Immunology:

- Innate immunity
- NK cells
- NKT cells
- Antigens
- Antibodies
- Complement System

- MHC I antigens expressed on: – all nucleated cells
  – platelets.

- MHC II antigens expressed on: – only APC's.

- T cells recognize peptides.

- T cells are self MHC restricted
  - Th cells are self MHC class II restricted
  - T_c cells " " " " I " .

- T cells require 2 signals for activation:

(a) TCR recognizes peptides in the groove of self MHC – SIGNAL 1

(b) Co-stimulation – SIGNAL 2

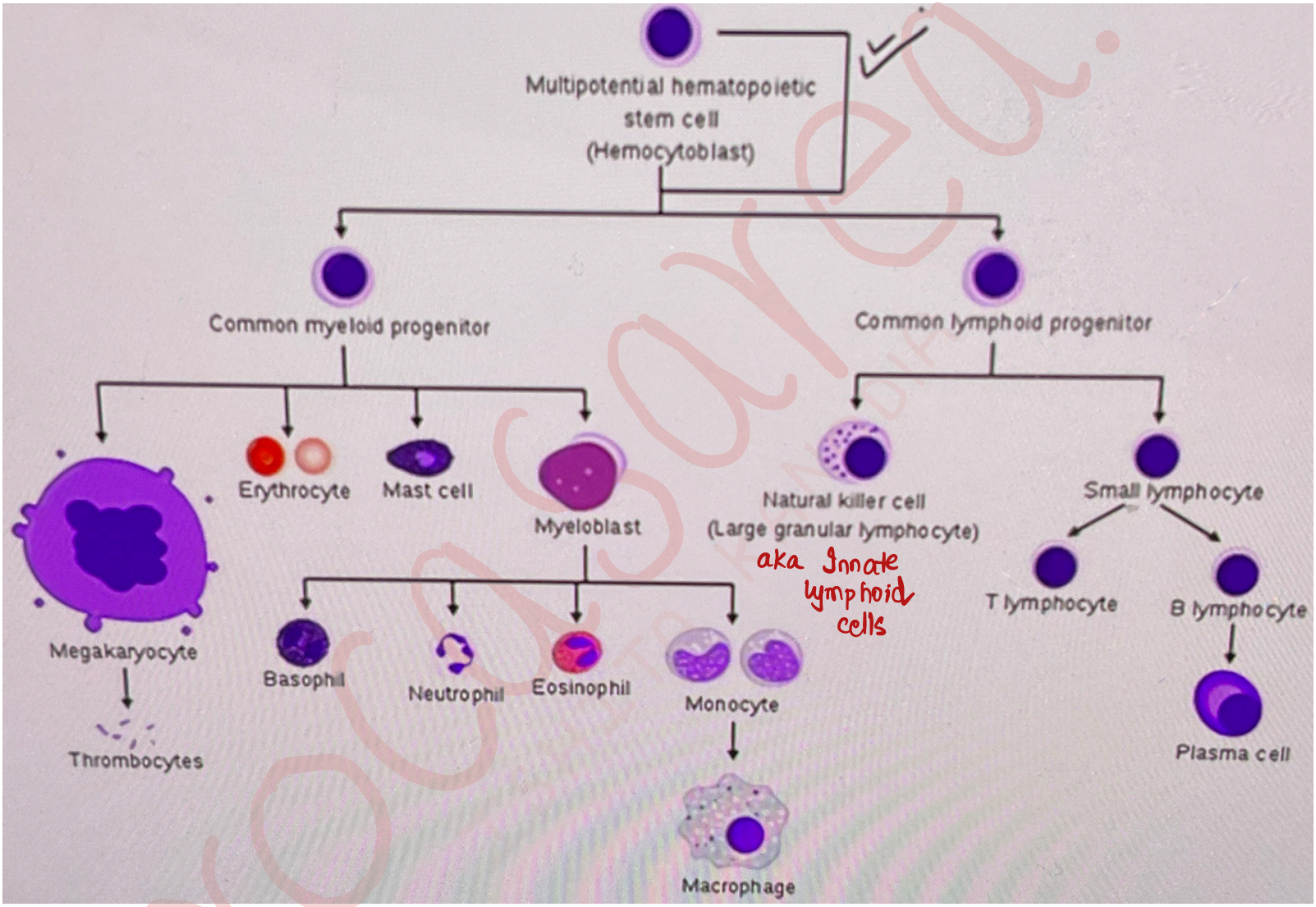
[CD 28 of T cell binds to B7 of APC].

