B cell development

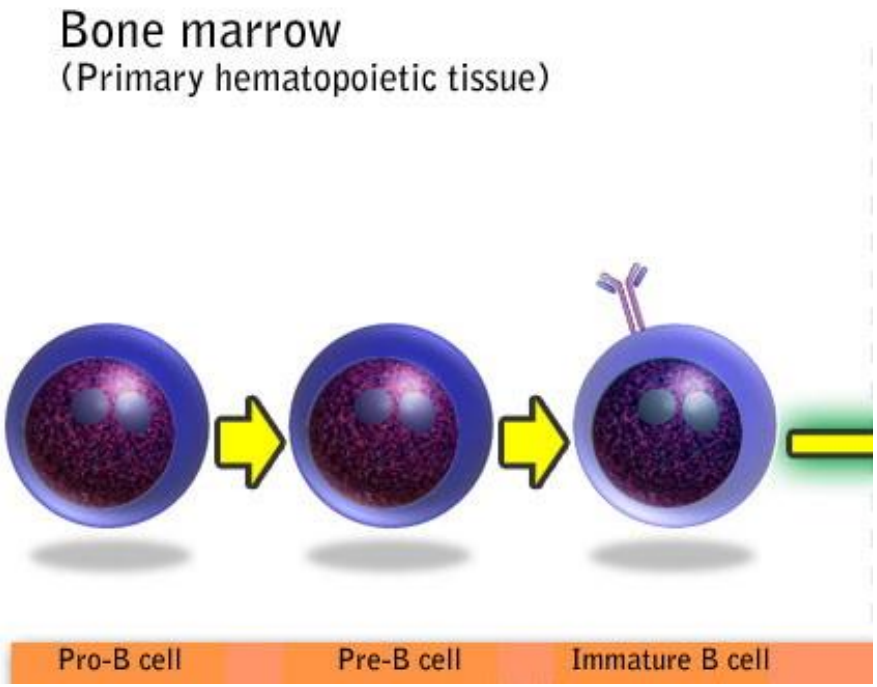
B Cell Development in Bone Marrow

Various stages of development of B cells in bone marrow are:

- **Stem cell**
- **Early Pro B cell**
- **Late Pro B cell**
- **Large Pre B cell**
- **Small Pre B cell**
- **Immature B cell**
- **Mature B cell**

Rearrangement and selection generate **mature B cells** expressing **mIgM** and **mIgD.**

Most of the B cells are **eliminated** by **negative selection** before they leave the bone marrow.



Negative selection (clonal deletion)

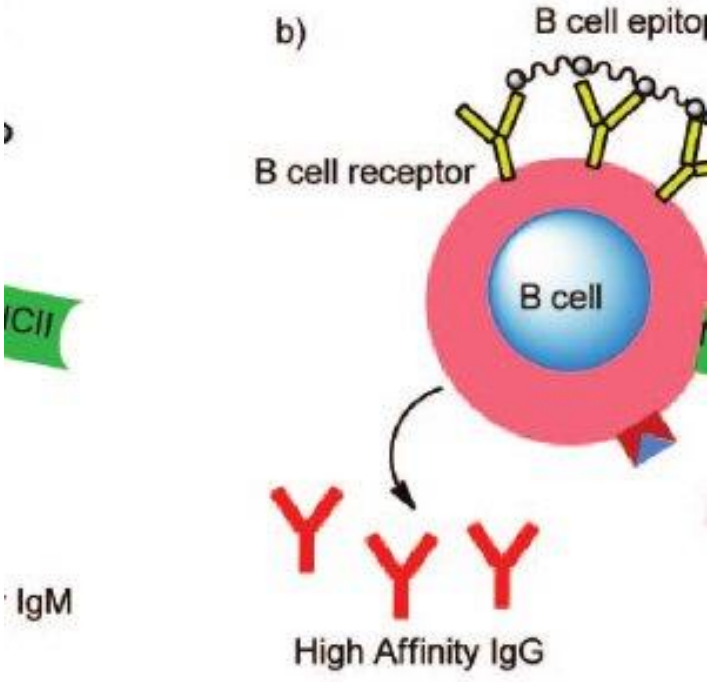
B cells undergo **negative selection (clonal deletion)** during maturation.

- If an **immature** B cell binds an antigen (self) in the bone marrow with **high affinity**, further maturation is stopped and B cell dies by **apoptosis.**

- **90%** of B cells which are generated undergo apoptosis **in the bone marrow.**

- Negative selection eliminates **potentially dangerous** (over active) B cells which can **react against self antigens.**

- This happens by **cross-linking of mIgM** by antigen on immature B cells.



- B cells that survive this process **leave the bone marrow** and **enter blood stream** to move to **peripheral (secondary) lymphoid organs.**

Activation and differentiation in peripheral lymphoid organs

-- There are **two peripheral** lymphoid organs, **spleen** and **lymph node**.

