Cooperation In Immune Responses

Antigen processing – how peptides get into MHC

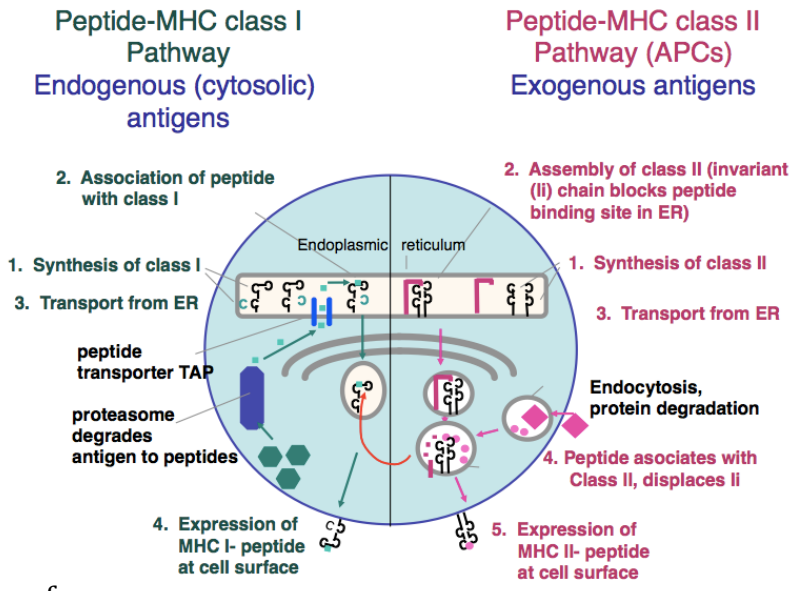
- Antigen processing involves the intracellular proteolytic generation of MHC binding proteins
- Protein antigens may be processed (degraded into peptides) either in endosomes or in the cytosol
- *Endosomal processing* results in presentation on Class II MHC molecules – exogenous antigens
- *Cytosolic processing* results in presentation on Class I MHC molecules – endogenous antigens

Endogenous pathway

- Cytosolic proteins degraded into peptides and are transported into the ER and loaded with MHC class I molecules and exported through golgi and then to cell surface

Exogenous pathway

- Endocytosed proteins are degraded in an endosome
- Class II MHC molecules are bound to invariant chain to ensure it doesn't bind to cytosolic proteins
- Class II MHC is transported and merges with endosome and MHC II is displayed on cell surface

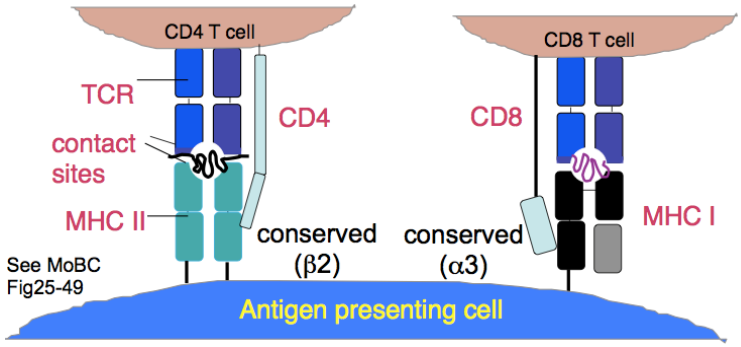


T Lymphocytes – 2 major groups

Tc lymphocytes (CD8+) (cytotoxic T lymphocytes)	Th lymphocytes (CD4+) (helper T lymphocytes)
Bind and kill: - Cells infected with intracellular pathogens - Neoplastic cells	Help B cells produce Ab Help activate macrophages Aid CTL Regulate immune responses
Peptides presented in MHC class I (from endogenous antigens)	Peptides presented in MHC class II(from 'exogenous' antigens)

TCR, MHC and co-receptors

- T cell activation occurs when their TCR binds peptide antigens displayed on MHC molecules
- CD4 T cell uses TCR to interact with MHC



