Immune tolerance

Course	Immunology
Date	@April 11, 2024
Status	Completed
Reading	☐

Self versus non-self discrimination

- Immune system must fight infection BUT tolerate self
- The immune system has evolved to recognise and dispose of foreign pathogens.
  - Fignt infection: Protection against viruses, bacteria, fungi, parasites
  - Autoimmunity: Destruction
    - E.g. rheumatoid arthritis, diabetes, scleroderma, multiple sclerosis, uveitis
- Diverse repertoire of T cells
  - Allows recognition of multiple antigens but means very few lymphocytes will recognise any given antigen

> 💡 Higher risk of self-reactivity comes with greater diversity

But how does the immune system distinguish its own cells and tissues (*self*) from the invaders (*non-self*)?

In fact there are several answers to this question.

The innate immune system

- The ultimate disposal mechanism for microorganisms is the **phagocyte**.
- Microbes have particular structures, pathogen-associated molecular patterns (**PAMPs**) which are recognised by pattern recognition receptors (**PRR**) on phagocytic cells.
- Our own healthy cells are left alone because they do not express PAMPs.

- However, as cells such as erythrocytes age there is gradual damage to carbohydrates on their surface which allows the ageing cell to be recognised and phagocytosed.
- Apoptotic cells are also disposed of due to the recognition of loss of membrane symmetry and subsequent engulfment by the phagocytes.
- The complement system is not normally triggered by our own cells because of complement inhibitory molecules on their surface.

The adaptive immune system

Each T and B lymphocyte carries surface receptors which are specific for a given antigen by means of which a huge range of foreign antigens are recognised.

- These antigen-specific receptors could potentially also recognise self-antigens since pathogens are made up of many of the carbohydrates, proteins and lipids which constitute our own tissues.
    - Same carbohydrates, proteins, and lipids as the host
- Nevertheless, in most cases, lymphocytes are fortunately unable to respond to self-antigens in a harmful way and we are said to be *tolerant* of our own antigens.

> 💡 Immune tolerance - prevents undesirable immune responses (e.g. self antigens, food)

There are two levels at which this tolerance occurs: **central** and **peripheral**.

Central tolerance

Central tolerance results from the elimination of self-reactive cells **during lymphocyte development in central (primary) lymphoid organs**

- B cells - Bone marrow
- T cells - thymus

B cell selection

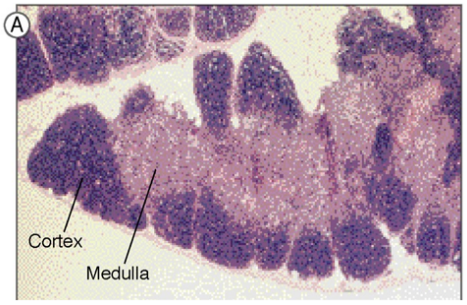
- Survival requires generation of a **functional** antigen receptor
- If an immature B cell binds a self-antigen in bone marrow, it undergoes:

- Receptor editing (change specificity)
- Deletion (negative selection)

T cell selection - thymic selection

Most of our knowledge about central tolerance has come from the study of T cell development.

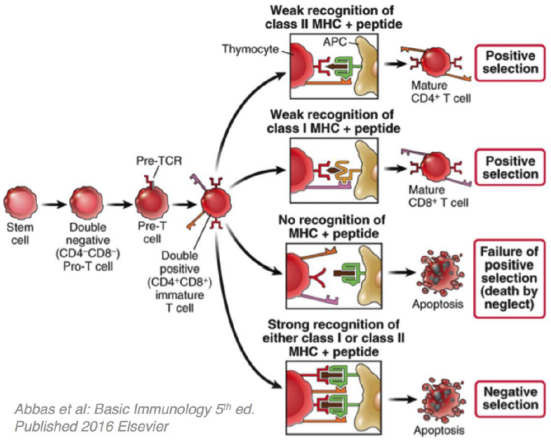
- T cells are educated in the thymus
  - Thymus: bi-lobed organ with outer cortex and inner medulla
  - T cell maturation starts from the outside (cortex) and goes inwards (medulla)



- T cell receptor (TCR) recognizes processed antigens bound to cell surface MHC molecules.
- Part of the **TCR** recognises the **foreign peptide**, and part of it recognises the **self MHC** molecule.
- The random nature of TCR gene rearrangements means that only a minority of T cells are capable of performing this task.

> 💡 T cells must recognise self MHC to be useful but not self-antigen

Many of the immature CD4 and CD8 double-positive T cells are useless because their TCRs do not recognise self MHC molecules at all → These T cells eventually undergo apoptosis.



