CLUSTER OF DIFFERENTIATION

CD (cluster of differentiation)

To understand cell-cell communication, it is important to have an **overview** of molecules involved.

The **cluster of differentiation** (abbreviated as **CD**) is a *protocol used for the identification and investigation of* ***cell surface molecules*** *present on* ***leukocytes***.

CD molecules can act in numerous ways, often acting as **receptors** or **ligands** important to the cell.

- The **CD nomenclature** was proposed and established in the 1st International Workshop and Conference on Human Leukocyte Differentiation Antigens (**HLDA**), which was held in Paris in 1982.

- This system was intended for the classification of the many **monoclonal antibodies (mAbs)** generated by different laboratories around the world against **epitopes** on the **surface molecules** of **leukocytes.**

- Since then, its use has expanded to **many other cell types**, and almost **400 unique CD clusters** and **subclusters** have been identified.

- The proposed surface molecule is assigned a CD number once **two** specific **monoclonal antibodies (mAb)** are shown to bind to the molecule.

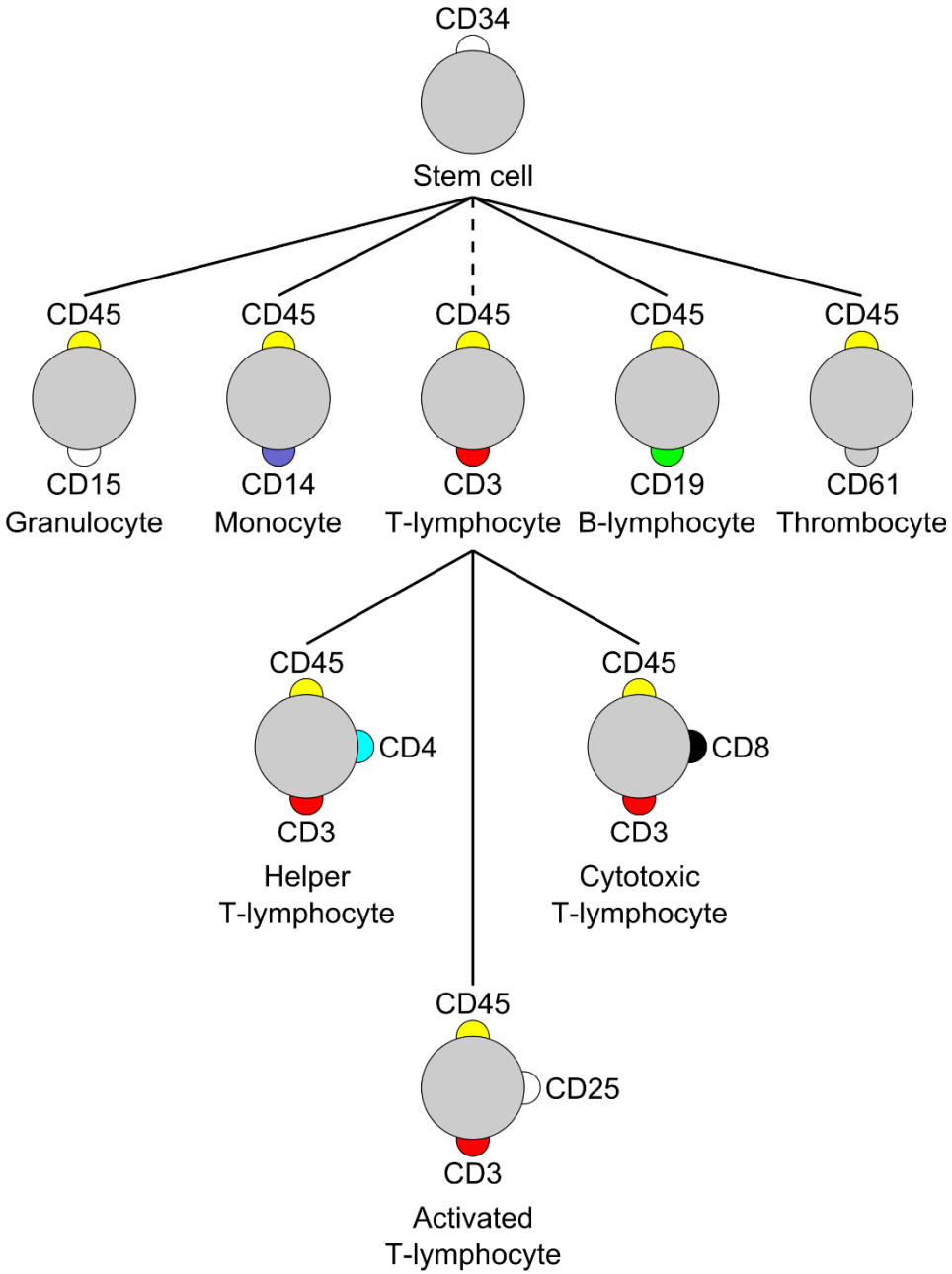
- If the molecule has not been well-characterized, or has only **one** mAb, it is usually given the provisional indicator **"w"** (as in "CDw186").