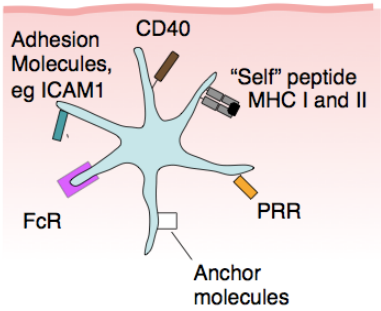
II and peptide, and uses CD4 as co-receptor which binds to conserved β2 region
- CD8 T cell uses TCR to interact with MHC I and peptide, and uses CD8 as a co-receptor which binds to α3 conserved region
- Antigen presenting cells have both MHC I and MHC II on cell surface

Three signals for effective activation of naïve T cells

Antigen presenting cell (dendritic cells are the best) must:
- Acquire and process antigen in compartments which gain access to MHC Class I and Class II pathways
- Interact with naïve T cells to induce effector T cells
  - Locate appropriate T cells in the secondary lymphoid tissue
  - Adhere to T cells
  - Present MHC associated peptides to T cells – Signal 1 - and provides 2 extra signals
  - Provide co-stimulation for T cell expansion – Signal 2
  - Induce T cell differentiation – Signal 3

Antigen presenting cells
- Include dendritic cells (the best) and macrophages
- Found as networks in most tissues allowing them access to invading pathogens
- APCs are specialised to take up antigens and display the peptides on their MHC molecules
- APCs become activated by binding PAMPs since they have pattern recognition receptors
- When activated, APCs migrate from tissues to local lymph nodes to present the antigen to T cells

Dendritic cells in non-inflamed tissues are highly efficient at capturing antigen but very poor as stimulators of naïve T cells
- Active in sampling the surrounding environment and take up molecules via macro-pinocytosis, mannose receptor and FcR
- Migration to the draining lymph nodes is restricted due to absence of PAMPs
- Low level of MHC II on plasma membrane
- Secrete TGF-beta – immunosuppressive cytokine



Dendritic cell maturation
- Essential for activation of naïve T cells
- Initiated by binding of pathogens
- Signalling by PRR (on dendritic cell) following ligation with molecular patterns (PAMPs) on pathogens
- Licensing of dendritic cell

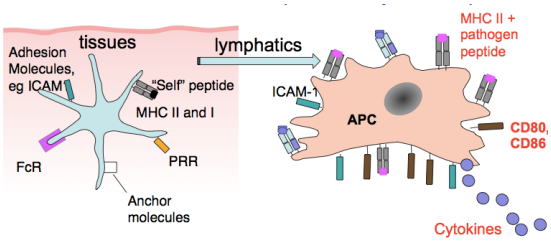
Binding PAMPs to dendritic cell PRR induces:
- Migration of dendritic cells to lymphoid tissue via the lymphatics
- Increased antigen processing
- Increased surface expression of MHC I and II
- Increased surface xpression of adhesion molecules

- Expression of co- stimulatory molecules such as CD80 and CD86 – an up regulation
- Secretion of cytokines e.g. TGFβ, IL-6 and IL-12
- Maturing dendritic cells lose capacity to capture antigen and becomes a presenting cell

Dendritic cell maturation events (induced by PAMPs)

<u>Licenced dendritic cells:</u>

- Display pathogen peptides on MHC – signal 1
- Up regulate expression of adhesion (e.g. ICAM-1) molecules
- Express co-stimulatory molecules (e.g. CD80, CD86) – signal 2
- Secrete selected cytokines – signal 3

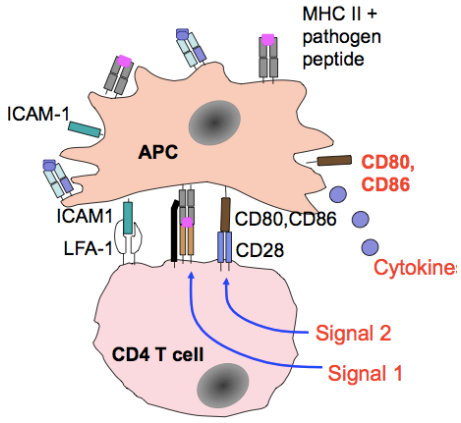


Once in the lymphoid tissue adhesion of T cells and APC is essential

- Naïve T cells must adhere to APCs – binding involves specific receptor ligand interactions e.g. ICAM-1 on APC and LFA-1 on T cells
- MHC peptide complexes – TCR interaction results from binding

