

T cells

Course	 Immunology
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Reading	<input checked="" type="checkbox"/>

Adaptive immunity is mediated by lymphocytes:

- **T-cells**
 - responsible for cellular immunity
 - it was adaptive immunity that could not be transferred by serum, but only by including live cells
 - Precursors of **T-cells (common lymphoid precursor)** originate in the bone marrow but must mature in the **thymus** before they become functional T-cells.
 - Macrophages and monocytes come from common **myeloid** precursors
 - Thymus shrinks when aging, might contribute to weaker immune responses
 - Less production of naive T cells
- **B-cells**
 - responsible for humoral immunity
 - B cells remain in the bone marrow

Features of adaptive immunity

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens

Feature	Functional significance
Clonal expansion	Increases number of antigen-specific lymphocytes from a small number of naive lymphocytes

Specificity

The key to adaptive immunity is specificity

- Innate immunity: Pattern Recognition Receptors (PRR)
- Adaptive immunity: Tailor-made to the invading microbe (BCR and TCR)

Diversity

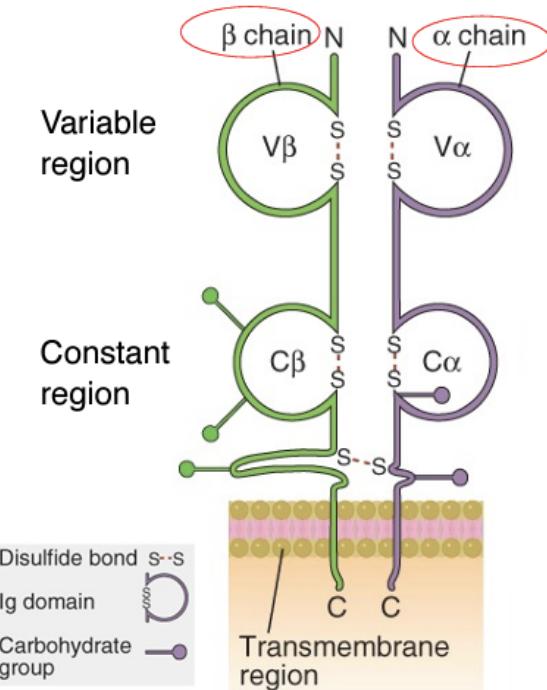
How is the adaptive immune system able to generate receptors to unseen antigens without predicting the future?

- The receptors of T and B cells are generated by **random gene rearrangement**

This creates a diverse repertoire

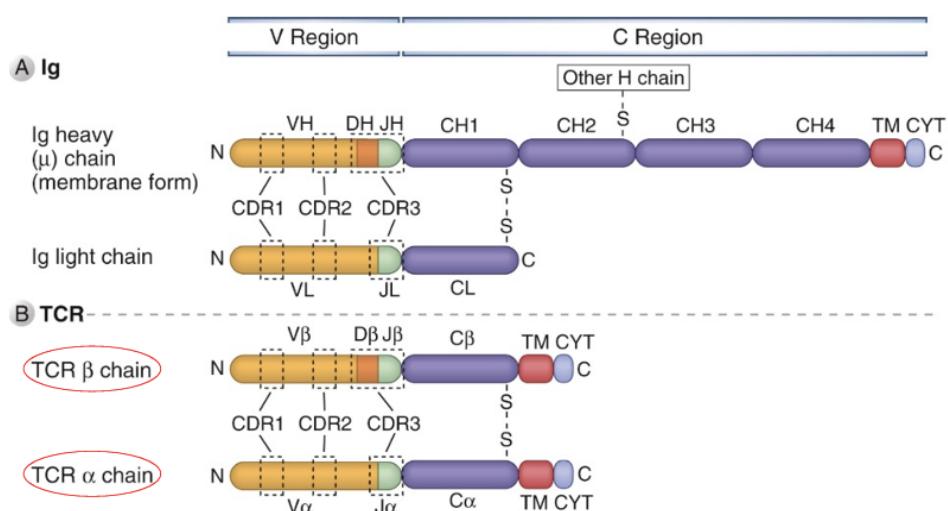
- Allows recognition of multiple antigens
- But means **very few** lymphocytes will recognise any given antigen
 - Thus clonal expansion is crucial for a sufficient T cell response