-- Mature B cells which enter peripheral lymphoid organs either **encounter an antigen (non-self), get activated** and **proliferate (clonal expansion)** or **apoptose (nearly 90%).**

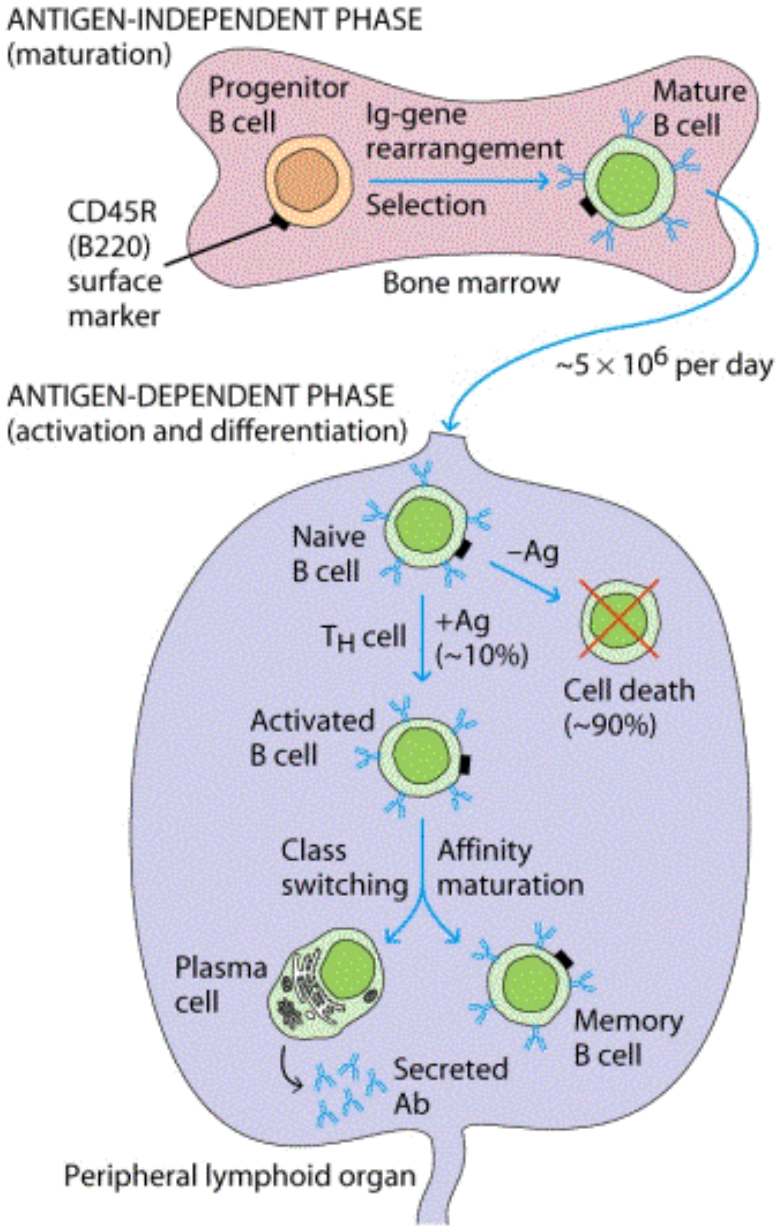
Apoptosis is a form of programmed cell death, or “cellular suicide.” It is different from necrosis, in which cells die due to injury. **Apoptosis** is an orderly process in which the cell's contents are packaged into small packets of membrane for “garbage collection” by immune cells.

-- So **only 1%** of the mature B cells produced in bone marrow survive and are activated

-- **Activated B cells** experience **class switching** and **affinity maturation** to differentiate into **plasma** and **memory B cells.**

Class switching of B cells is the process whereby an activated B cell changes its antibody production from IgM to either IgA, IgG, or IgE depending on the functional requirements.

Affinity maturation is the process by which antibodies gain increased affinity, avidity, and anti-pathogen activity and is the result of somatic hypermutation (SHM) of immunoglobulin genes in B cells, coupled to selection for antigen binding.


ANTIGEN-INDEPENDENT PHASE
(maturation)
Progenitor
B cell
Ig-gene
rearrangement
Selection
Mature
B cell
CD45R
(B220)
surface
marker
Bone marrow
~5 × 10^6 per day
ANTIGEN-DEPENDENT PHASE
(activation and differentiation)
Naive
B cell
–Ag
TH cell
+Ag
(~10%)
Cell death
(~90%)
Activated
B cell
Class
switching
Affinity
maturation
Plasma
cell
Memory
B cell
Secreted
Ab
Peripheral lymphoid organ