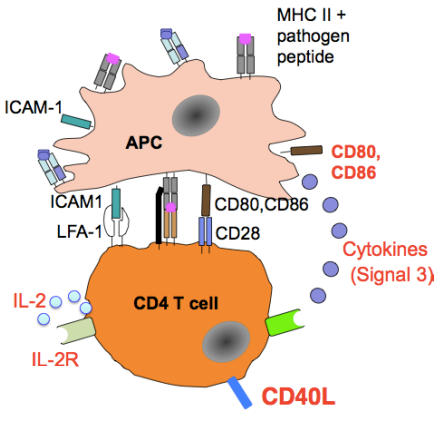
Induction of CD80 and CD86 on the dendritic cell now enables activation of antigen specific CD4 T cells

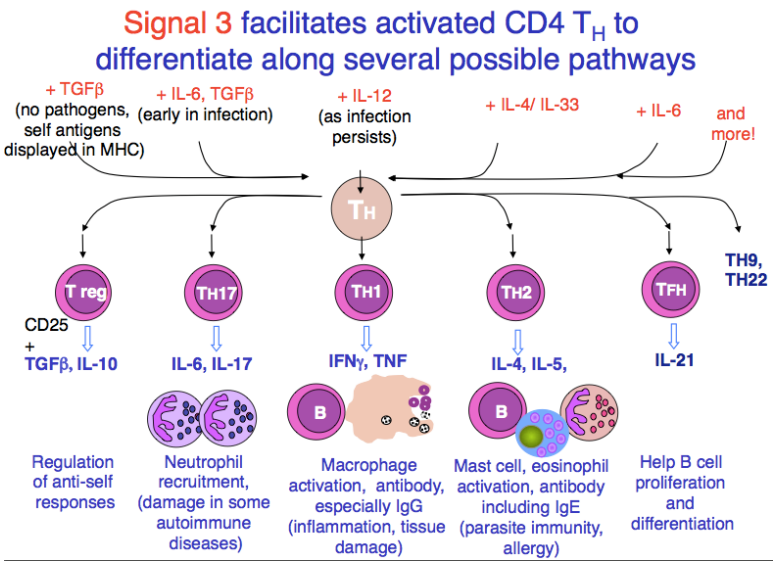
- Binding the TCR to MHC-peptide (signal 1)
- Ligation of CD28 on the T cell by CD80, CD86 on the mature dendritic cell (signal 2) provides signals to induce activation and proliferation of the naïve antigen specific T cell



On receiving signal 1 and 2, the activated CD4 T cell

- Now expresses CD40L
- Expresses IL-2 receptor, secretes IL-2 and now proliferates
- With signal 3, differentiates to perform its effector function (help neutrophils, macrophages, B cells and CD8 T cells)





- TFH = T follicular helper cell
- IFN = interferon
- TNF = tumour necrosis factor

The activation of CD4+ T helper cells is the critical step for the activation of the adaptive immune system

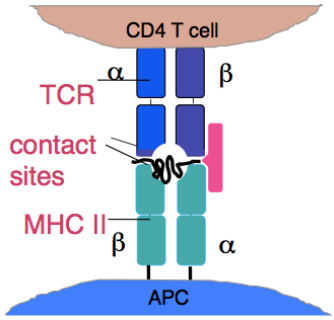
- Help B cells to produce antibodies in lymph nodes
- Aid production of cytotoxic T cells in lymph nodes
- Help the activation of the macrophages in tissues
- Aid neutrophil recruitment in tissues

T helper cells are activated in only restricted settings

- By antigen presenting cells expressing Class I MHC
- When signals are received from the innate immune system (PAMPs interact with PRR) to provide co-stimulation – dendritic cells need to be licenced and activated