Structure of the TCR

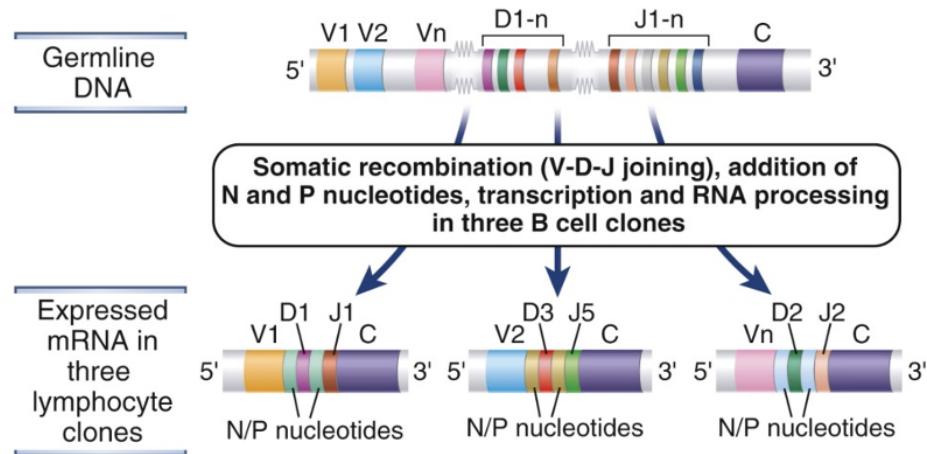


- Heterodimer
- ~90% T cells have TCR alpha beta (divided into CD4+ and CD8+ T cells)
 - Constant region and variable region
- 5-10% T cells have TCR gamma delta (enriched in skin, gut)

- Structure of TCR is similar to BCR
 - Beta chain: VDJ, constant region, transmembrane region
 - DJ joins together first
 - Random addition and deletion
 - Alpha chain: VJ
 - Identical twins will have different TCRs