- The **CD system** is commonly used as **cell markers**; this allows cells to be defined based on what molecules are present on their surface.

- These markers are often used to **associate** cells with certain **immune functions or properties**.

- Using **one** CD molecule to define populations is **uncommon**.

- **Combining different markers** has allowed to identify cell types with **very specific definitions** within the immune system.


CD34
Stem cell
CD45
CD15
Granulocyte
CD45
CD14
Monocyte
CD45
CD3
T-lymphocyte
CD45
CD19
B-lymphocyte
CD45
CD61
Thrombocyte
CD45
CD4
CD3
Helper
T-lymphocyte
CD45
CD8
CD3
Cytotoxic
T-lymphocyte
CD45
CD25
CD3
Activated
T-lymphocyte

- Some CD proteins **do not** play a role in **cell signaling**, but have other functions, such as **cell adhesion**.

- Cell populations are usually defined using a **'+'** or a **‘-'** symbol to indicate whether a certain cell fraction **expresses or lacks** a CD molecule.

  For example, a **"CD34+ , CD31-"** cell is one that expresses **CD34**, but not **CD31.**

Some important CD molecules

CD34

- **CD34** molecule is present on certain cells within the human body.
- It is a cell surface **glycoprotein** and functions as a cell-cell adhesion factor.
- It may also mediate the attachment of **stem cells** to **bone marrow extracellular matrix** or directly to **stromal (connective tissue) cells.**
- CD34+ cells are normally found in the **umbilical cord** and **bone marrow** as **hematopoeitic cells, endothelial progenitor (ancestor) cells,** and **endothelial cells of blood vessels.**

