

Biomedical
Science

Molecular
Genetics



HMG 442 | Fall 2026-2027

Inherited Immunodeficiencies

T and B cell Development and Genetic Defects of these pathway



Free Session

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Brief Introduction

The purpose of this lecture is to give a broad overview of the major stages of **T-cell development**.

- T-cells are key regulators of **acquired immunity**, and their functions are determined by events that occur during a complex developmental process in the **thymus**. An understanding of T-cell development is fundamental to our understanding of immune responses.
- The interaction of the **T-cell receptor (TCR)** expressed by a developing T-cell (**thymocyte**) with self-antigens presented by stromal cells in the thymus determines the ultimate fate of that thymocyte.
- Only a **small fraction of thymocytes** become the mature T-cells that patrol the body's periphery and respond to foreign antigen.
- The molecular interactions that lead to the elimination of self-reactive thymocytes (**negative selection**) and the survival of those that can potentially mount protective immune responses (**positive selection**) are complex.

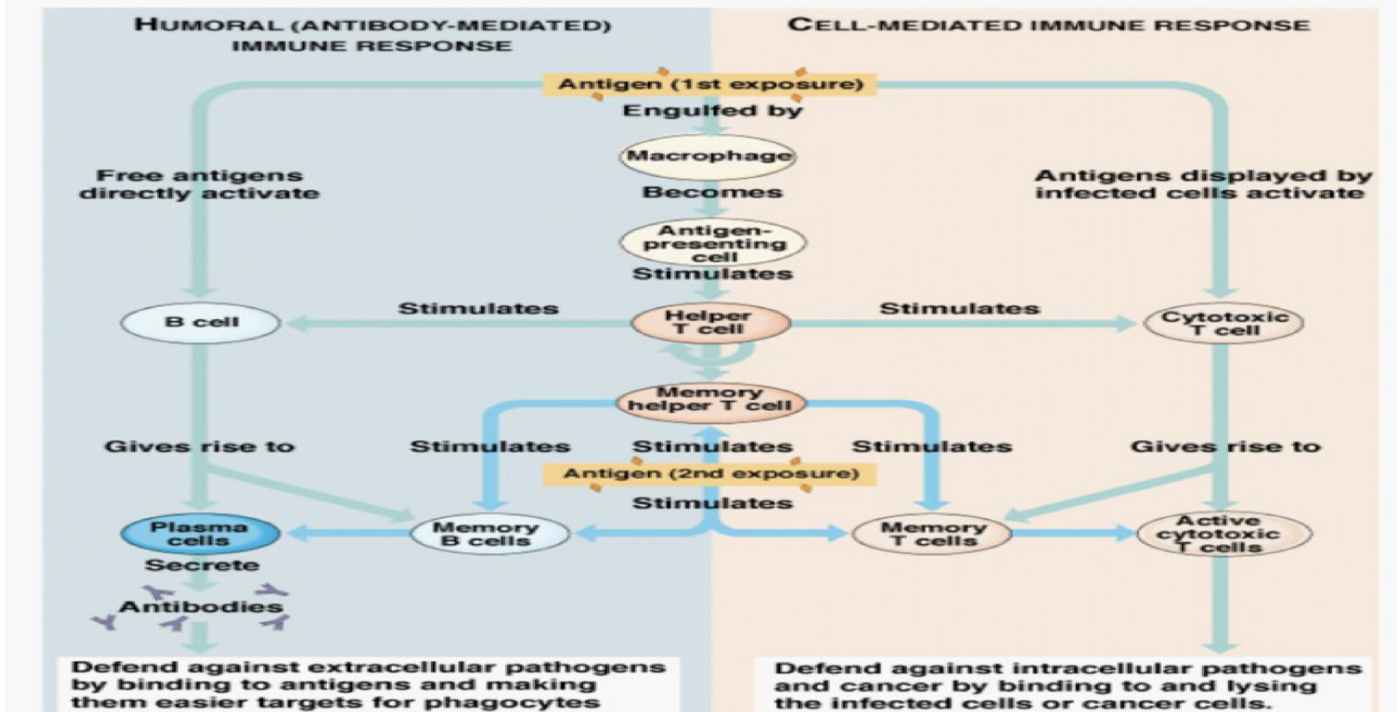
HOW IT HAS BEEN STUDIED

Understanding has been greatly enhanced through the use of **genetic tools**, particularly mutant mouse models such as **transgenic mice** and **gene-targeted or "knockout" mice**. T-cell development has been further dissected with the help of in vitro culture systems such as **fetal thymic organ culture (FTOC)**.