- T cell development starts from stem cell developing into double negative pro-T cell (CD4- CD8-)
    - Note that there is no TCR at this stage, not really T cells
- Pre-TCR develops on Pre-T cells
- Double positive (CD4+ CD8+) immature T cell
    - Maturation of T cells is defined by expression of CD4 and CD8 co-receptors
    - Start to express heterodimeric TCR and bind to some stromal cells in the thymus (thymic epithelial cells) - act as APCs in the context of thymus

Cells whose **TCRs** have various affinities for binding **self MHC** molecules (usually containing a self peptide) are first **positively selected** on **thymic epithelial cells** in the **thymic cortex**.

- If bind to MHC II, requiring a CD4, it becomes a mature CD4+ T cells and stop expressing CD8, vice versa: MHC I - CD8
- If no useful interaction is made with the MHC and peptides, the double positive T cell undergo apoptosis, failure of positive selection (death by neglect)
    - Positive signals - survival signals

However, many of these cells are potentially harmful because their TCRs have a high affinity for a complex of **self peptide** and a self MHC molecule (or even an MHC molecule alone).

- These **autoimmune T cells** are eliminated by the induction of **apoptosis** when they interact with **dendritic cells** and **macrophages** in the **thymic**

medulla (**negative selection**).

How does all possible self-peptide expressed in the thymus?

- AIRE: Autoimmune regulator
  - Transcription factor in the thymus that switches on expression of tissue-restricted antigens.
  - Peptides that are associated with particular peripheral tissues. E.g. insulin
- A similar process of negative selection, but not involving MHC, is thought to occur in the **bone marrow** during the development of **B cells**.

> 💡 The AIRE transcription factor causes thymic expression of tissue-specific self antigen. AIRE deficient mutation causes autoimmune disease.

Negative selection of T cells in the thymus leaves T cells with only a weak affinity for self MHC molecules.

These cells form the pool of T lymphocytes that are exported from the thymus as **single-positive (CD4 or CD8) cells**.

In the periphery, they have the potential to recognise a complex of **foreign peptide plus self MHC** molecules and to become activated if the affinity of the interaction exceeds a certain threshold.

Peripheral tolerance

Peripheral tolerance prevents harm from any self-reactive cells that manage to **escape deletion in the primary lymphoid organs**.

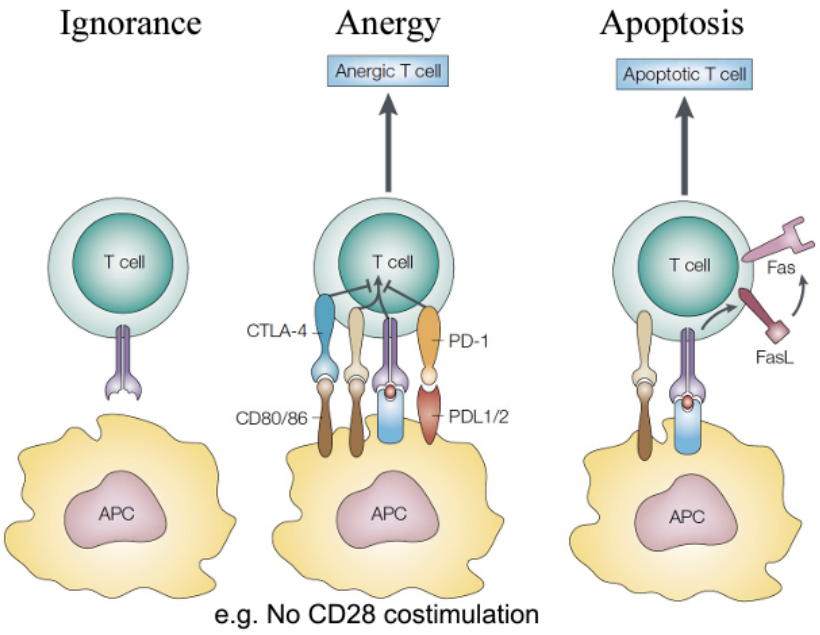
- Occurs outside of the thymus or bone marrow
- Lymph nodes, spleen, cutaneous lymphoid tissues

Such escape can occur because, for example, not all self-antigens are present in the primary lymphoid organs.