B7.1 – CD80 ← → B7.2 – CD86.

Lymphoid Organs:

Primary: site of maturation of lymphocytes

- Bone marrow : B-cells
- Thymus : T-cells (formed in bone marrow but mature in thymus).



Secondary: Mature Ag specific lymphocytes first encounter Ag

↓

effector & memory B & T cells

- lymph nodes
- spleen
- MALT

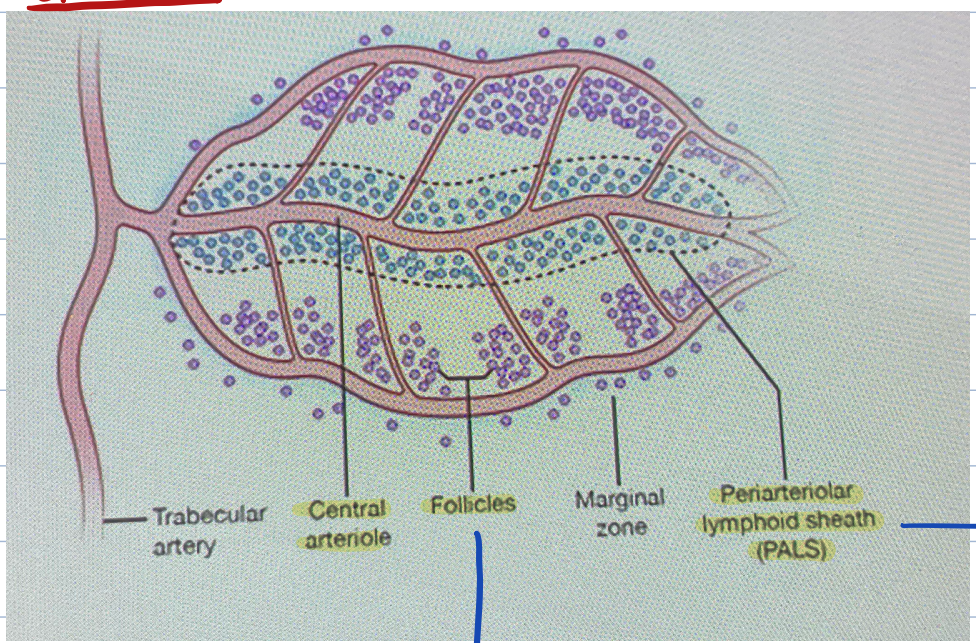
Lymph node:

Cortex : B cell dependent area

Paracortex: T cell dependent area

Medulla: macrophages & plasma cells.

SPLEEN:



→ T cell dependent zone

B cell dependent zone

Immunity: protection from infectious pathogens including host reactions against cancers, tissue transplant & self antigens.

Innate	Adaptive/ Acquired
→ 1st line of defence	→ 2nd line of defence
→ always present since birth	→ developed during lifetime by experience (activated only on exposure to antigen)
→ no lag phase (immediate action)	→ Lag time of response
→ Receptors of innate immunity recognize broad molecular patterns shared by several pathogens ⇒ PAMP's [pathogen associated molecular patterns].	→ Receptors recognize organism specific antigens • T cell receptors (TCR) • B cell receptors (BCR)
eg: – TLR-4 receptor recognizes LPS of gram -ve bacteria – flagellin – ssRNA.	
• These receptors aka Pattern Recognition Receptors (PRR's)	→ narrow specificity & unlimited diversity.
→ PRR's have a broad specificity but limited diversity	→ genes for these receptors are generated by somatic recombination in primary lymphoid organs.
→ PRR are encoded in germ-line DNA.	
→ No memory.	→ memory present.

Components of Innate Immunity:

① Anatomical & physiological barriers

(a) skin with acidic pH (due to lactic acid & other fatty acids in sebum)

(b) mucosum membranes

(c) Acidic pH of stomach

(d) Antimicrobial peptides in blood & mucous secretions

eg: α, β - defensins, hepcidins, cathecidines

(e) Lysozyme & other hydrolytic enzymes in tears, saliva & mucous secretions

(f) Commensal Flora - provide colonisation resistance

② Monocytes, tissue macrophages → marker: CD14

③ Neutrophils, eosinophils, basophils → marker: CD66b

④ NK cells (marker ⇒ CD16, CD56)

⑤ Mast cells

⑥ Dendritic cells

⑦ NKT cells

⑧ γδ T-cells.