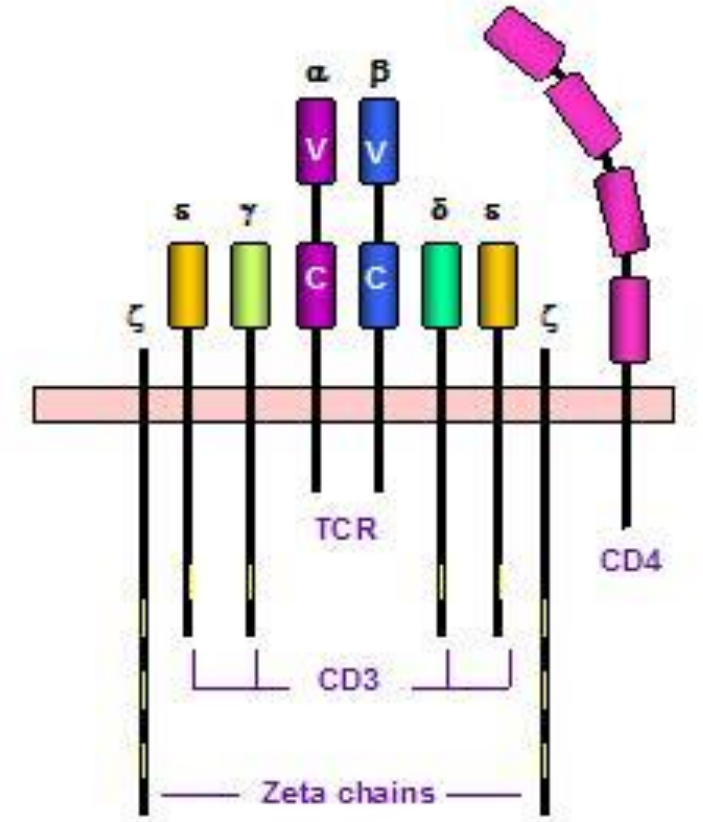
CD45

- **CD45** is a protein which was originally called ***leukocyte common antigen*** because it is present in all leukocytes**.**
- It is a member of the **protein tyrosine phosphatase (PTP)** family which are known to be **signaling molecules**.
- These molecules regulate a variety of cellular processes including **cell growth, differentiation, mitotic cycle,** and **oncogenic transformation.**
- It is a **type I transmembrane protein** (N-terminus extracellular) which is in various forms present on all **differentiated hematopoietic cells** except erythrocytes and plasma cells.

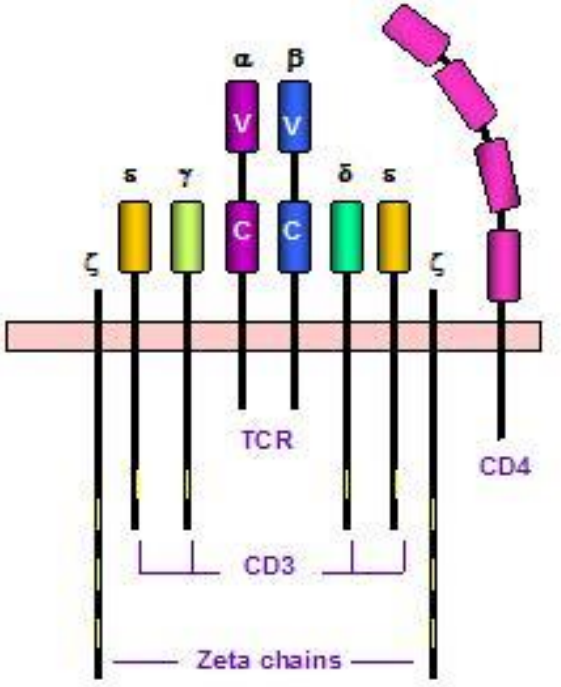
CD3

- **CD3** is a protein complex and is composed of **four** distinct chains.
- In mammals, the complex contains a **CD3γ** chain, a **CD3δ** chain, and two **CD3ε** chains.
- These chains associate with the **TCR** and the **ζ-chain** to generate an activation signal in T cells.
- The **TCR, ζ-chain** and **CD3** molecules together comprise the **TCR complex**.

- The transmembrane region of the **CD3** chains is **negatively** charged, a characteristic that allows these chains to associate with the **positively** charged TCR chains (**TCRα** and **TCR β**).



- The **intracellular tails** of the **CD3** molecules contain a single conserved motif known as an **immunoreceptor tyrosine-based activation motif (ITAM)** which is essential for the signaling capacity of the **TCR**.