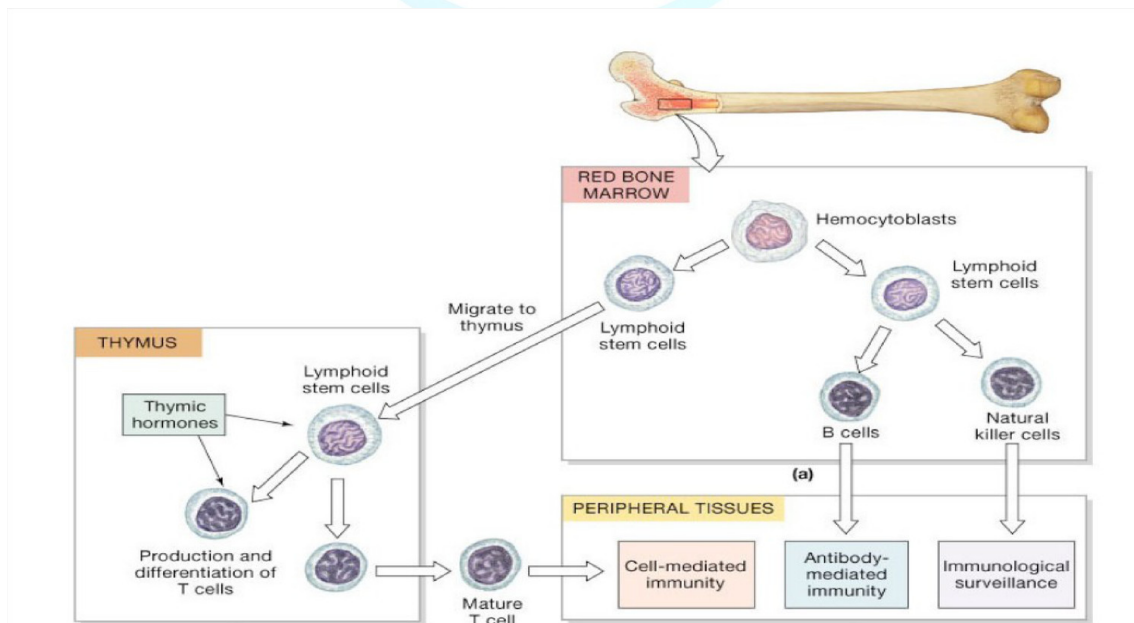


Overview of the Immune Response

Overview of the Immune



Lymphocyte Development & Lymphoid Organs





The Lymphocytes · T-cells

- Arise in the **bone marrow** BUT migrate to the **thymus gland** to mature.
- T-cell receptors **cannot recognize free antigens alone**; they can only recognize antigens when presented on cell-surface **Major Histocompatibility Complex (MHC)** molecules.
- **CD4** → T_H · **CD8** → T_C