⑨ Complement System: 11 complement proteins + several regulatory proteins

- C1q, C1r, C1s ⇒ C1 complex ($C1q_1r_2s_2$)
- C2 - C9

Most abundant complement protein: C3.

→ generally synthesized in liver

Complement	Site of Synthesis
C3, C6, C9	Liver
C5, C8	Spleen
C2, C4	Macrophages
C1	Intestinal epithelium
C7	– Not Known –

Pattern Recognition Receptors: Properties

- Broad Specificity
- Limited diversity
- Encoded in the germline DNA.

① **Secreted Molecules:** present normally in blood

- **C-Reactive Protein:** reacts with C carbohydrate antigen of pneumococcus
  - β-globulin ; synthesized in the liver
  - recognizes phosphocholine residues on any pathogen

↓

activates the complement system

- **Mannose-Binding Lectin:**
  - when it recognizes mannose residues on the surface of any pathogen

↓

activates complement system

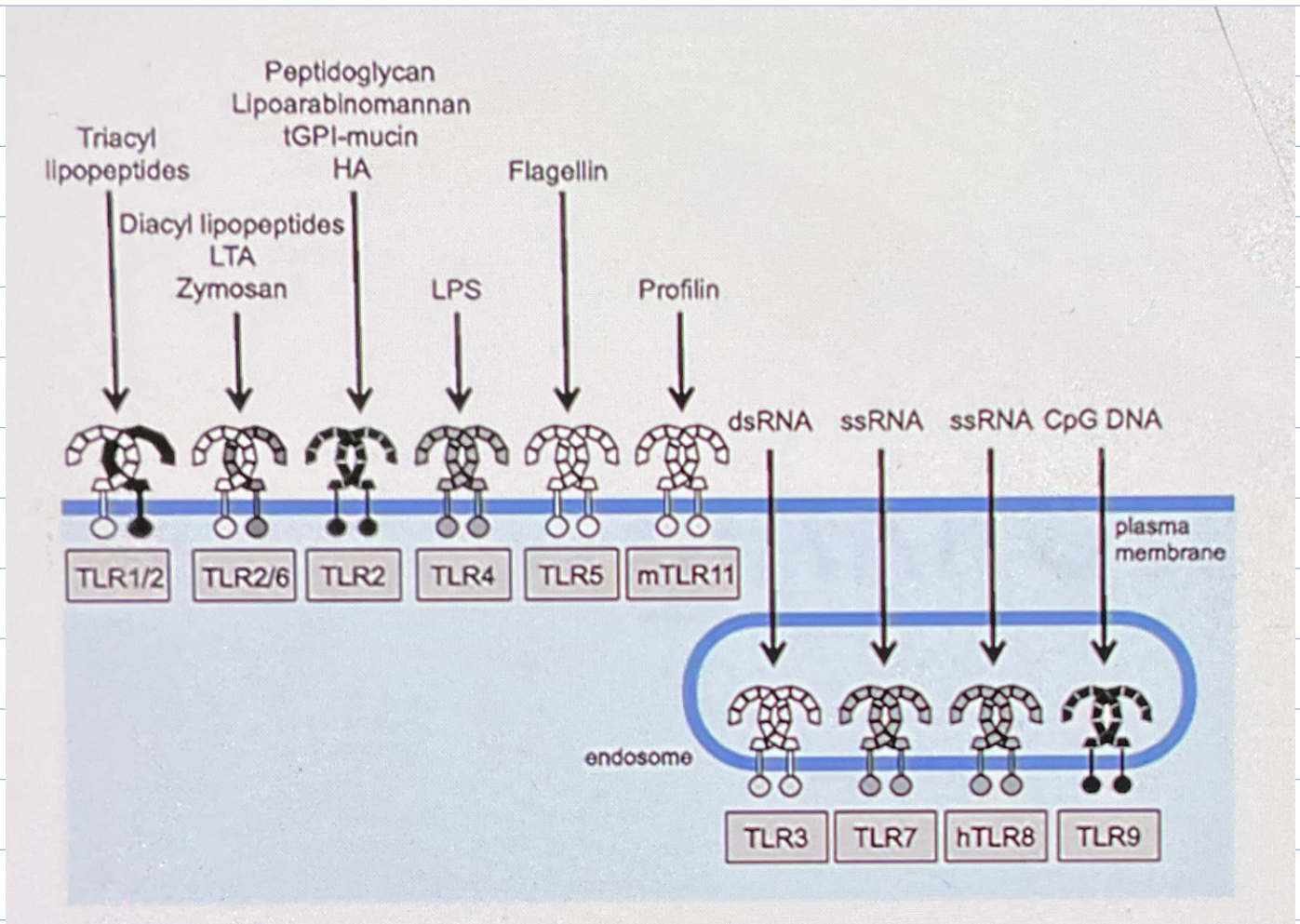
② Phagocytosis Receptors: present on phagocytic cells
→ on binding their PAMPs
↓
induce phagocytosis of antigen
eg: - Glucan receptors
- Mannan "
- Scavenger "