Two mechanisms

- Cell intrinsic mechanisms
- Cell-extrinsic mechanisms (regulatory T cells)

Cell-intrinsic mechanisms of peripheral tolerance

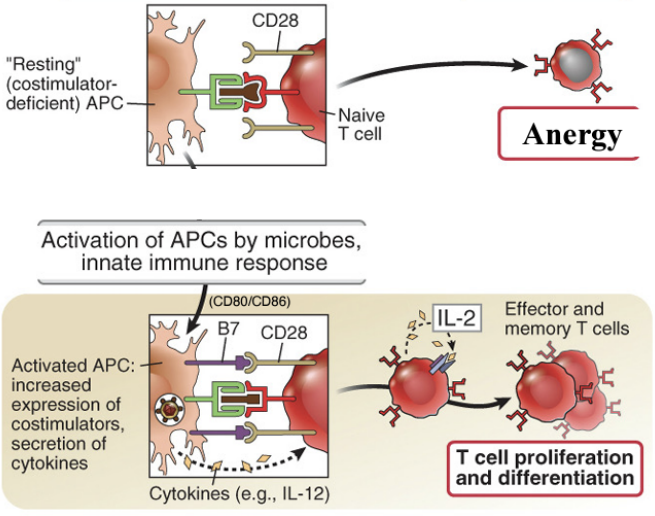


Ignorance

T cell never encounter its peptide.

Anergy

- Note that anergy is not a permanent state but quite long-lasting state



Lymphocytes in the periphery are normally kept in an unresponsive state through **clonal anergy** which is the result of the cells **not receiving** the **pathogen-triggered co-stimulatory signals** necessary for activation of the cell.

- Only signal 1 (TCR - peptide), no costimulatory signals (CD80/86 on APC to CD28 on T cell)
- Negative signals outweigh the positive signals
  - CTLA-4 binds to CD80/86
    - Remove co-stimulation or prevents full activation
  - PD-1 on T cells bind to PDL1/2
    - Prevent phosphorylation that would normally happen in a positive signalling
- Infection might contribute to autoimmune disease by breaking the anergy and inflammation may allow self-reactive T cells to become activated

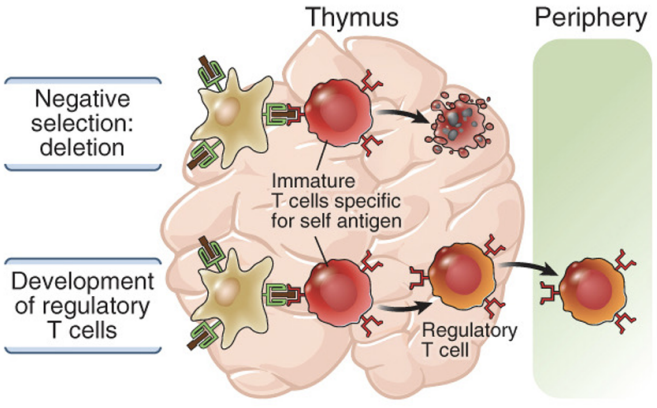
Apoptosis

- During the process of T cell activation the apoptosis process might be activated involving Fas and FasL
  - Evidenced by people with mutations in Fas and FasL suffer from autoimmune diseases

Cell extrinsic tolerance: Regulatory T cells

Regulatory T cells (1-2% of the CD4 population)

- Tregs develop in the thymus, subpopulation of CD4 cells
  - Some can develop in the periphery from naive T cells (develop into a Treg instead of Th1, Th2, or Th17)
  - If T cells bind strongly but not strongly enough to get deleted then develop into Treg (fall into a special intermediate state)



- Express CD25 (IL-2 receptor alpha)
    - IL-2 receptors that allow high affinity binding to IL2, one of the way to suppress other T cells
    - Take up IL-2 more effectively than other T cells
- Express the transcription factor Foxp3
    - Transcription factors that drive the development of Tregs phenotype
- Express the regulatory protein CTLA-4
    - Conventional T cells don't express CTLA-4 unless they are activated, but Tregs do

Experiment looking into Tregs importance

Our own T cells are dangerous unless kept in check by CD25+ Tregs

- T cells recognising self peptide are not rare (5-10% periphery)

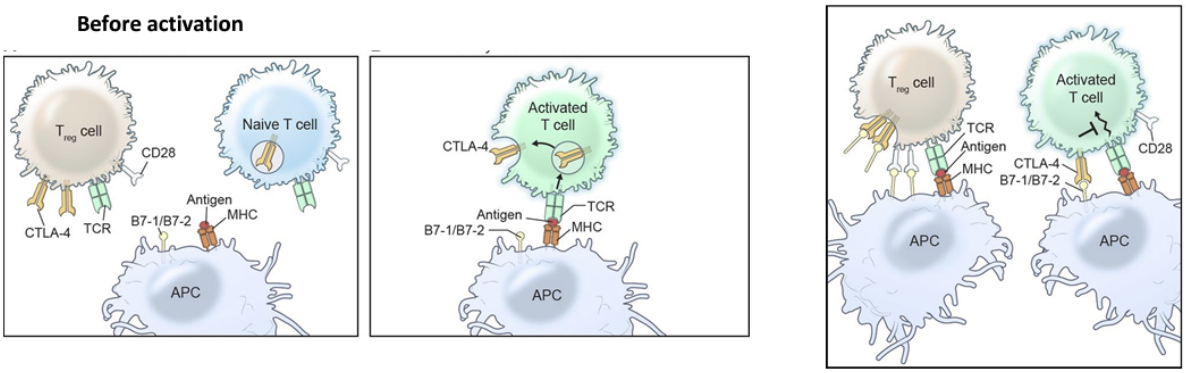
Sakaguchi (1996)