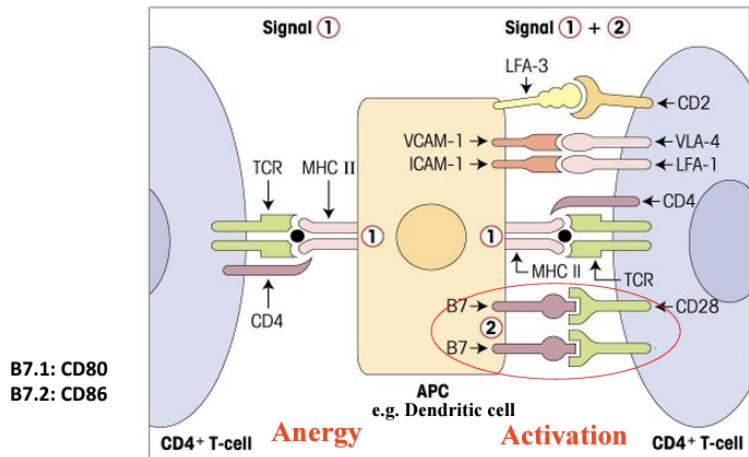


- Generation of TCR diversity



TCR signalling requires the CD3 complex

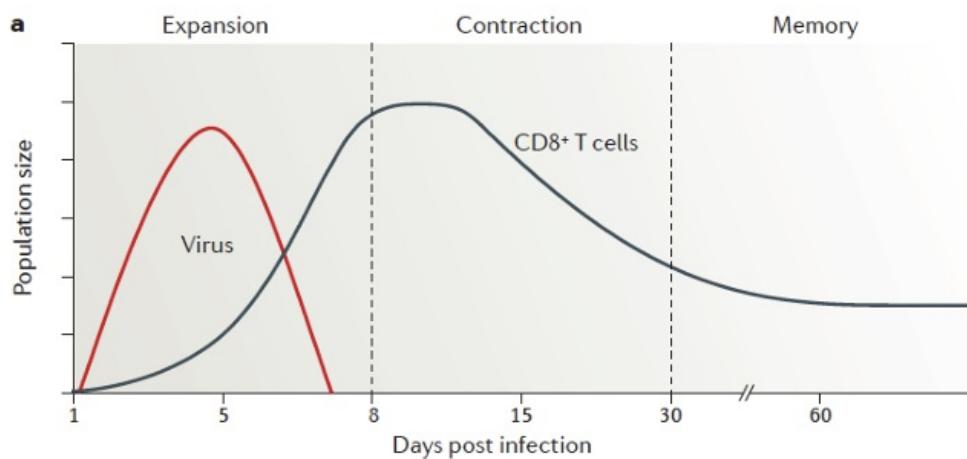
- CD3: complex of invariant chains (gamma, delta, epsilon, zeta)
- TCR is crucial for recognition but there is no signalling pathway for T cell activation
 - TCR makes a complex with CD3, which allows signalling transduction (especially the zeta chain)
 - CD3 sometimes used to identify T cells
- TCR signal is not sufficient for T cell activation, which is in a state called anergy, anergic cell not respond to any antigen in the future, even if both signals are present later on (note that it is not a permanent state), circulate around the body until they undergo apoptosis
 - Thus requires co-stimulation, secondary signal
 - B7-1, B7-2 or CD80, 86 in the APC interacts with CD28 on the T cell



Signal 1 (activation) : TCR-CD3 complex binds to peptide-MHC complex. Signal 2 (survival): CD28 - CD80/86. Signal 3 (differentiation): Releasing IL-2 by T cell itself or neighboring T cells (autocrine or paracrine); activated T cell produce CD25 (IL2 R alpha)

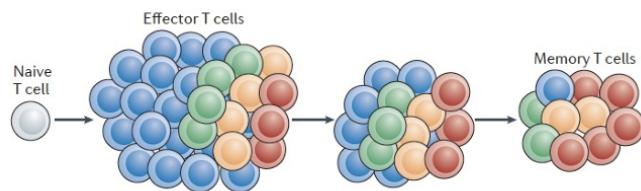
The kinetics of a T cell response

Three phases



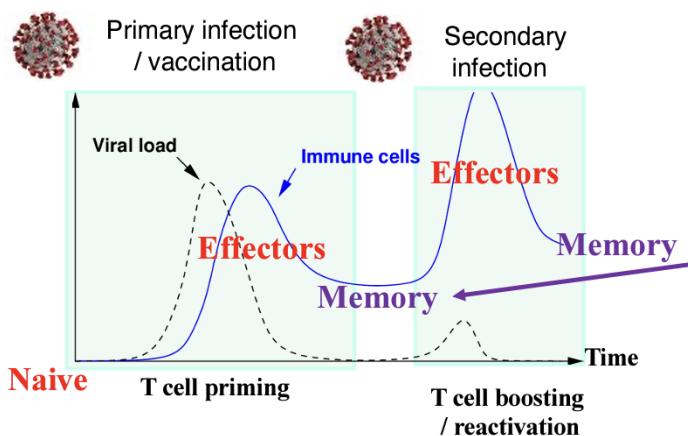
1. Expansion phase
2. Contraction phase - effector cell death
3. Memory phase - long-lived memory, surveillance, rapid recall
 - Expand when needed, and the T cells die after the infection is cleared