Types

- Helper T cells
- Cytotoxic T cells
- Suppressor T cells

Crucial steps

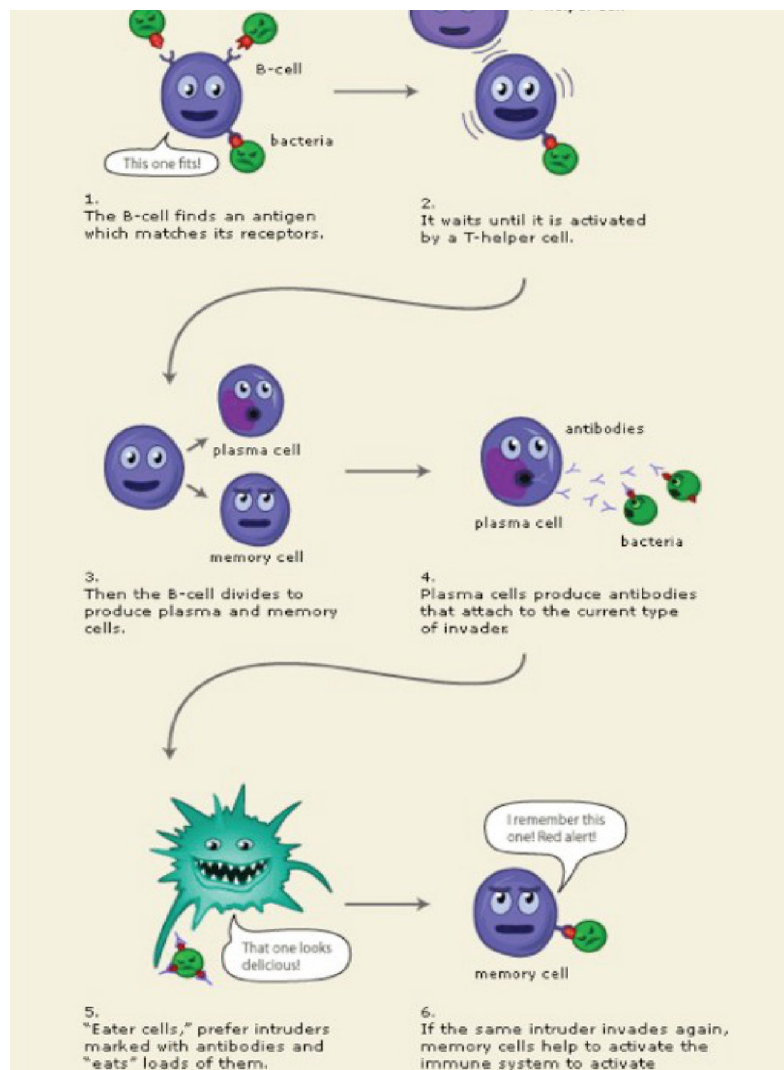
- A naive T cell encounters antigen combined with an MHC molecule on a cell
- T cell proliferates
- Differentiates into **memory T cells** and various **effector T cells**

The attribute that distinguishes antigen recognition by most T-cells from recognition by B-cells is **MHC restriction.**



The Lymphocytes · B-cells

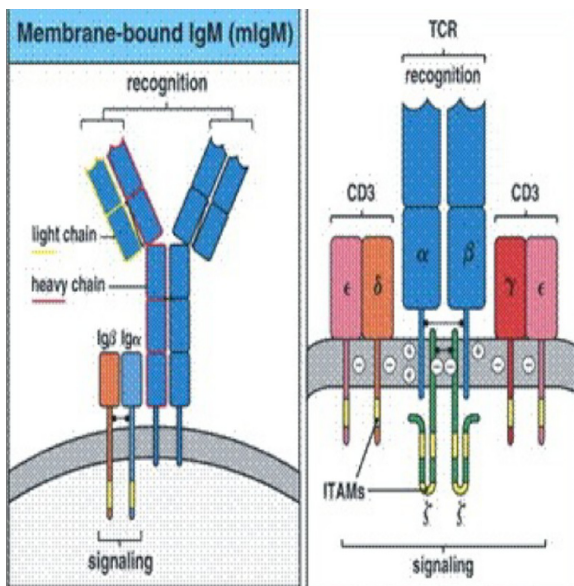
- B lymphocytes **mature within the bone marrow**; when they leave it, each expresses a **unique antigen-binding receptor** on its membrane.
- **Plasma cells** live for only a few days — they secrete enormous amounts of antibody (**2000 per second**).





T & B Cell Receptors

T-cell receptors (TCRs) and B-cell receptors (BCRs) have **different structures**, thus they bind to different molecular structures and have **different genetic codes**.



T-cell receptors (TCRs)

Enable the cell to bind to, be activated by and respond to an **epitope presented by antigen-presenting cells (APC)**.