- Mice depleted thymus - no T cell production
- If given total T cells (including Tregs, the mice are healthy)
- If given CD25 depleted T cells (no Tregs but other T cells) - autoimmune
    - About 5-10% of peripheral T cells are autoimmune

Multiple mechanisms of action

- Secrete inhibitory cytokines (e.g. IL-10, TGFbeta)
- Use the regulatory protein CTLA-4 to modify APC (block or remove co-stimulatory ligands)
    - Homologue of CD28, binds to CD80/86
    - Competition, CTLA-4 has higher affinity
    - Temporarily remove CD80/86 so that APC cannot activate T cells
- Bind and consume IL-2 (a growth factor for T cells) - CD25
    - Other T cells don't have IL-2 thus cannot proliferate
- Etc.

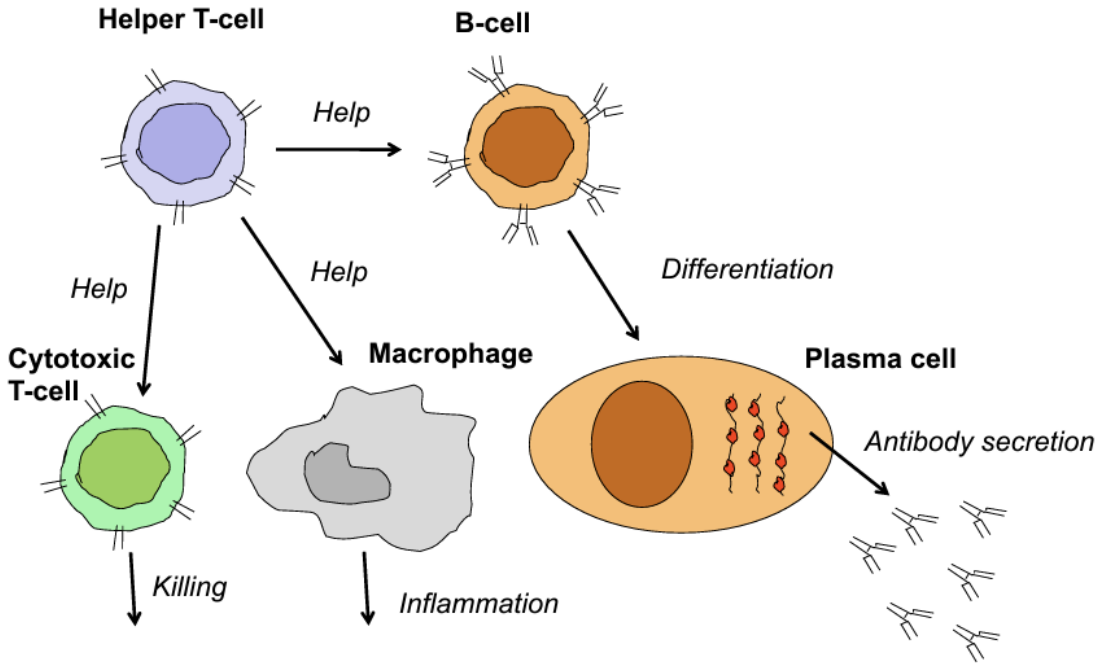
Mechanisms of CTLA-4 function



- CTLA-4 binds to B7-1/B7-2 (CD80/86), the same ligands as CD28, with much higher affinity, thus out-competing CD28
    - Conventional T cells: CTLA-4 only express after activation (also limit the amount of T cell proliferation)
    - Treg: CTLA-4 always present
- Cells expressing CTLA-4 (such as Tregs) can remove B7 ligands on APCs thus preventing CD28 co-stimulation
    - Temporal effects as the APC can later express CD80/86

Why is controlling T cells so important?

- Helper T cells control many other cell types
    - Self-reactive B cells will be controlled if self-reactive T cells are not activated



Breakdown in tolerance to self-antigens can lead to **autoimmune disease**.

Tolerence - Summary

- Essential to stop your immune system killing you
- Both T and B cells can become tolerised
- Central tolerance
  - Bone marrow (B cells), Thymus (T cells)
- Peripheral tolerance
  - Intrinsic: Ignornance, Anergy, Apoptosis
  - Extrinsic: Regulatory T cells
- Prevents harmful immunity