③ Cell Surface, Cytoplasmic & Endosomal Receptors:
→ they induce cytokine release by activation of nuclear transcription factor [NTF - kB].

• Toll-like receptors (TLRs): named after toll protein (present in fruit fly of drosophila) which have a similar structure
→ In humans there are 10 known TLRs

TLR	LIGAND	MICROORGANISM
TLR - 1	Triacyl lipopeptides	• Mycobacterial cell wall • Gram -ve cell wall
TLR - 2	- Peptidoglycan - Zymosan - Lipomannans	• gram +ve bacteria • Fungal cell wall • Mycobacterial cell wall
TLR - 3	ds RNA	• certain viruses
TLR - 4	- Lipopolysaccharide (LPS) - F protein - G glycoprotein	• all gram - ve bacteria • respiratory syncytial virus • Rhabdoviruses

TLR	LIGAND	MICROO
TLR-5	Flagellin	• Bacteria
TLR-6	Diacyl lipopeptides	• Mycobacterial cell wall • Gram +ve cell wall
TLR-7 TLR-8	ss RNA	• Viruses
TLR-9	unmethylated CG dinucleotides	• Viruses • bacteria
TLR-11	Profilin	• Toxoplasma cell wall



- **NOD-like Receptors (NLRs):** cytosolic;
  → recognize PAMP's [bacterial cell wall components]

- **RIG-like helicases (RLHs):** cytosolic
  → recognize viral RNA

- **(ALRs) AIM-2 Like Receptors:** cytosolic
  → recognize viral & bacterial DNA

- **C-type Lectin like receptors:** on cell surface
  → recognize bacterial carbohydrates.

Innate Lymphoid Cells [ILCs]:

→ lack antigen-specific receptors, but behave like helper T cells
∴ secrete cytokines

- Group 1 ILCs → secrete IFN-γ, TNF
- Group 2 ILCs → secrete IL-4, 5, 13
- Group 3 ILCs → secrete IL-22, 17, IFN-γ.

Natural Killer Cells (NK): belong to group 1 ILCs.
→ 5-10% of circulating lymphocytes
→ aka Null Cells ∵ they lack antigen-specific receptors
→ aka Large Granular lymphocytes
→ 12-15 μm in size
→ Marker ∵ CD16 - F_cR for IgG1
• CD56 - Neural CAM.

→ they are responsible for killing virus infected cells & malignant cells.
- NK cells recognize these cells due to reduced expression of MHC I