- **CD8 T cells** destroy the cells they bind to, such as virus cells.
- **CD4 T cells** group together to cause inflammation, which isolates an infected area so it can heal — helps build immunities.

B-cell receptors (BCRs)

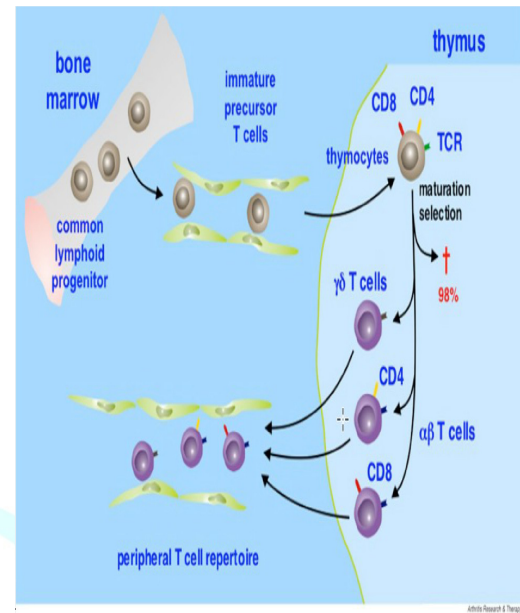
Enable the cell to bind, be activated by and respond to an **epitope on molecules of a soluble antigen**.

- B cells bind to these toxins and digest them into smaller pieces.
- The response ends with descendants of the B cell secreting **antibodies** (via the plasma cells).



Development and Maturation · The Thymus

- In the thymus, developing T cells — known as **thymocytes** — proliferate and differentiate along developmental pathways that generate **functionally distinct subpopulations** of mature T cells.
- Aside from being the main source of all T cells, it is where T cells **diversify** and then are shaped into an effective primary T-cell repertoire by an extraordinary pair of selection processes (**+ and – selection**).



Positive and Negative Selection of T Cells

Positive selection

- Permits the survival of only those T cells whose TCRs are capable of **recognizing self-MHC molecules**.
- It is thus responsible for the creation of a **self-MHC-restricted repertoire** of T cells.
- Cells that **fail** positive selection are eliminated within the thymus by **apoptosis**.