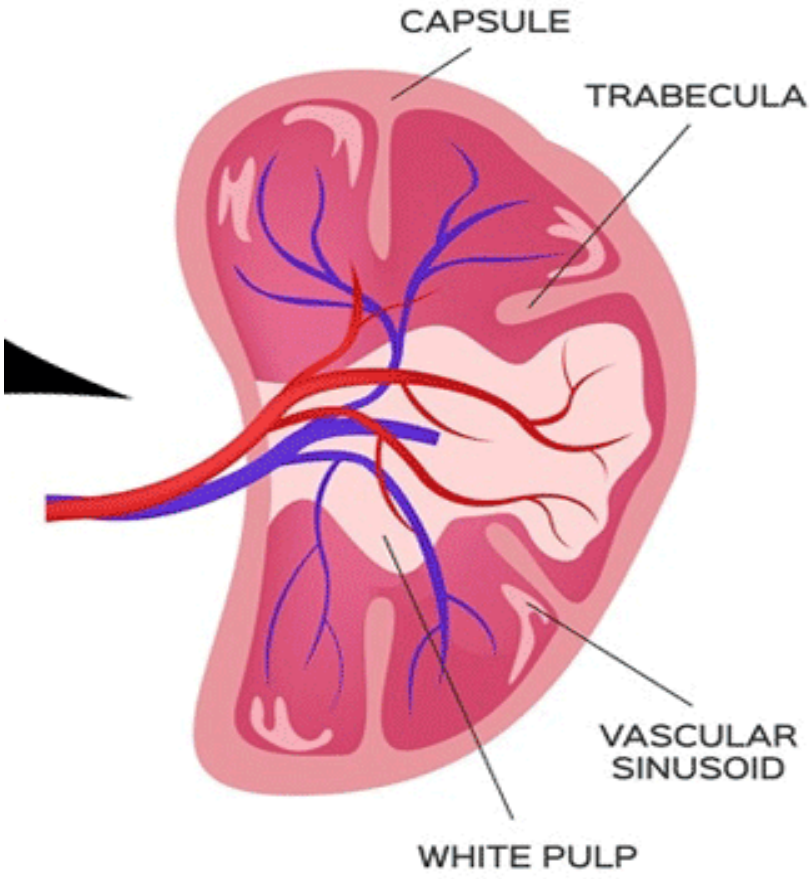
Peripheral lymphoid organs

- Peripheral lymphoid organs, spleen and lymph nodes have **distinct areas** of B cells and T cells.

- Beside **lymphocytes**, peripheral lymphoid tissues are composed of **several other types** of leukocytes, principally **macrophages** and **dendritic cells**.

Spleen

The lymphoid tissue of the spleen is the **white pulp**.



- Newly formed lymphocytes enter the spleen via the blood, from which they migrate to the **appropriate areas of the white pulp.**

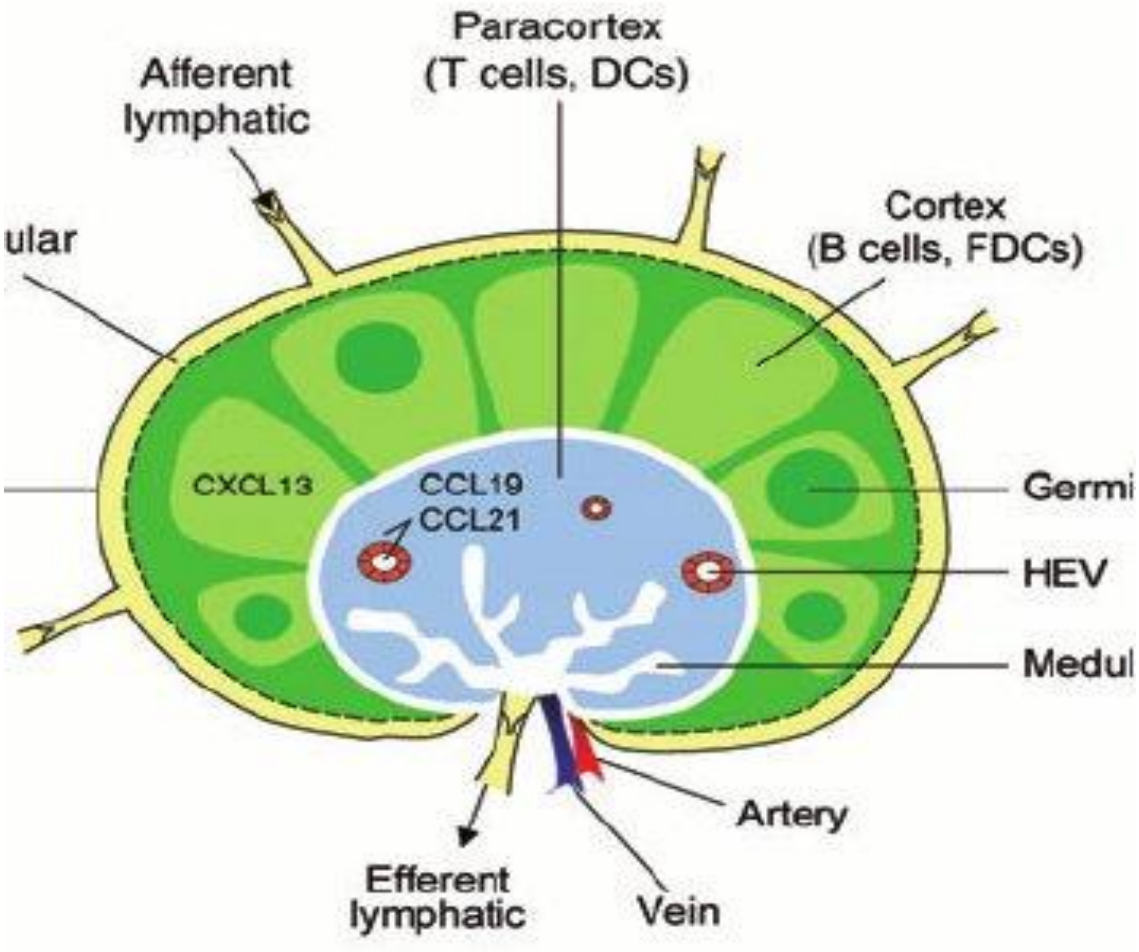
- Lymphocytes that survive their passage (10%) through the spleen **leave via the marginal sinus**.