Two goals of T cell response



1. Immediate: produce enough effector T cells to clear the infection
2. Long-term: produce a protective memory response

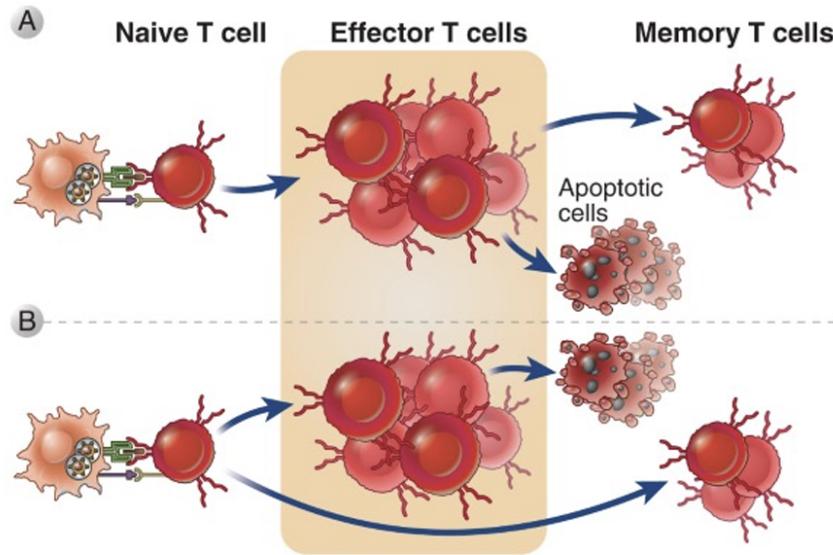
T cell memory



- Higher starting magnitude
- Lower activation threshold
 - Not so much need of co-stimulation
- Immediate effector function
- More rapid expansion
- Primary response: 5-7 days; secondary response: 1-3 days

T cell memory generation

- Whether the T cells differentiate into memory T cells directly or they are effectors in the beginning



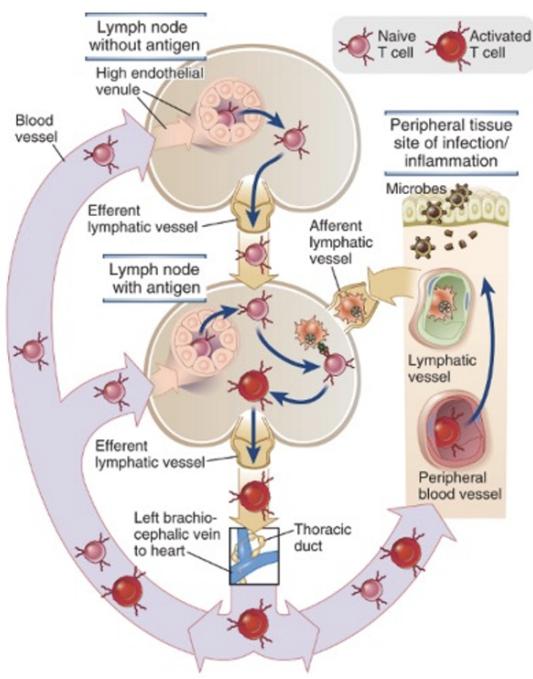
T cell differentiation

- Change in some surface molecules (CD45RA/RO, CD28, CD27)
 - CD45RA: naive T cells, CD45RO: memory T cells (encountered antigen)
- Change in chemokine receptor expression (e.g. CCR7, change in migration)
 - Control migration, naive and central memory have CCR7+, able to migrate to T cell zone of the lymph node
- Change in selectin/integrin expression
 - CD62L+, L-selectin on naive T cells and central memory
 - CD62- on effector memory T cells
- Change in activation threshold

T cell recirculation

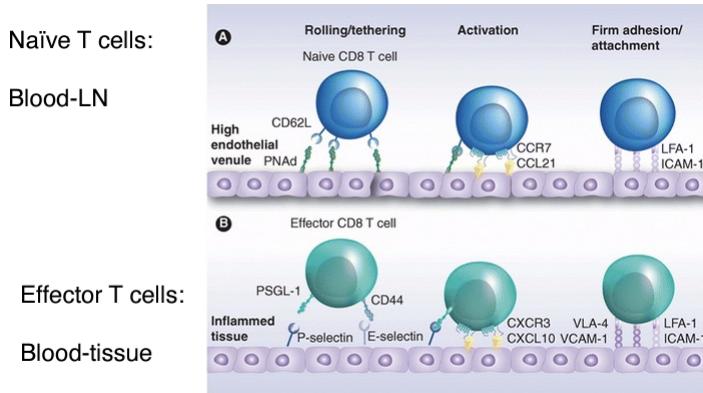
- T cells normally exist in a resting state (naive) and recirculate through the blood and lymph nodes
- Less than 5% lymphocytes are in blood at any one time
 - Most of them are in the LN or tissues
 - Some memory T cells are permanently resident in the tissue

Migration of naive and effector T cells



- LN without Ag:
 - Naive T cells circulate in and out in search of Ag (blood - LN - lymphatics - blood)
 - Via higher endothelial venule (HEV)
- LN with Ag:
 - Naive T cells are activated and effector T cells are generated (blood - LN - lymphatics - blood)
 - Effector T cells migrate (activated endothelium)
 - Perform effector functions at the site of infection (LN - lymphatics - blood - tissue)