Superantigens – Don't require processing before activating T cells

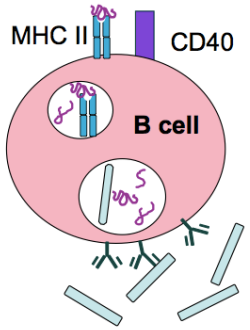
- Don't bind in MHC II binding groove, can link conserved regions of TCR and MHC II with particular groups of Vβ chains of many TCR
- Bypass recognition of peptide binding groove and ligate TCR directly with MHC II
- 2-20% of all T cells may be activated – normally peptide antigen might activate $1/10^5$ T cells
- Stimulation of a large amount of T cells releases lots of cytokines such as IL-1 and IL-2 as well as TNF which leads to significant pathology e.g. toxins from staphylococcus infection



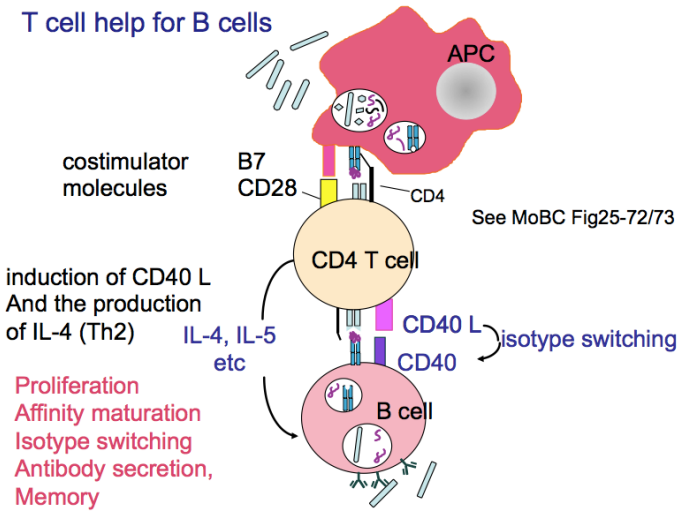
T cell help for B cells

Activated B cells act as APC

- Antigens that bind to BCR are internalised by receptor-mediated endocytosis. Antigen peptides are displayed on the B cell Class II MHC
- B cell can now present the peptide antigen to T cells allowing T cells which have been previously activated by dendritic cells to provide help for B cells
- Exogenous pathway – break down protein into peptides and loaded onto MHC II

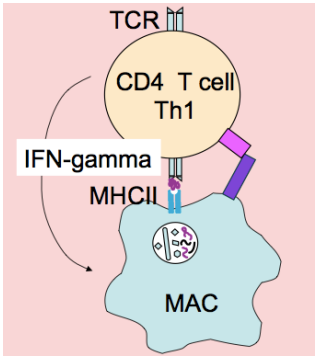


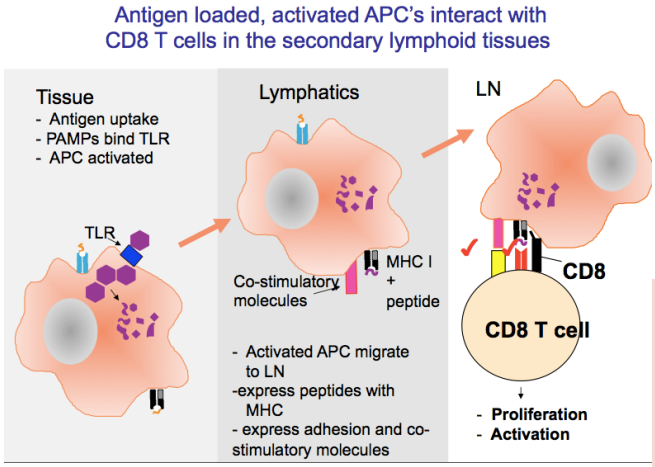
- T cell interaction occurs in the lymph nodes
- Uses the same TCR t see antigen from B cell as APC
- Interacts with B cell to signal it to switch isotypes
- B cell will eventually produce memory cells for recognition so that it can produce antibodies of higher affinity and faster rate when antigen next encountered



