to T cell activation<br>• Note that TCR (which provides antigen specificity) varies between T cell clones, but the CD3 complex (which provides signal transduction) is common to all T cells<br>• Ultimately leads to the activation of transcription factors<br>  ○ **NFκB** (nuclear factor kappa-light-chain-enhancer of activated B cells)<br>  ○ **AP-1** (activator protein 1)<br>  ○ **NFAT** (nuclear factor of activated T-cells)<br>• Transcription factors translocate to the nucleus of T cells to affect transcription of genes involved in T cell proliferation and differentiation (e.g. **IL-2** expression – the promoter for the IL-2 gene contains multiple regulatory elements that must be bound by these transcription factors to initiate IL-2 transcription; IL-2 is essential for promoting T cell proliferation and differentiation into effector T cells) |
| Step 4 | Co-stimulation<br>• T cells require additional signals to achieve full activation<br>• **Two signal hypothesis**<br>  ○ Signal 1 = antigen recognition (TCR + MHC + peptide)<br>  ○ Signal 2 = co-stimulatory signal from APC (co-stimulatory molecules – CD80 (B7-1) and CD86 (B7-2), CD40, cytokines, or a combination of both)<br>  ○ Both signals are required for T cell activation<br>  ○ Signal 1 alone leads to **T cell anergy** (long-lived unresponsiveness, never going to be able to be activated again; also no survival signals– **peripheral tolerance**)<br>• **B7-1** (CD80) and **B7-2** (CD86) expressed on APC (*activated* DCs)<br>• **Expression is increased when APC encounters a microbial antigen, adjuvant, or in inflammation**<br>• **B7 binds to CD28** (expressed on all T cells) |



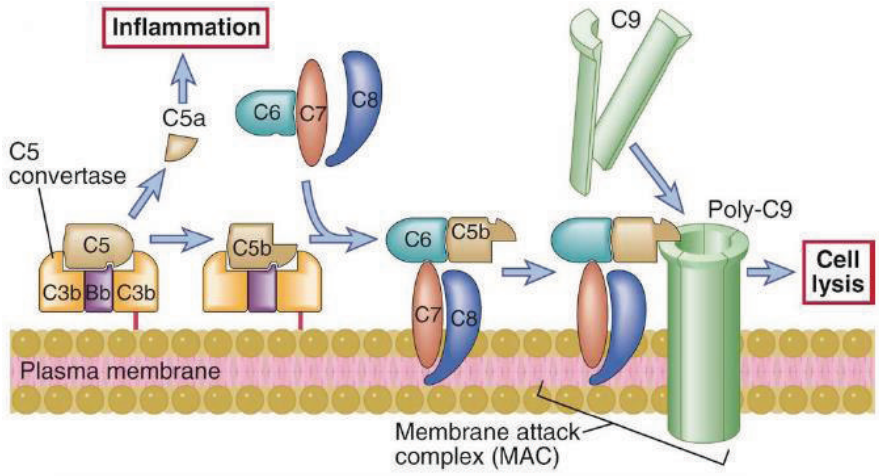

- **GC B cells** are undergoing rapid mutation and affinity maturation
- **Dark zone** – lots of B cells
- **Light zone** – less B cells, but there are FDCs
- **Follicular dendritic cells (FDC)** are found only in lymphoid follicles. FDCs provide a critical source of antigen for GC B cells. They are involved in **displaying antigen-bound antibody complexes for the selection of GC B cells**
- Competition among B cells: FDCs will **provide survival signals to the B cells** that **out compete** the others for binding to the antigen being selected. **B cells that receive no signal die**
- At the same time, IgM is getting rid of the antigens, so less FDCs are presenting antigens. Hence B cells must also compete with less of the "resource"

- 2-7 days after antigen exposure, some activated Th cells that migrate to meet activated B cells at the edge of the follicles will be triggered by these antigen-presenting B cells to differentiate into **follicular helper T cells ($T_{FH}$ cells)**
- $T_{FH}$ tells B cells to go back to follicular zone to **undergo further rounds of proliferation** (4-5 times)



**Key points on complement activation**

1. **Opsonisation of pathogens** (early steps)
    - Microbes acquire a coat of covalently attached C3b (acts as an opsonin)
    - These microbes are phagocytosed by cells recognising C3b via the type 1 and type 2 **complement receptors** (**CR1**/CD35 and CR2/CD21)
    - Follicular dendritic cells (FDC) thought to express complement receptors to capture antigens for display to B cells in germinal centres
2. **Killing of pathogens** (late steps)
    - Binding of C5 to C5 convertase results in the proteolysis of C5, generating C5b and C5a
    - The remaining components, C6, C7, C8, and C9, bind sequentially
    - The final protein in the pathway, **C9**, **polymerises** to form a **pore** in the cell membrane (**membrane attack complex**) through which water and ions enter the cell




3. **Recruitment of inflammatory and immunocompetent cells**
    - C3a and C5a are **anaphylatoxins** – potent stimulators of inflammation
    - They are bi-products of the complement cascade
    - Some cells express surface **receptors for C3a and C5a**
        - E.g. **mast cells** – leads to **degranulation**; stimulates release of **chemoattractants** and **vasodilators (IL-1, TNFα)**
        - Leads to **upregulation of adhesion molecules on endothelial cells** (chemoattractant) to allow T cell rolling
    - C5a is a potent **chemoattractant of neutrophils and phagocytes** to the inflamed tissue