- Site of infection / Peripheral tissue



Rolling/tethering

- L-selectin (CD62L) binds to sugar on the endothelium
- PSGL - P selectin (effector T cells)
 - CD44 - E selectin

Activation

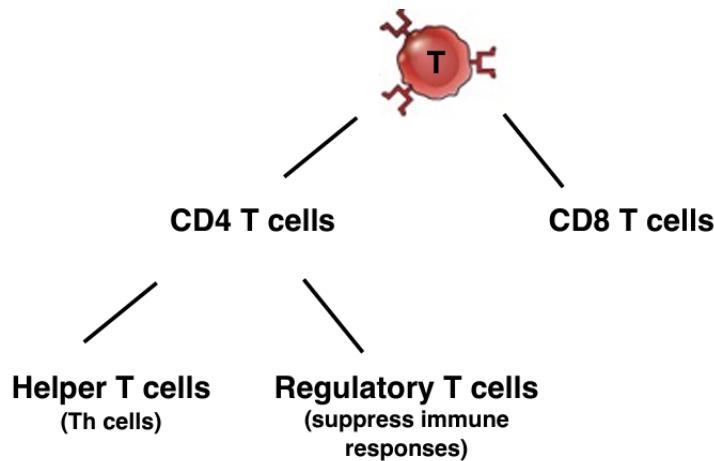
- CCR7 - CCL21
- CXCR3 - CXCL10 (effector T cells)

Firm adhesion/attachment

- LFA-1 (integrin) - ICAM-1 (glycoprotein)

- VLA-4 (integrin) – VCAM-1
 - LFA-1 – ICAM-1

T cell subsets



Following antigenic stimulation, individual T-cells **proliferate** and develop into specific **effector** cells.

- Multiple subsets adapted for different functions and secrete different cytokines

Each T-cell gives rise to a '**clone**' of effector cells, but since most antigens have many different **epitopes** (the actual antigenic structures recognised by lymphocytes), several clones are normally selected (**clonal selection**) to participate in a polyclonal immune response.

Functionally, alpha-beta T-cells can be roughly divided into three populations; **helper T-cells (Th)** and **regulatory T-cells (Tregs)**, most of which express the **CD4** cell surface molecule, and **cytotoxic T-cells (Tc or cytotoxic T lymphocytes, CTL)** most of which express the **CD8** cell surface molecule.

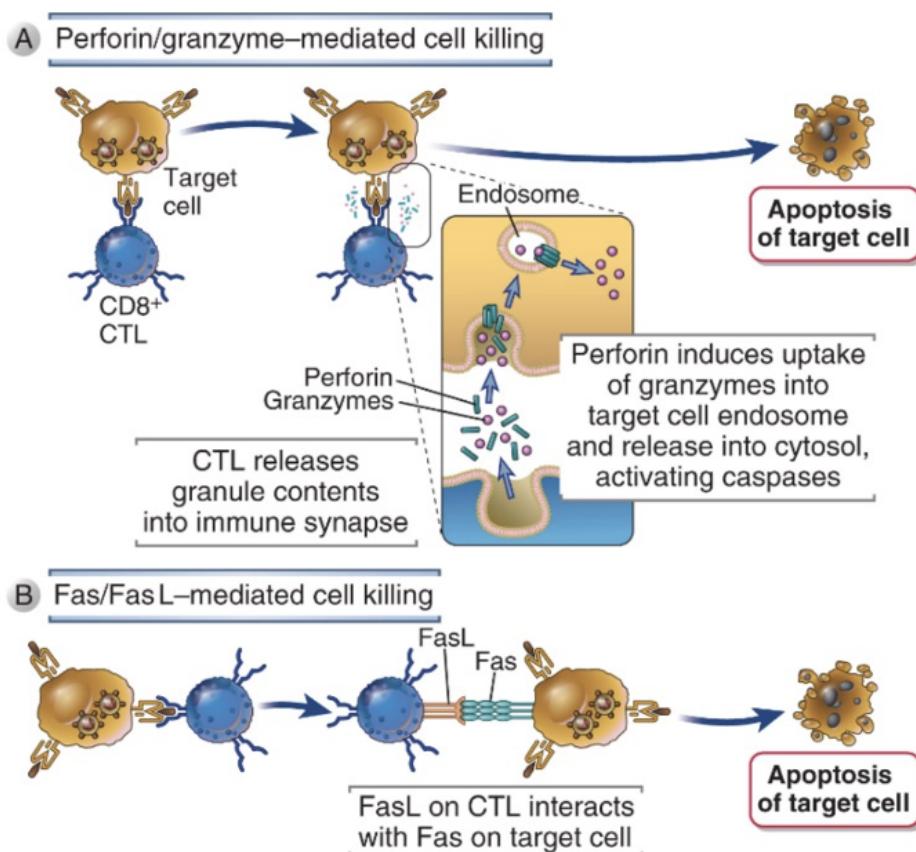
All T cells express surface **CD3** molecules which transduce the signal from the TCR into the T-cell.