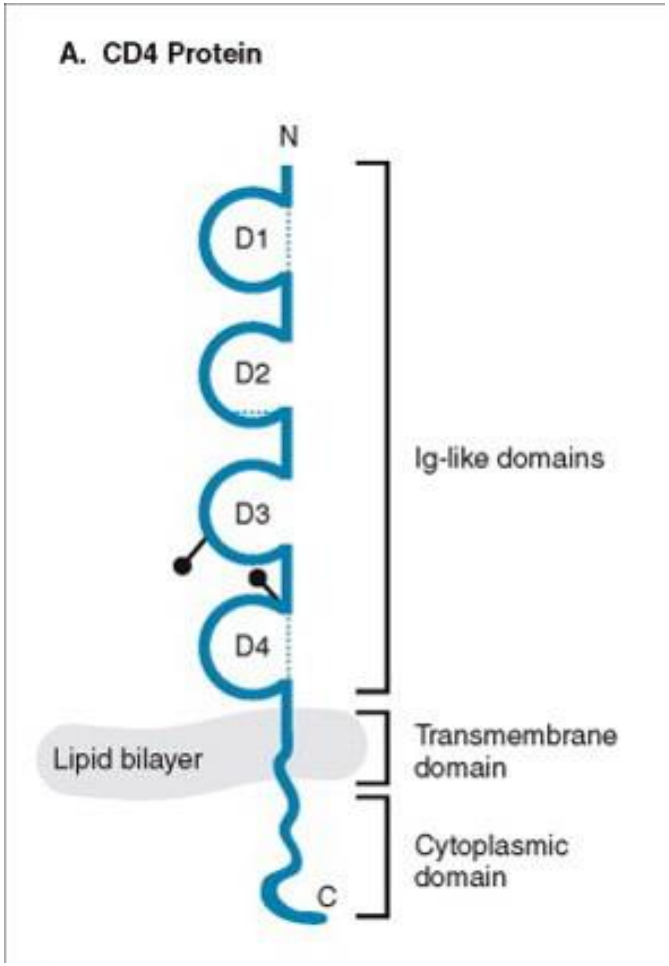
CD4

CD4 is a **glycoprotein** expressed on the surface of **T helper cells, regulatory T cells, monocytes, macrophages,** and **dendritic cells.**

CD4 has **four** immunoglobulin domains (D1 to D4) that are exposed on the extracellular surface of the cell:

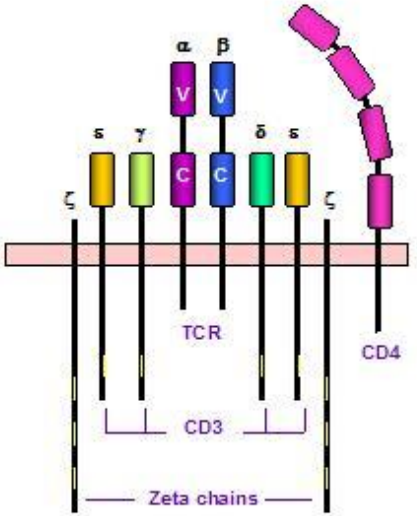
•**D1** and **D3** resemble **IgV** domains.

•**D2** and **D4** resemble **IgC** domains.



- On T cells, CD4 is a **co-receptor** that assists the **TCR** to activate its T cell following an interaction with an **APC.**

- With its **intracellular portion,** CD4 amplifies the signal generated by the TCR by recruiting **tyrosine kinase lck (lymphocyte specific),** which is essential for activating many molecules involved in the signaling cascade of an activated T cell.