- Within the white pulp are **clearly separated** areas of T cells and B cells.

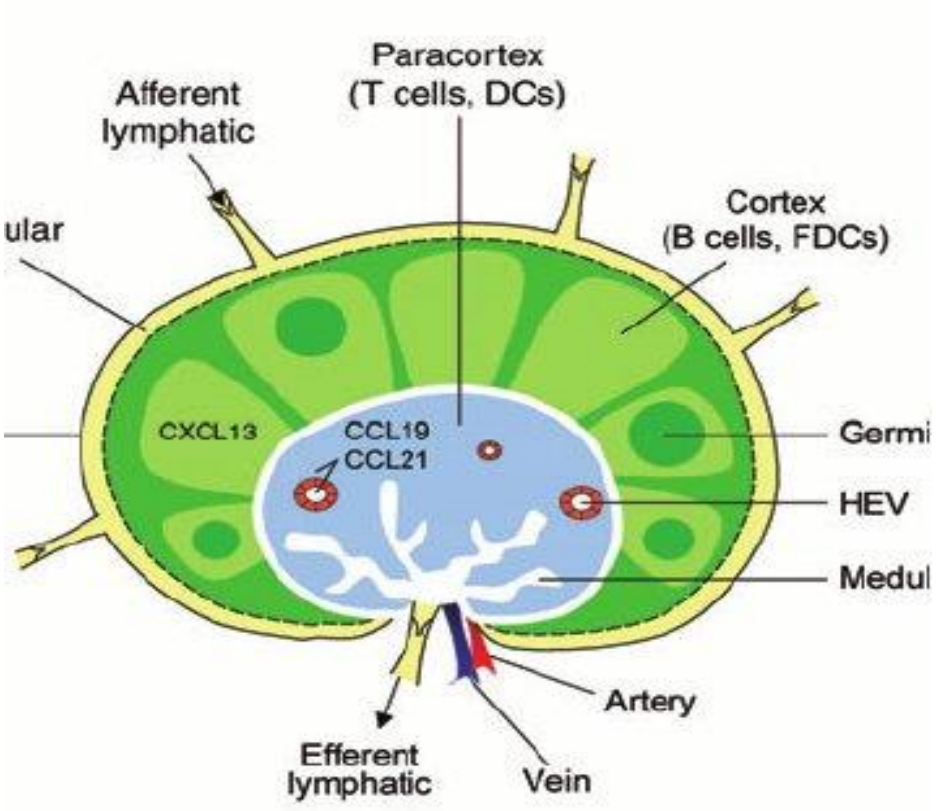
- Areas for B cells are called **B cell follicles**.

Lymph nodes

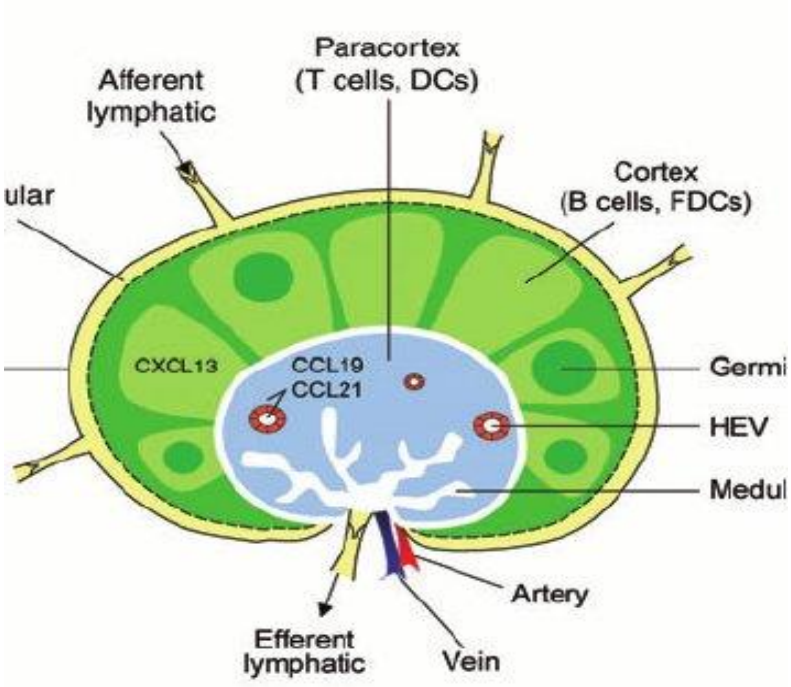
- Lymph nodes have a very **similar architecture to the spleen.**