Cytotoxic T cells (CD8)

- Induced by IL-12 from naive CD8+ T cells to cytotoxic T lymphocytes (CTL)
- Recognise small peptides produced inside other cells (endogenous antigens) and bound to the MHC class I molecules on the surface

- Virus must infect the APC to activate the T cells
 - MHC I is presented on all cells but DCs are required to activate the T cells
- Cross presentation allow exogenous antigens presented by MHC I and activates CD8 cells to become effector T cells
- Once the **TCR** has recognised the **MHC-peptide** complex on the virus-infected cell, the T cell develops into a fully **functional cytotoxic cell** which can then kill cells infected with the same virus by inducing **apoptosis** in them.
- CD8 T cells can make cytokines
- CD8 T cells may need CD4 T cell “help”

CD8 T cell killing of infected cells



Perforin/granzyme mediated cell killing

- Granule-dependent killing

- Have cytotoxic granules containing enzymes called **granzymes** and **perforin**
- Perforin, which like the MAC of complement that punches a hole in the infected cell.
 - It facilitates the entry of the granzymes
 - Once inside the granzymes activate other enzymes called **caspases** which mediate **apoptosis**

Fas/FasL-mediated cell killing

- Death receptor-dependent pathway
- Direct interaction of the **FasL (Fas ligand)** molecule on the surface of the cytotoxic T cell with the death receptor **Fas (CD95)** on the target cell leading to apoptosis of the target cell.
 - CTL can also cause activation of caspases in the infected cells
 - CD8 cells can also release **inflammatory cytokines**, including TNF- α , and IFN- γ .



Immunological synapse: immune cell and target cell are in very close proximity so the cytotoxic molecules will not damage healthy cells

Helper T cells (CD4) - Conductors of the immune orchestra

T cells which express **CD4** molecules on their cell surface (CD4+ T cells, or simply CD4 T cells) recognise small peptides bound to **MHC class II molecules**.

CD4 T cells are often referred to as **Helper T cells (Th)**.

Different types of CD4 T cells play are involved in protection against different types of pathogens; The function of different CD4 T cells is determined by the types of cytokines they produce.

Which type of Th cell will develop is determined by the characteristics of the pathogen through the expression of different PAMPs and by the cytokines present-produced upon infection.

Effector T cells	Defining cytokines	Principal target cells	Major immune reactions	Host defense
Th1	IFN- γ	Macrophages	Macrophage activation	Intracellular pathogens
Th2	IL-4 IL-5 IL-13	Eosinophils	Eosinophil and mast cell activation; alternative macrophage activation	Helminths
Th17	IL-17 IL-22	Neutrophils	Neutrophil recruitment and activation	Extracellular bacteria and fungi

The diagram illustrates the differentiation of a T cell into three distinct effector T cell types: Th1, Th2, and Th17. Each type is associated with specific markers (T-bet for Th1, GATA3 for Th2, ROR γ t for Th17) and defining cytokines (IFN- γ for Th1, IL-4, IL-5, IL-13 for Th2, IL-17, IL-22 for Th17). The Th1 cell is shown activating a macrophage. The Th2 cell is shown activating an eosinophil. The Th17 cell is shown recruiting and activating neutrophils.