CD8

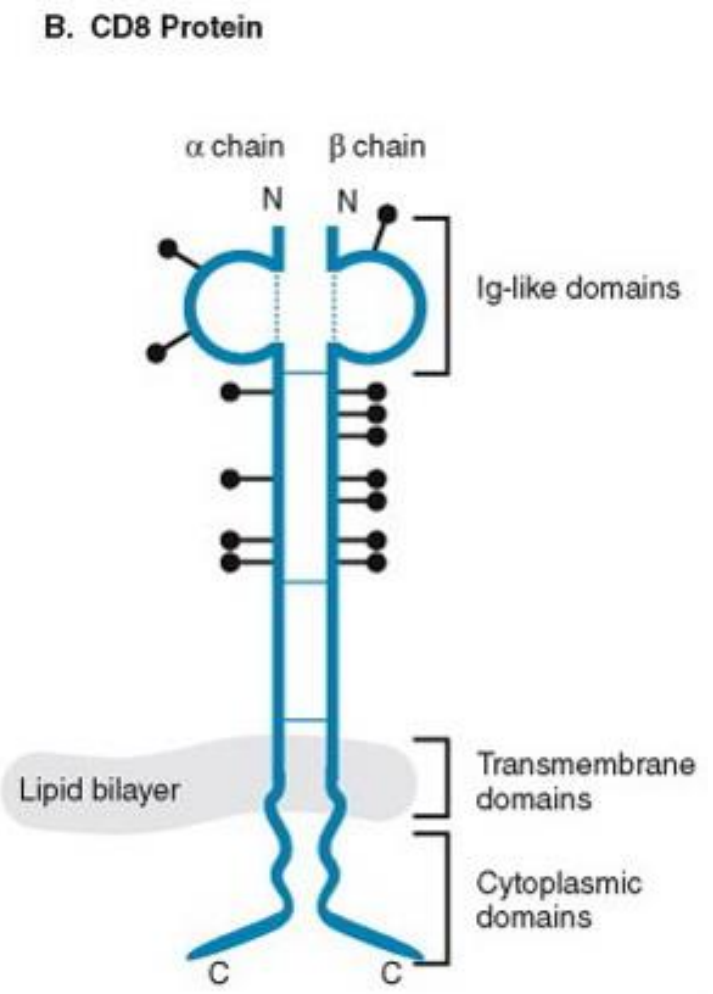
- **CD8** is a **transmembrane glycoprotein** that serves as a **co-receptor** for the **TCR.**
- Like the TCR, CD8 binds to a MHC molecule, and is specific for **class I MHC.**