- **B-cell follicles with similar structure and composition** to those in the spleen are located just under the outer capsule in cortex.

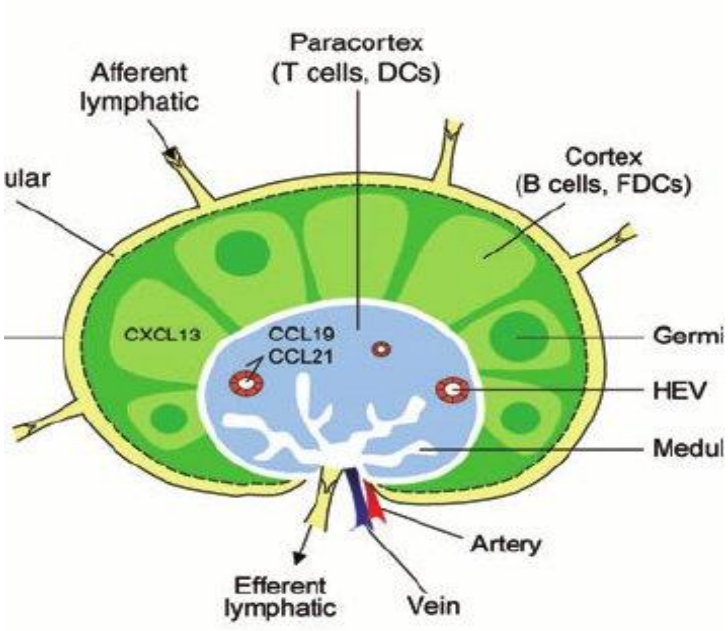


- Newly formed lymphocytes enter the lymph node from the blood through the walls of specialized blood vessels, the **high endothelial venules (HEVs),** which are located within the **T-cell zones (paracortex)**.



- **Naive B cells** migrate through the T-cell area to the **B cell follicle** where, unless they encounter their specific antigen and become activated, they remain for about a day.

- B cells and T cells leave the lymph node via the **efferent lymphatic**, which returns them eventually to the blood.