Th1 cells - microbes

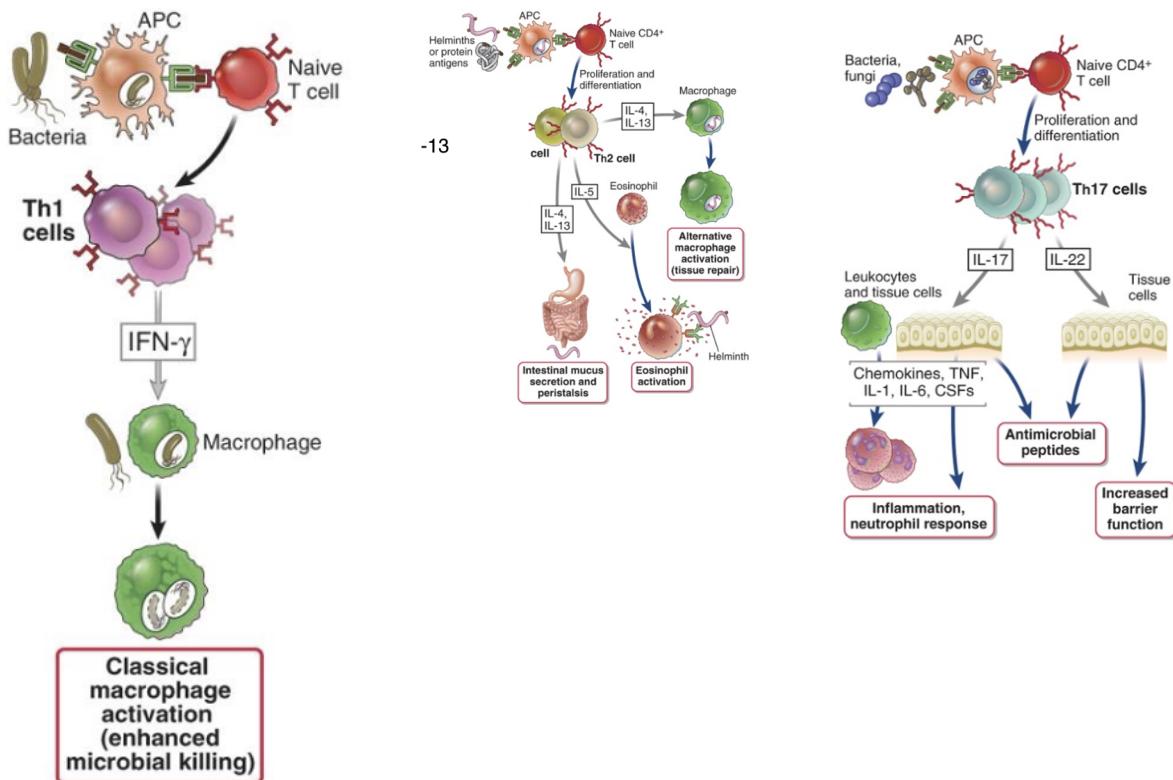
- Marker T-bet (transcription factor), STAT4, STAT1
- Induced by IL-12, IFNgamma
- Produce cytokine **IFNy and TNF α**
- Activates **macrophages (IFNgamma)**

Th2 cells - parasite

- Marker GATA3
- Induced by IL-4
- Produce **IL-4, IL-5** and **IL-13** and other cytokines
- May present CD25
- Act on **eosinophils (IL-5)**, mast cells and **basophils** and promote antibody class switching to IgE
- IL-4 and IL-13 turns macrophages to tissue repair

Th17 cells - bacteria, fungi

- Marker ROR γ t
- Induced by IL1, 23, 6 and TGFbeta
- Secrete **IL-17 and IL-22**
- Important in **neutrophil recruitment** and activation, as well as promote **tissue inflammation**
- Important in the gut and barrier function



- Polarising cytokines sometimes referred to as the third signal other than TCR-peptide and co-stimulation

Follicular Helper T cells (Tfh cells)

- Defining marker CXCR5 (access B cell follicles), BCL6 (transcriptional repressor, prevents premature and differentiation of GC B cells)
- Induced by IL-6, IL-21**
- Specialised to help **activate B cells** to make antibodies.
 - Specifically, T cell help is required for class switching, somatic hypermutation and generation of memory B cells.