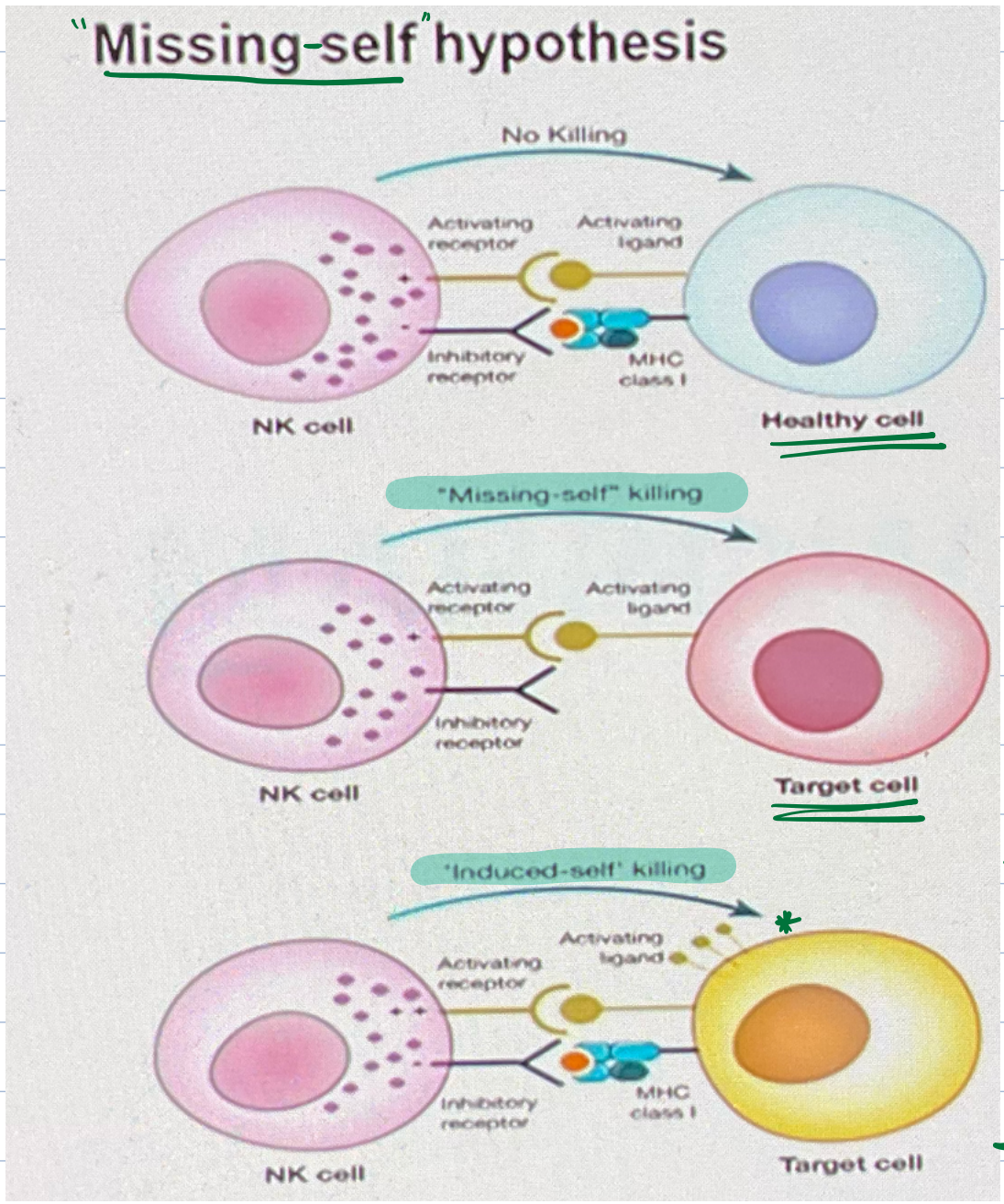
→ NK cells have 2 types of Receptors

Activating Receptor

→ recognize ligand expressed on 'stressed' cells

Inhibitory Receptor

→ Ligand : MHC I

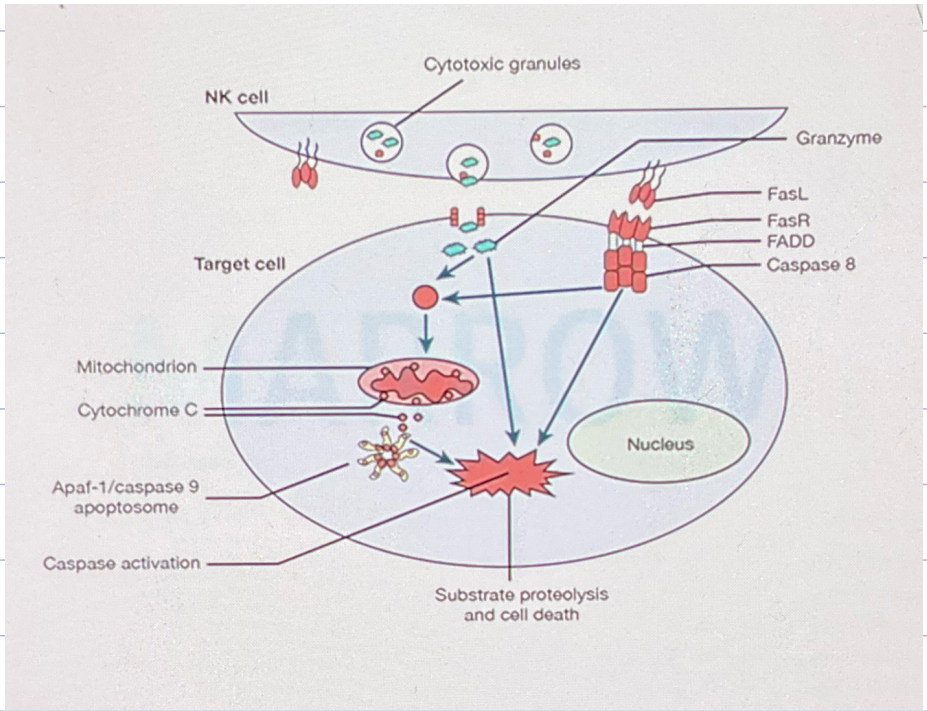


Though MHC I is found, many activating ligands (*) are also found
∴ Killing is induced.

NK cells induce apoptosis by:

(a) Degranulation – release of perforins & granzyme B (cytotoxic granules)

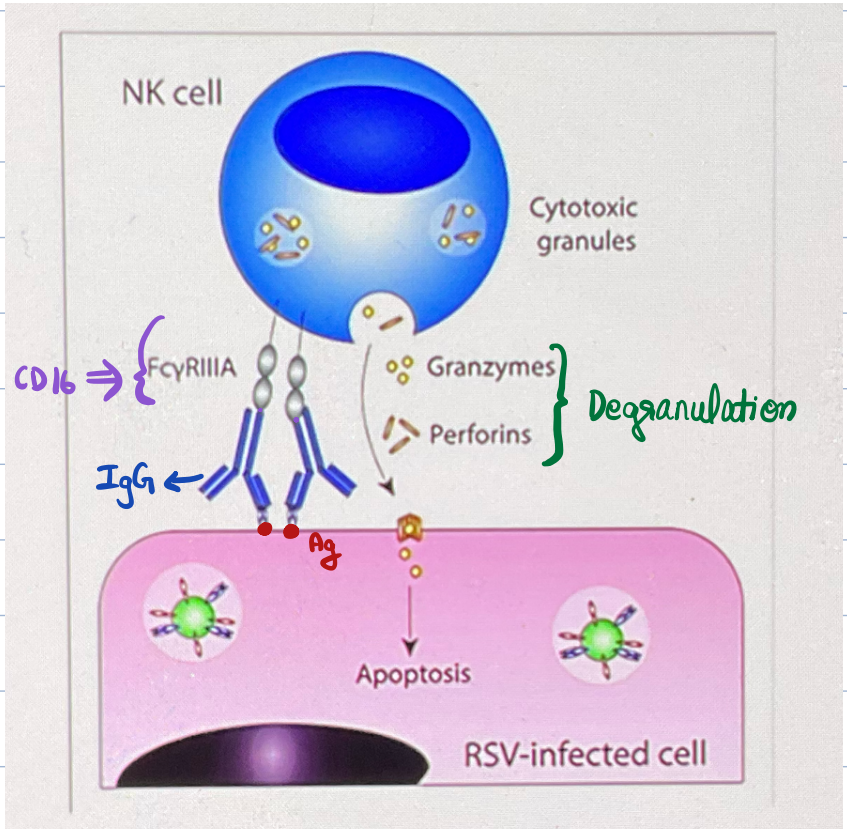
(b) Express FAS L (ligand) → Caspase activation → apoptosis of target cell



(C) Secrete Cytokines
- IFN - γ — Macrophage activating cytokine
- TNF α — Binds to TNF R on target cell & induces apoptosis
- Chemokines
  - CCL-3
  - CCL-4
  - CCS-5 / RANTES

} attraction of immune cycles

(d) Antibody - Dependant Cell Cytotoxicity [ADCC]: non - phagocytic killing of an antibody - coated cell or an antigen



Cytokines which activate NK cells - IL - 2, 12, 15
- IFN α
- IFN β.