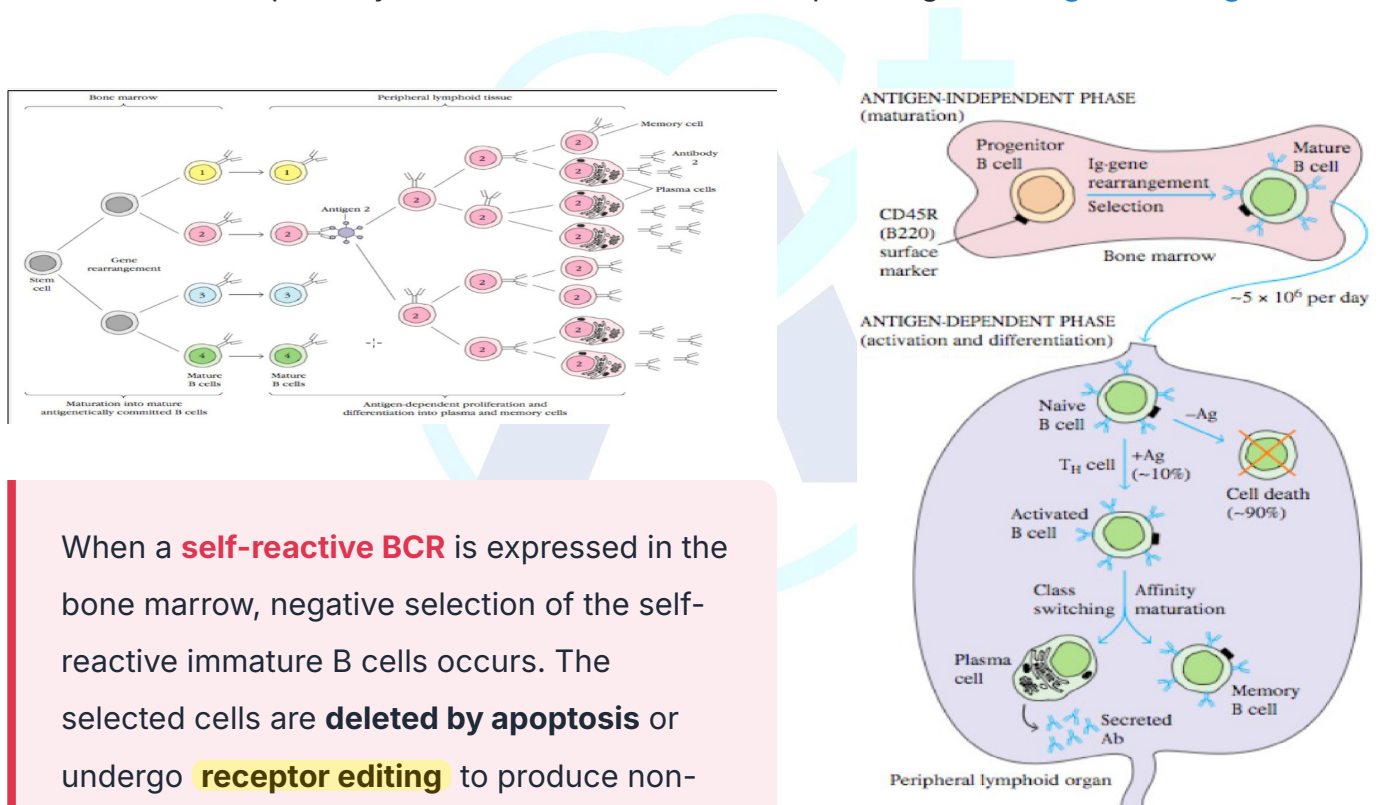
Negative selection

- Eliminates T cells that **react too strongly with self-MHC**, or with self-MHC plus self-peptides.
- Cells bearing **high-affinity receptors** for self-MHC alone, or self-antigen presented by self-MHC, are removed — which results in **self-tolerance**.
- An extremely important factor in generating a primary T-cell repertoire that is **self-tolerant**.



B Cell Maturation and Development

- B cells develop in **bone marrow** and undergo antigen-induced activation and differentiation in the **periphery**. Activated B cells can give rise to **antibody-secreting plasma cells** or **memory B cells**.
- During B-cell development, sequential **Ig-gene rearrangements** transform a pro-B cell into a mature B cell expressing membrane immunoglobulin M (**mlgM**) with a single antigenic specificity.
- Further development yields mature naive B cells expressing both **mlgM** and **mlgD**.