Tfh are specialised to provide help for B cell proliferation and differentiation into memory and plasma cells producing high affinity antibodies (in lymphoid follicles).

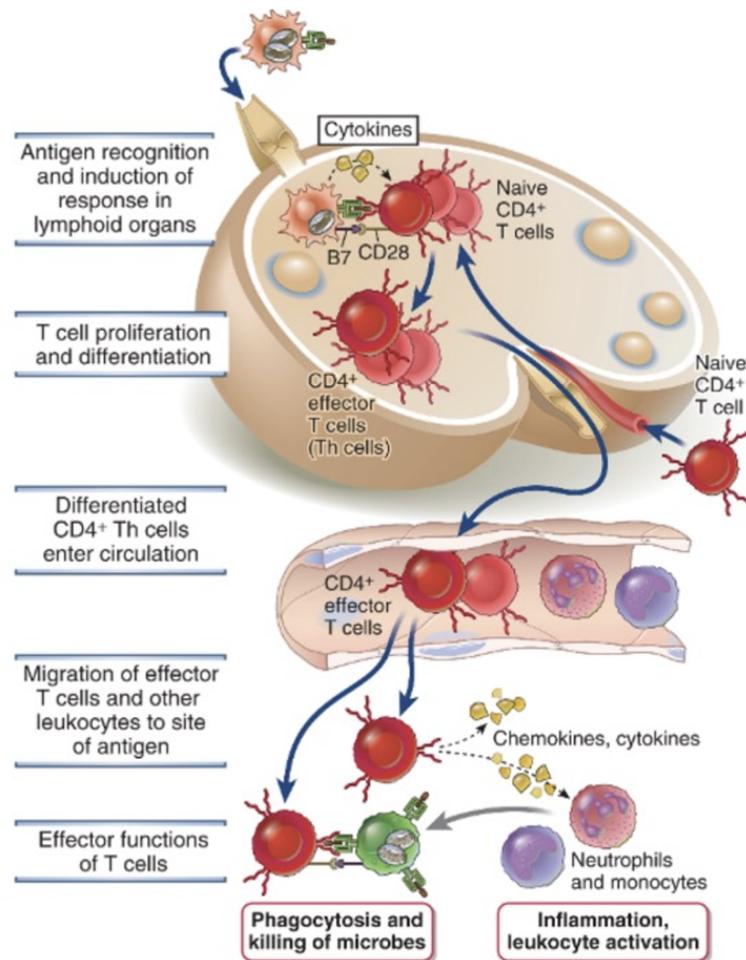
- Tfh cells can make a variety of cytokines (e.g. IL-21) leading to production of different types of antibody appropriate for the invading pathogen.
 - IL-4 in sensitisation
- IL-21** is also crucial for proliferation and differentiation of antibody producing plasma cells.

In addition T cell provide additional co-stimulatory signals for example via the **CD40 ligand (CD40L)** on the T-cell surface engaging **CD40** on the B-cell surface.

Regulatory T-cells - 1-2% of CD4+ population

- Suppress immune responses and are essential for immune homeostasis.
- Express high levels of a regulatory protein called CTLA-4 and can also secrete cytokines such as IL-10 and TGFbeta which can mediate immunosuppressive functions.
- Foxp3 is a transcription factor critically involved in the development and function of regulatory T cells (Tregs).
 - Leads to expression of CD25, CD103 (alphaE integrin), GITR (Glucocorticoid-Induced TNFR family Related gene)

In addition to development of effector function, individual T cells, like B-cells, can develop into **memory cells** which are responsible for mounting enhanced immune responses against antigens previously encountered by the organism.



Summary

- T cells develop in the thymus
- Randomly generate a TCR - large repertoire
- T cells require their antigen to be presented
- After infection, useful T cells undergo clonal expansion
- Following activation effector and memory cells are generated
- T cells migrate from blood to LN to peripheral tissues
- Naive, effector and memory cells have different phenotype and different migration patterns
- T cells can be CD4 (helper or regulatory) or CD8 (cytotoxic)
- CD8 T cell kill infected / transformed cells
- CD4 helper T cells coordinate immune responses