- Vessels that bring lymph to lymph nodes are called **afferent** lymphatics

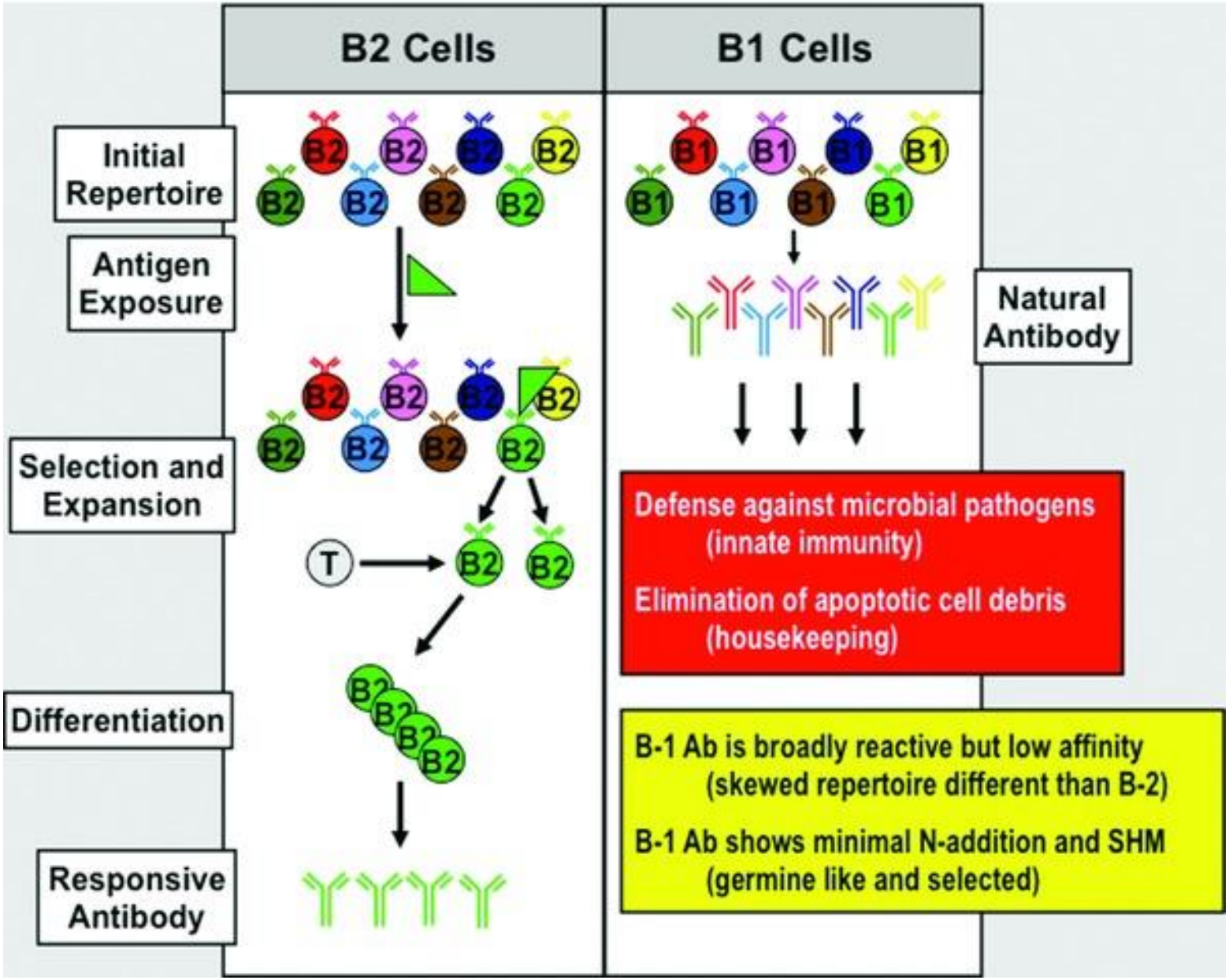
Two lineages of B cells

B-1

- Express **CD5** and **mIgM**
- **Less than 5%** of circulating B cells
- More than **95%** of B cells in **peritoneum**
- Appear during **fetal development** (arise in the bone marrow)
- Produce **low affinity**, **broad specificity mIgM** (natural antibody) required to launch an immune response

B-2

Majority of the mature B cells **expressing the BCR** (B cell receptor).


B2 Cells
B1 Cells
Initial Repertoire
Antigen Exposure
Selection and Expansion
Differentiation
Responsive Antibody
Natural Antibody
T
Defense against microbial pathogens (innate immunity)
Elimination of apoptotic cell debris (housekeeping)
B-1 Ab is broadly reactive but low affinity (skewed repertoire different than B-2)
B-1 Ab shows minimal N-addition and SHM (germine like and selected)

B Cell Activation and Proliferation

- **Antigen-driven B cell activation** and **clonal selection** of mature B cells leads to generation of **plasma** and **memory B cells.**

- This process is regulated by two types of antigens:

1. **TI (Thymus independent)**
2. **TD (Thymus dependent)**

TI antigen

Thymus independent antigen

No direct contact with **TH (T helper)** cells **required**

TD antigen

Thymus dependent antigen

Requires direct contact with **TH (T helper) cells**

TI antigen

TI- Type 1

Bacterial cell wall components, e.g., **LPS** on gram-negative bacteria

TI- Type 2

Repetitious molecules e.g. polymeric proteins, bacterial cell wall polysaccharides with repeating units, bacterial flagellin

Activation of B cells by TI antigens

TI-1

These antigens have **intrinsic** B cell activation activity by attaching to **Toll-like receptors**

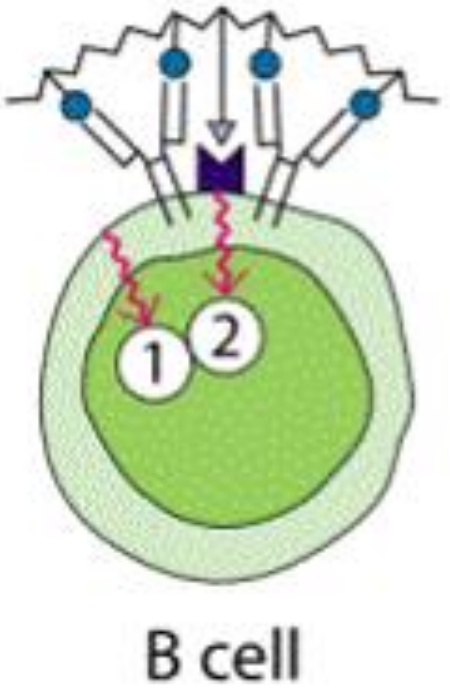
- **Antigen concentration** is **important**
- **Low concentrations** activate B cells **specific for an Ag epitope**
- **High concentrations** lead to **polyclonal activation**
- Activate mature B cells by **cross-linking the BCR** (mIgM and associated molecules)

TI-2

- They also activate mature B cells by **cross-linking the BCR**
- Require **TH cell cytokines** for efficient **B cell proliferation** and **class switching**

There are **two** signals for activation :

1. Attachment to **BCR**
2. Attachment to **CD 45R**



* CD45 is present on all mature white blood cells except plasma cells.