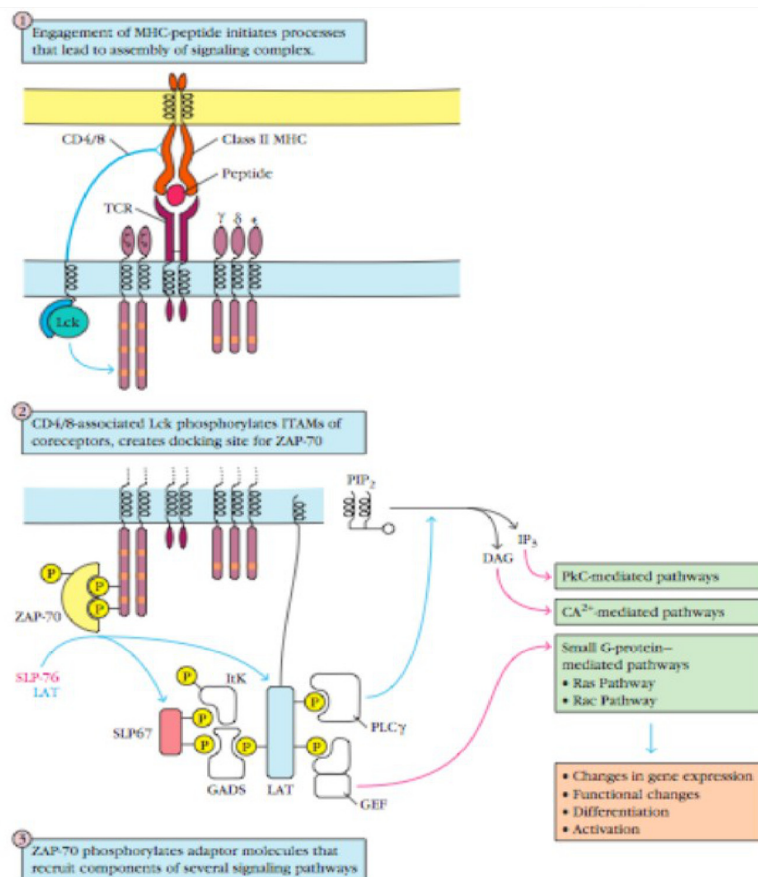


When a **self-reactive BCR** is expressed in the bone marrow, negative selection of the self-reactive immature B cells occurs. The selected cells are **deleted by apoptosis** or undergo **receptor editing** to produce non-self-reactive mlg.



Activation of T Cells

- T_H-cell activation is initiated by interaction of the **TCR-CD3 complex** with a peptide-MHC complex on an antigen-presenting cell.
- Activation also requires the activity of **accessory molecules**, including the coreceptors **CD4** and **CD8**.
- Many different **intracellular signal-transduction pathways** are activated by the engagement of the TCR.