- Under the influence of these cytokines:

NK cells ⟶ LAK cells (Lymphokine Activated Killer Cells)

Antigen (Ag): - when it enters the body, recognized by the immune system (antigenicity)
- able to induce an immune response (immunogenecity)

Hapten (Incomplete Ag): - antigenic, but not immunogenic

- Hapten + Carrier protein ⟶ Antigen (immunogenic)

Determinants of Immunogenicity:

1. **Chemical Nature:**
   - Proteins > polysaccharides > nucleic acid > lipids.
   - more the varieties of residues present in the substance, greater is its immunogenicity
2. **Molecular Weight:**
   - minimum: 5,000 – 10,000 D
   - more the Mol. wt., greater is the immunogenicity.
3. **Foreignness:** more distant the origen of a substance, greater is the immunogenicity.
4. **Susceptibility to Host (lysozomal) Enzymes**

Antigens
- T-dependent Ag
- T-Independent Ag

T- Independent Antigens	T dependent Antigens
→ B cells do not require the help of T_H cells to form Ab against such Ag. - simple proteins - polysaccharides - lipids - nucleic acids	→ T_H are required for B cells to produce Abs against such Ag - complex proteins
→ Polyclonal activation of B cells	→ Stimulation of Ag-specific B cells
→ IgM (mainly) formed ⇒ class switching is absent.	→ IgM $\xrightarrow[\text{switching}]{\text{class}}$ IgG, A, E (+)
→ Low affinity Abs are formed ⇒ affinity maturation is absent. (by somatic hypermutation)	→ Low affinity Abs $\xrightarrow[\text{maturation}]{\text{affinity}}$ High affinity Abs (+)
→ memory is absent	→ memory is present.

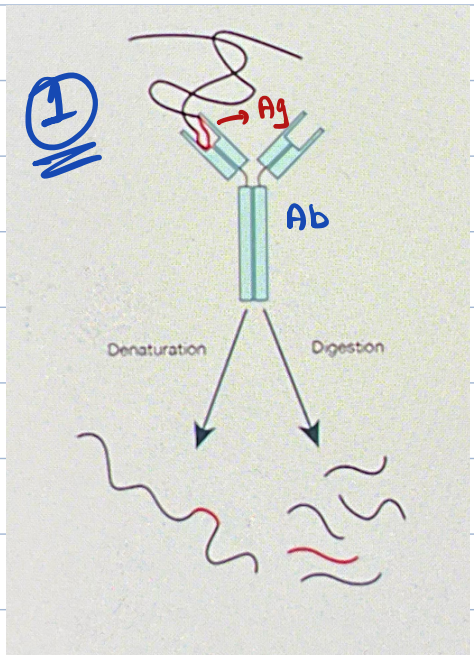
Epitope: small distinct part of an Ag which is recognized by the adaptive immune system (TCR / BCR / Ab)

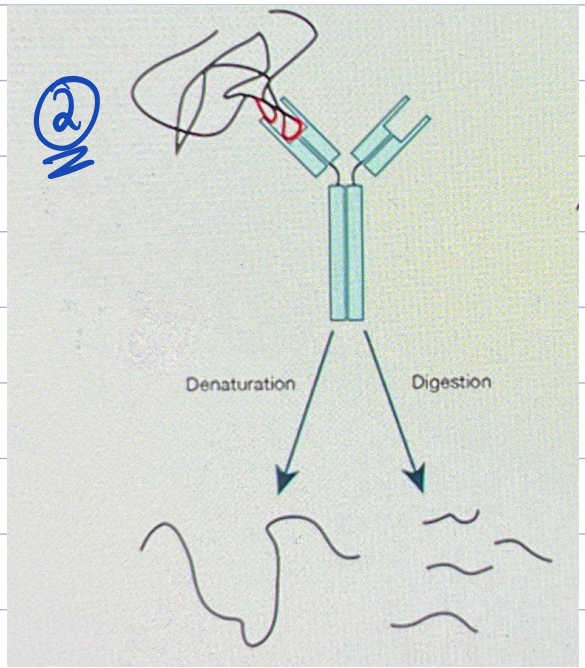
→ one Ag has many epitopes, against many of which an immune response is generated.