TD antigens

These antigens **activate** B cells in various steps:

- Once a BCR binds a TD antigen, the antigen is taken up into the B cell through **receptor-mediated endocytosis**, degraded, and presented to T cells as peptide pieces in complex with **MHC-II molecules** on the cell membrane.

- **T helper (TH) cells**, typically follicular T helper (TFH) cells, that were activated with the **same antigen** recognize and bind these MHC-II-peptide complexes through their **T cell receptor (TCR).**

- Following **TCR-MHC-II-peptide binding**, T cells express the surface protein **CD40L** as well as cytokines such as **IL-4** and **IL-21**.

- **CD40L** serves as a necessary co-stimulatory factor for B cell activation by binding the B cell surface receptor **CD40**.

- It promotes B cell **proliferation**, **Ig class switching;** and **somatic hypermutation** (which leads to affinity maturation).

* Somatic hypermutation is **a process that allows B cells to mutate the genes that they use to produce antibodies**.

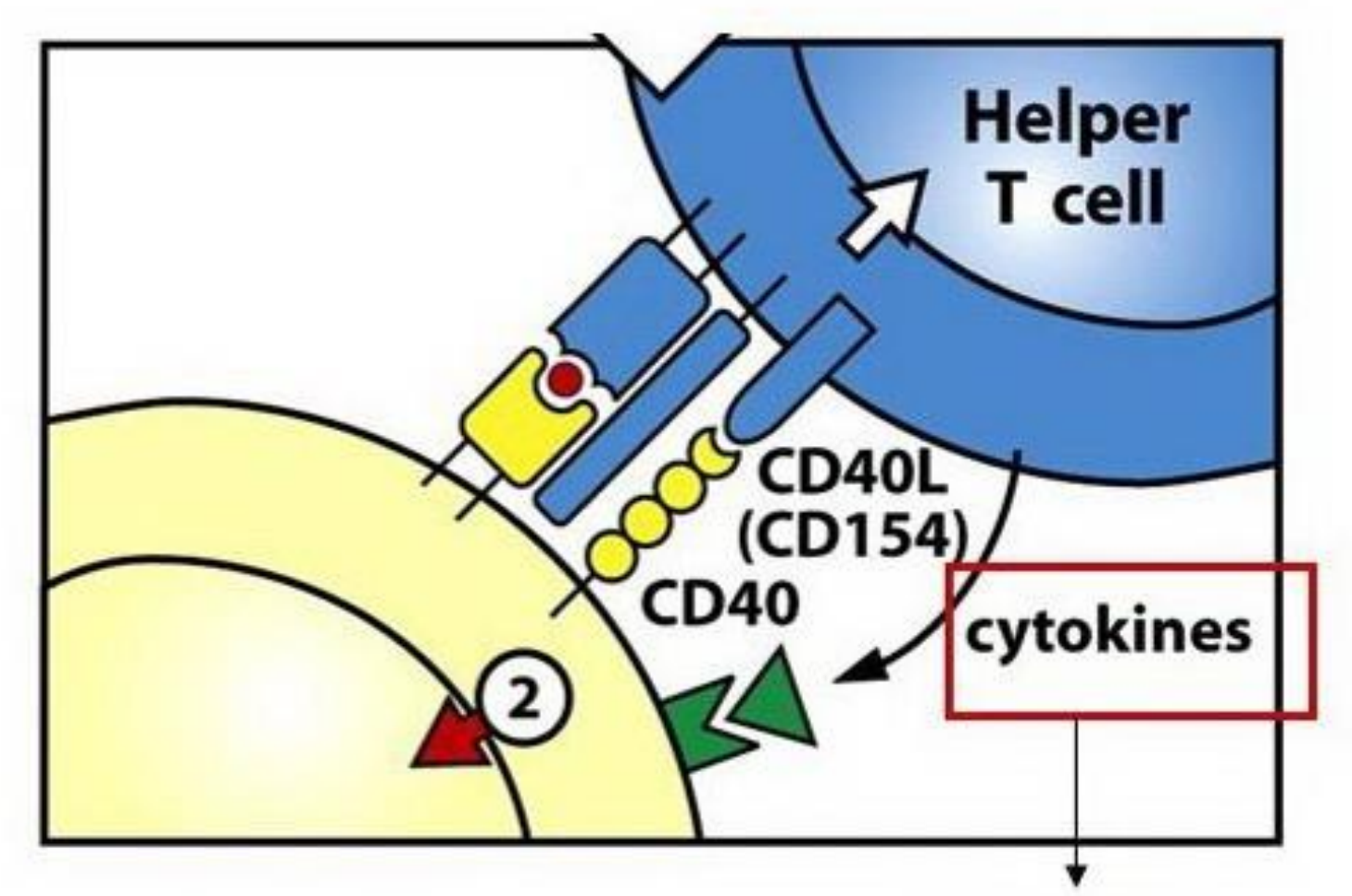
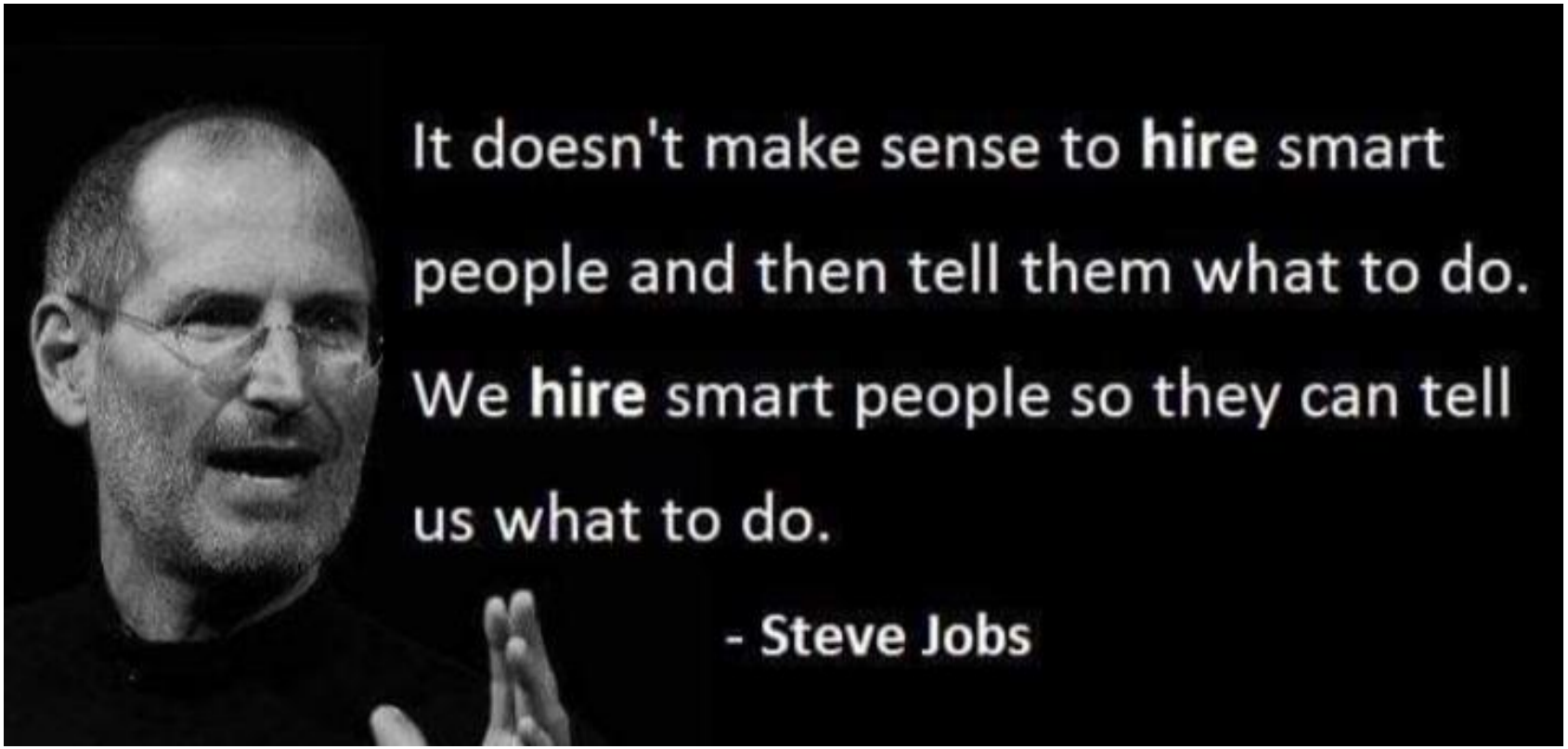

Helper
T cell
CD40L
(CD154)
CD40
cytokines
2

TABLE 11-2 Properties of thymus-dependent and thymus-independent antigens

Property	TD antigens	TI ANTIGENS	
		Type 1	Type 2
Chemical nature	Soluble protein	Bacterial cell-wall components (e.g., LPS)	Polymeric protein antigens; capsular polysaccharides
Humoral response			
Isotype switching	Yes	No	Limited
Affinity maturation	Yes	No	No
Immunologic memory	Yes	No	No
Polyclonal activation	No	Yes (high doses)	No


It doesn't make sense to **hire** smart people and then tell them what to do. We **hire** smart people so they can tell us what to do.
- Steve Jobs


Thank You!