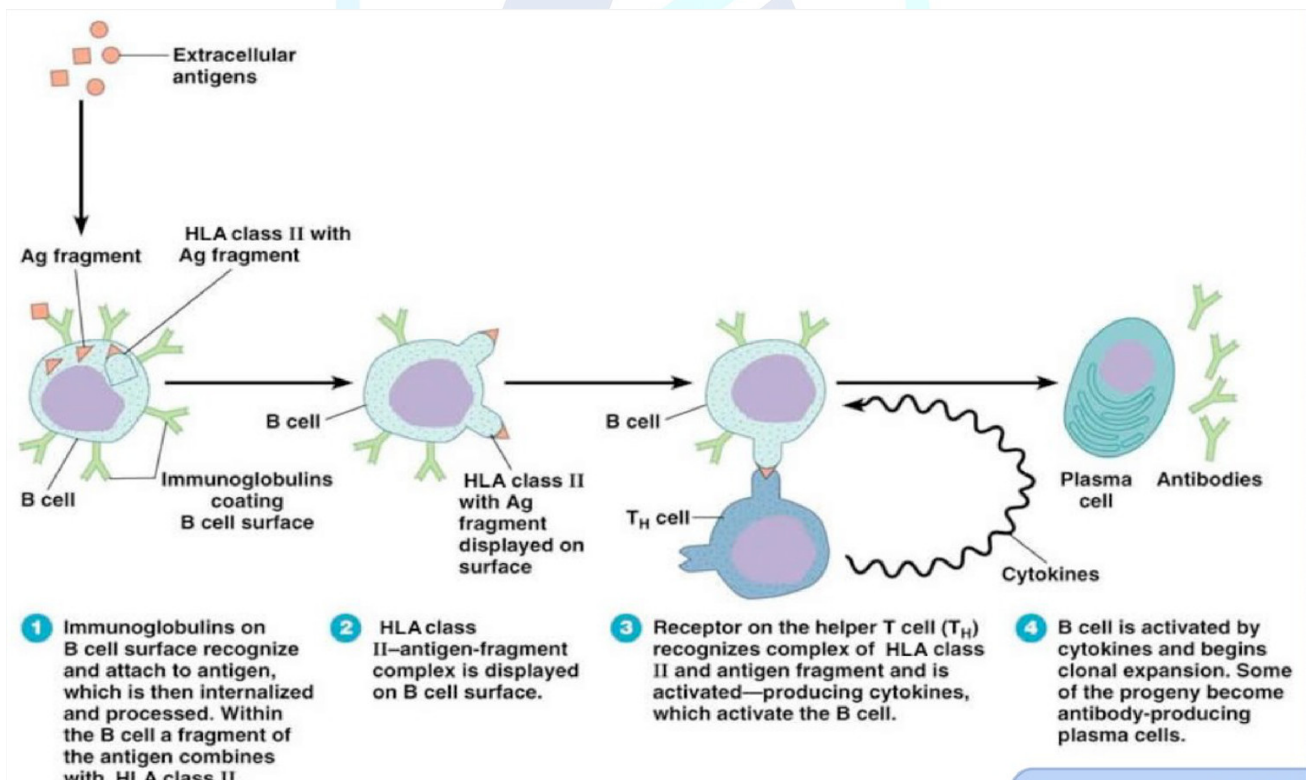




B Cell Activation

B-cells are activated when **antigen binds to receptors** on the B-cell surface, followed by a **co-stimulatory signal**, usually provided by a helper T-cell.

- Antigens that require co-stimulation by a T-cell to activate a B-cell are **T-dependent antigens** and are usually proteins.
- In order for the helper T-cell to stimulate the B-cell **both must be activated** — this usually requires that the B-cell internalize the antigen, process it, and then present it on the cell surface bound to a **class II HLA molecule**.
- The HLA–antigen complex is recognized by a receptor on the surface of the T-cell (the **T-cell receptor, or TCR**).





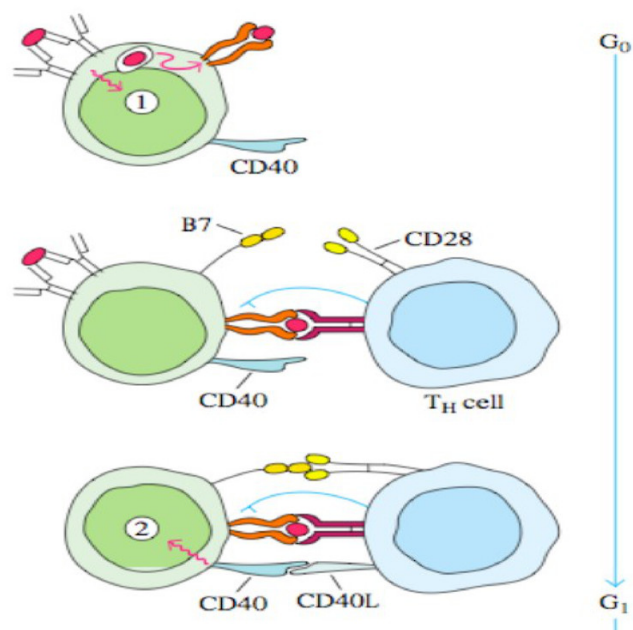
B Cell Activation · Co-stimulation

- The B-cell expresses an activation receptor on its surface (**CD40**) that binds to a complementary ligand (**CD154**) on the surface of the helper T-cell.
- This interaction will **co-stimulate the B-cell**, activating it to clonally proliferate.
- In addition, the helper T-cell will secrete **interleukins** that will promote growth and antibody production by the activated B-cell.
- The helper T-cell would normally have been activated by interaction with a macrophage or dendritic cell, but the **B-cell can act as an antigen-presenting cell** as well.
- The B-cell can express **B7 proteins** on its surface which will bind to **CD28** on the surface of the helper T-cell.
- The combination of **TCR-HLA/antigen binding** and **B7-CD28 binding** will activate the T-cell.

(a) Antigen crosslinks mlg, generating signal ①, which leads to increased expression of class II MHC and co-stimulatory B7. Antigen-antibody complexes are internalized by receptor-mediated endocytosis and degraded to peptides, some of which are bound by class II MHC and presented on the membrane as peptide-MHC complexes.