T cell help for macrophages
Activated, antigen specific CD4 cells migrate to the infected site and activate tissue macrophages

- CD4 cells leave lymph nodes and enter circulation
- Activated T cells induce macrophage activation including increased killing of phagocytosed organisms and release of a range of cytokines

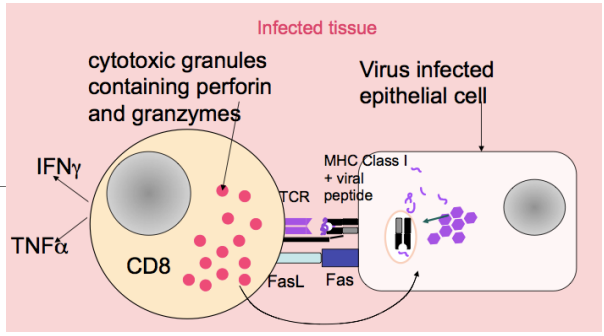




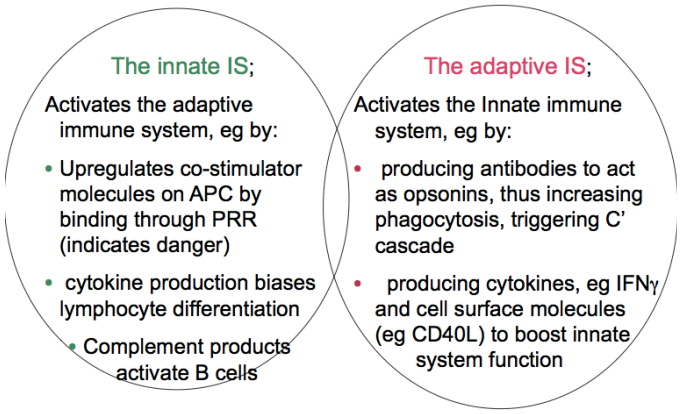
- MHC I enables them to present peptides to CD8T cells

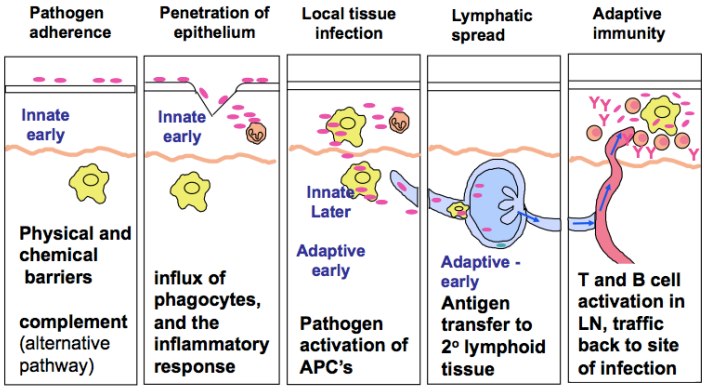
Activated, virus specific CD8 cells migrate to the infected site and can now kill virus infected target cells

- Cytotoxic T cells trigger death by creating holes in the target membrane (perforin) and inducing apoptosis (granzyme, Fas)