- It is predominantly expressed on the surface of **cytotoxic T cells**, but can also be found on **natural killer cells**.

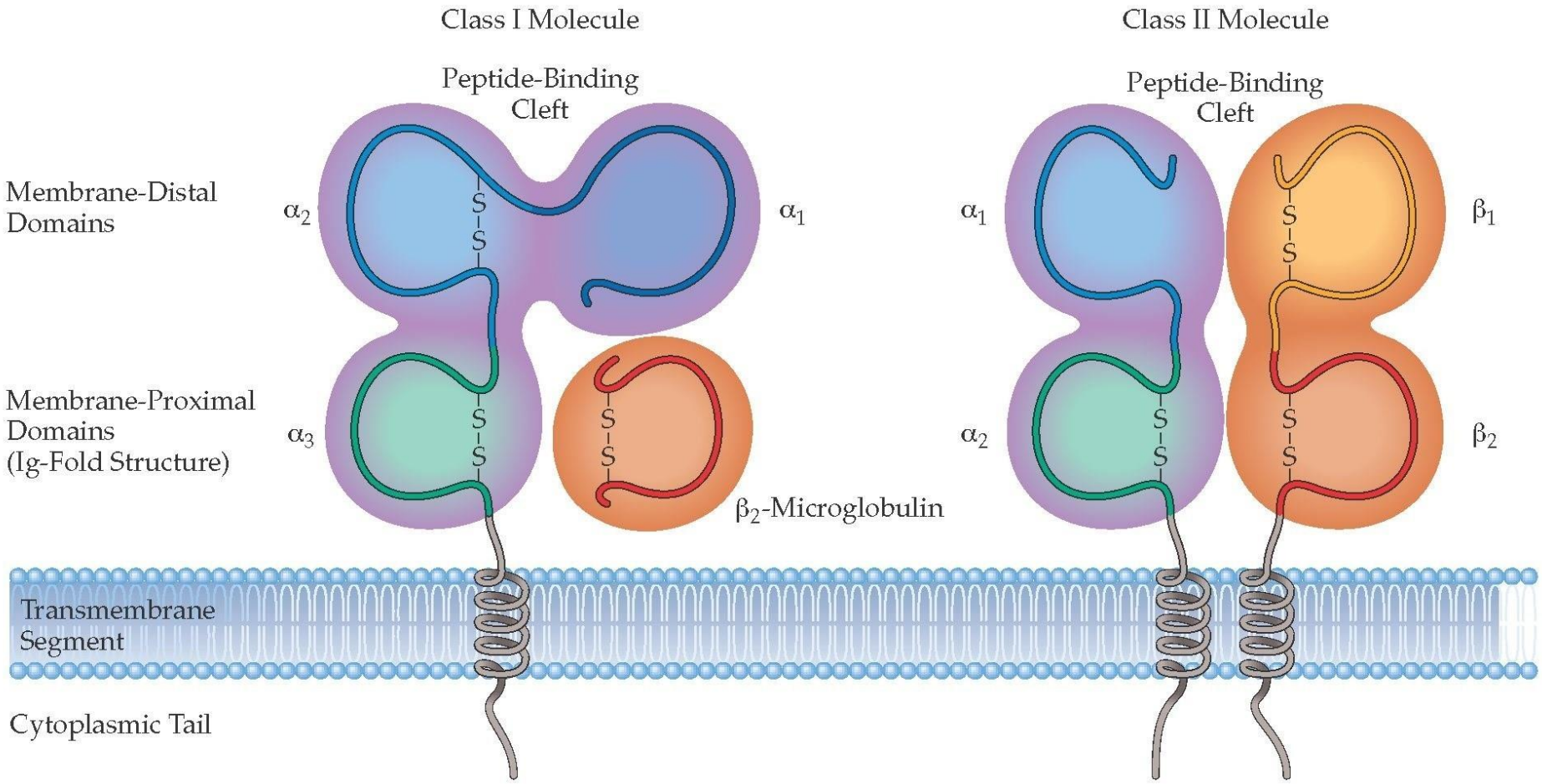
To function, **CD8** forms a dimer, consisting of a pair of CD8 chains.