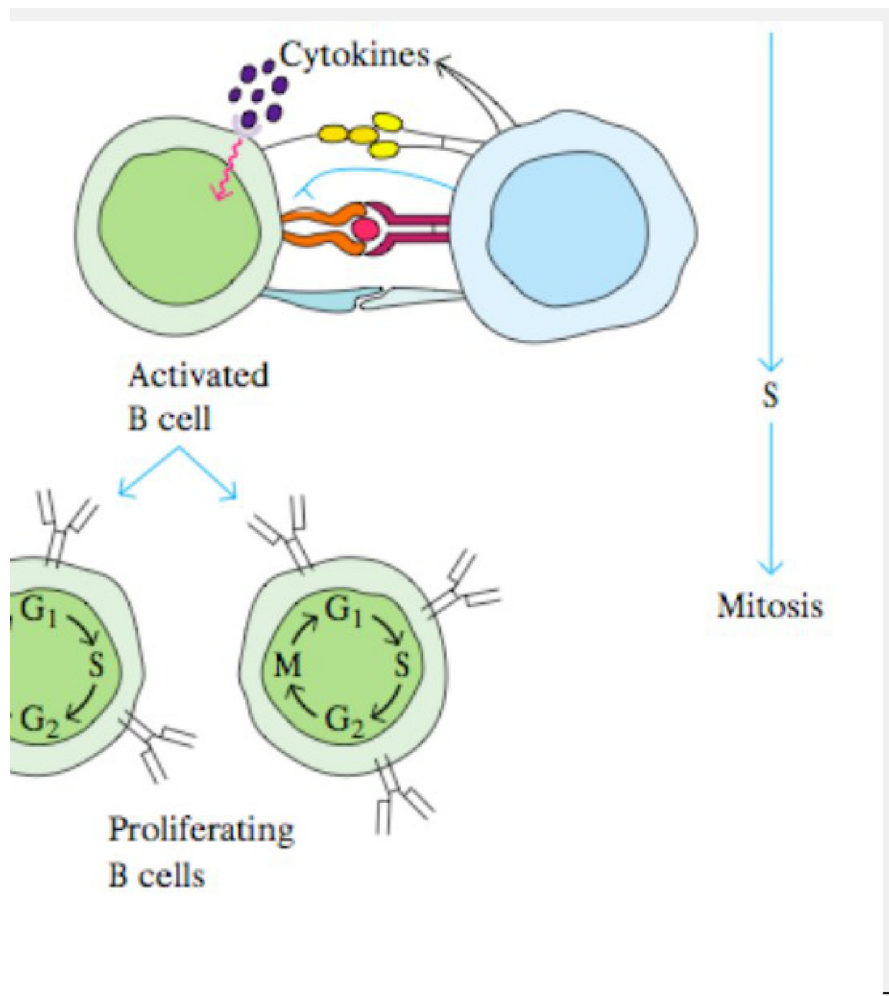
(b) T_H cell recognizes antigen-class II MHC on B-cell membrane. This plus co-stimulatory signal activates T_H cell.

(c) 1. T_H cell begins to express CD40L.
2. Interaction of CD40 and CD40L provides signal ②.
3. B7-CD28 interactions provide co-stimulation to the T_H cell.





From Activation to Proliferation



1

B cell begins to express **receptors for various cytokines.**

2

Binding of cytokines released from T_H cell to a **directed helper signal.**

3

Signals that support the progression of the B cell to **DNA synthesis** and to **differentiation.**



To Summarise...

T-CELLS 3

Where they come from

- Arise in the **bone marrow**
- Mature in the **thymus**
- Helper, cytotoxic and suppressor types

B-CELLS 2000

Antibody output

- Mature within the **bone marrow**
- Plasma cells live only a **few days**
- They secrete **2000 antibodies per second**

KEY RULE MHC

MHC restriction

- TCRs cannot recognise **free antigen**
- Antigen must be presented on **MHC**
- This is what distinguishes T-cell from B-cell recognition

SELECTION 2

Shaping the repertoire

- **Positive** — keeps self-MHC-restricted cells
- **Negative** — removes self-reactive cells
- Failures are removed by **apoptosis**

RECEPTORS 2

TCR vs BCR

- **TCR** binds an epitope presented by an APC
- **BCR** binds an epitope on a soluble antigen
- Different structures and different genetic codes

ACTIVATION 2

Signals required

- Antigen binding to the receptor
- A **co-stimulatory signal** from a helper T-cell
- **CD40-CD154** and **B7-CD28** interactions

B CELL MATURATION AT A GLANCE

Pro-B cell



Ig-gene rearrangement



Mature B cell · mIgM



Naive B cell · mIgM + mIgD



Plasma cell / memory B cell