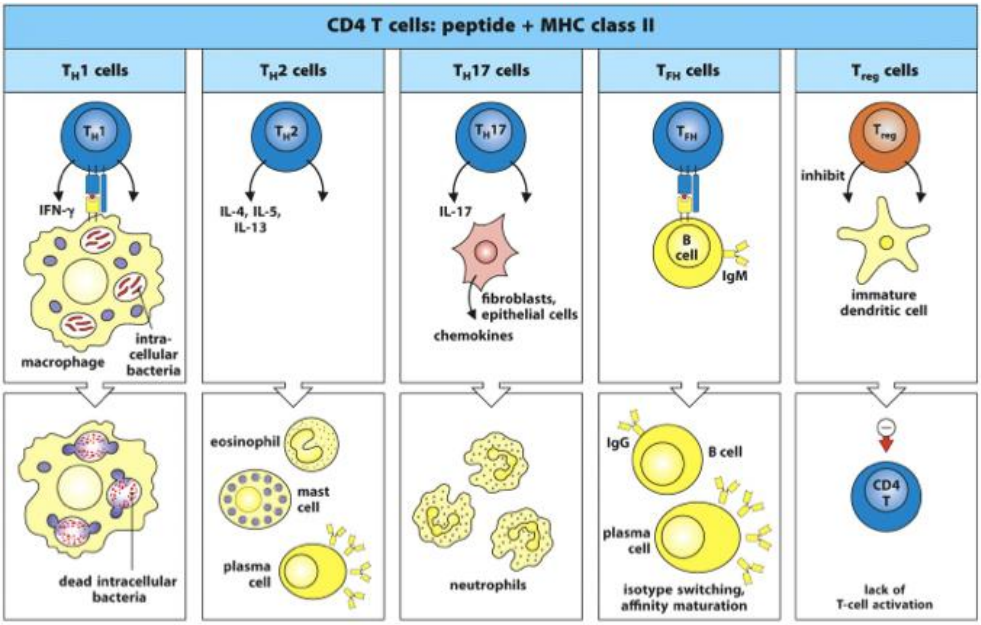
The Innate and the Adaptive Immune System interact

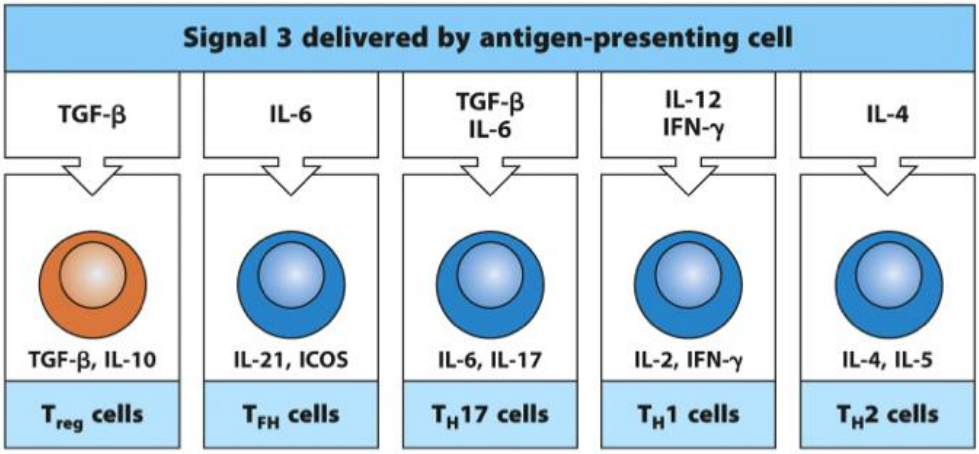




Summary of infection and the immune response

- Body tries to prevent adherence
- Macrophage and neutrophil activation
- Recruitment of more cells and pathogens activate APC
- Movement from tissues to draining lymph nodes to induce adaptive immune response
- CD4 or CTL activation and induction of antibody production





	CD8 cytotoxic T cells	CD4 T_H1 cells	CD4 T_H2 cells	CD4 T_H17 cells	T_{FH} cells	CD4 regulatory T cells (various types)
Types of effector T cell						
Main functions in adaptive immune response	Kill virus-infected cells	Activate infected macrophages Provide help to B cells for antibody production	Provide help to B cells for antibody production, especially switching to IgE	Enhance neutrophil response Promote barrier integrity (skin, intestine)	B-cell help Isotype switching Antibody production	Suppress T-cell responses
Pathogens targeted	Viruses (e.g. influenza, rabies, vaccinia) Some intracellular bacteria	Microbes that persist in macrophage vesicles (e.g. mycobacteria, *Listeria*, *Leishmania donovani*, *Pneumocystis carinii*) Extracellular bacteria	Helminth parasites	*Klebsiella pneumoniae* Fungi (*Candida albicans*)	All types	