The most common form of CD8 is composed of a **CD8-α** and **CD8-β** chain.

Less-common **homodimers** of the **CD8-α** chain are also expressed on some cells.

The **extracellular IgV-like domain** of **CD8-α** interacts with the **α3** portion of the **Class I** MHC molecule.




Class I Molecule
Peptide-Binding Cleft
Membrane-Distal Domains
Membrane-Proximal Domains (Ig-Fold Structure)
α2
α1
α3
S
S
β2-Microglobulin
Transmembrane Segment
Cytoplasmic Tail
Class II Molecule
Peptide-Binding Cleft
α1
β1
α2
β2

CELL - CELL COMMUNICATION

Cell-cell communication can essentially be divided into:

a) communication by cell-cell contact

b) communication by secretion of cytokines

Critical cell-cell contact events

In the generation of immune responses there are at least **3 critical cell-cell contact events** required.

First event

- The **first event** is when a **naive T cell** initially contacts its' **specific antigen** (via APC).
- In normal situations the critical APC is the **dendritic cell**.
- Because of the requirement for MHC presentation this is an **obligate** cell contact event.

Second event

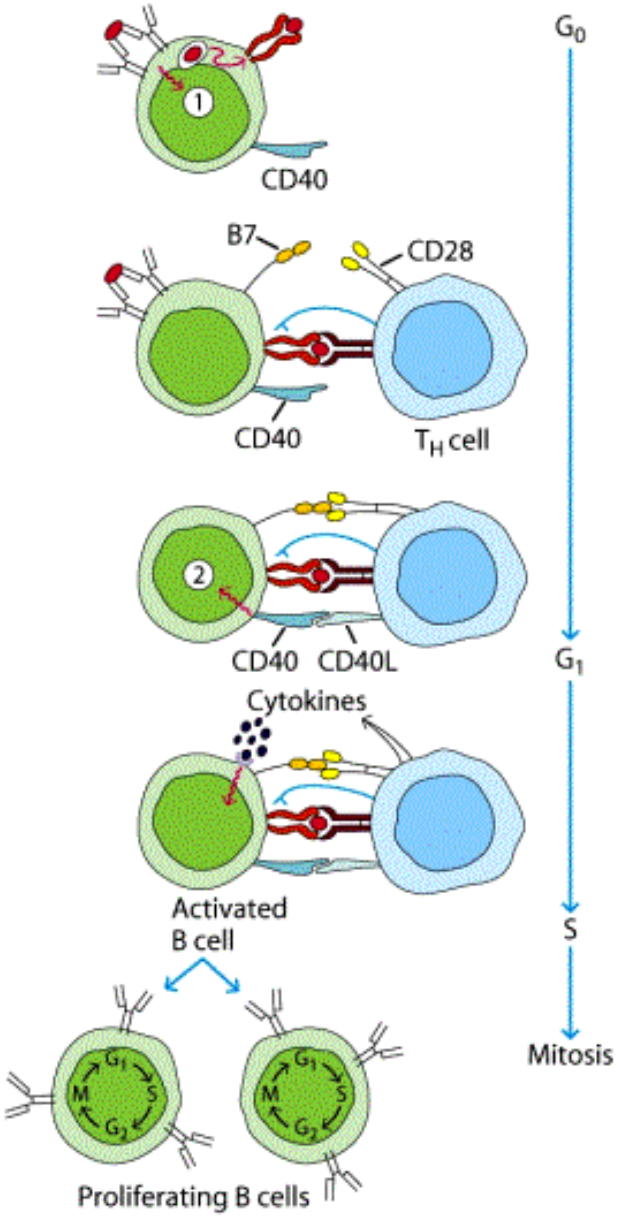
- The **second** essential cell-cell contact is between the activated **T helper cell** and an **antigen-specific B cell.**
- Most antigens are what we term **T-dependent**, that is the antibody response to them absolutely requires **T cell help**.
- This help is delivered by both **cytokines** and **cell-cell contact.**
- B cells bind specific antigen directly via their **surface Ig**, endocytose, process and present it on their **class II MHC molecules.**
- This enables them **to be recognized by activated T cells** (for specific antigen).

- This cell-cell interaction also requires **CD28** binding to **CD 80** or **CD 86** on the B cell.

- In addition, activation of the T cell induce expression of a molecule called **CD40** ligand or **CD40L** which binds to **CD40** on B cells.

- Crosslinking **CD40** promotes B cell proliferation, prevents apoptosis of germinal-center B cells and promotes immunoglobulin isotype switching.

- The **CD28- CD 80/CD 86** and **CD40-CD40L** receptor ligand interactions are both essential for the dialogue between B and T cells.


G0
1
CD40
B7
CD28
CD40
TH cell
2
CD40
CD40L
G1
Cytokines
Activated
B cell
S
Mitosis
G1
M
S
G2
Proliferating B cells

Third event

- The **third** cell-cell interaction essential in immune responses is the binding of activated B cells with **follicular dendritic cells (FDC)**, which have migrated into a specialized structure in lymphoid organs called **germinal centers.**

- **FDC** are **specialized stromal cells** which hold the **intact** (unprocessed) antigen on their surface in the form of **long-lived immune complexes.**

- Follicular DCs receptors **CR1**, **CR2** and **FcγRIIb** trap antigen **opsonized** by complement or antibodies.

- Among other molecules, Follicular Dendritic Cells express **CD23** which binds to GC (germinal center) B cells via their **CR2** receptor and stimulates **differentiation** to **plasma cells**.

- Also to become selected as a future **memory cell**, GC B cells must bind the antigen presented on FDCs, otherwise they enter **apoptosis**.


ARIF ALI/AFP


"NO MATTER HOW GOOD
OR BAD YOUR LIFE IS,
WAKE UP EACH MORNING
AND BE THANKFUL YOU
STILL HAVE ONE.


Thank You!