- epitopes against which immune response is generated: Immuno-Dominant Epitopes.

2 Types of Epitopes:

① **Linear / Sequential**: formed by residues next to each other in the primary structure of Ag.





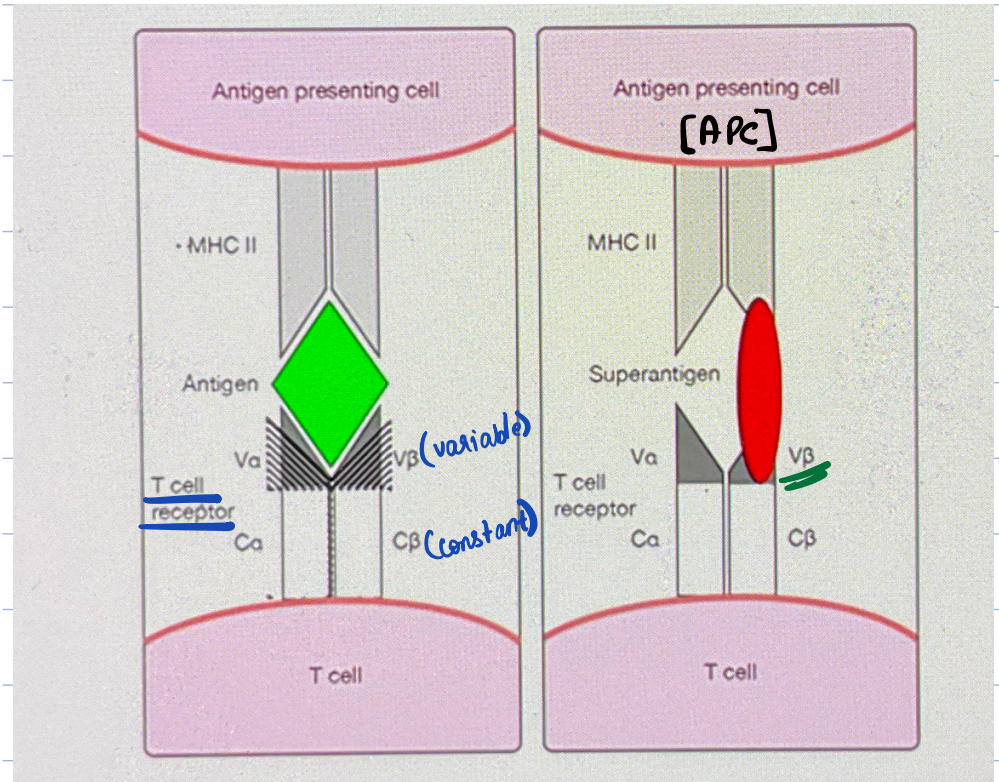
② **Conformational / Discontinuous Epitope**: formed by residues that are far apart in the primary structure of Ag, but are brought close to form epitope due to tertiary / quaternary folding of Ag.

→ T cells always recognize linear peptide epitopes only
→ B cells recognize both kind of epitopes.

Heterophile Ags: Ag that are shared over genera, classes & kingdoms
eg: Forssman ag → present in all prokaryotes & eukaryotes. (except rabbits).

Isoantigen: Ag present only in some members of the same species.
eg: - Blood group Ag
- Rh factor
- MHC Ag

Superantigens: T cell mitogens ⟹ can activate large number of T cells. (5 - 20%)



[Normal Ag < 0.0001%]

→ Super Ag need not be processed in the lysozome of APCs

→ They directly bind to MHC II of APC at a site lateral to the usual Ag presenting groove

→ They need to be recognized by just Vβ of TCR

(Many T_H cells share a common Vβ region)

→ 5 - 20% T_H cells recognize the Super Ag & get activated

⇓

All produce cytokines

⇓

TSS (toxic shock syndrome)

Affinity Maturation: connected with preferential survival of germinal centre (GC) B cells that have acquired increased affinity for antigen via somatic hypermutation of their Ig genes.

↓

Entry of naive & memory B cells

↓

Clonal expansion & mutation of B cells

↓

Binding of Ag by high-affinity B cells (by T-cell selection)

↓

Presention of Ag by FDC (follicular dendritic cells)

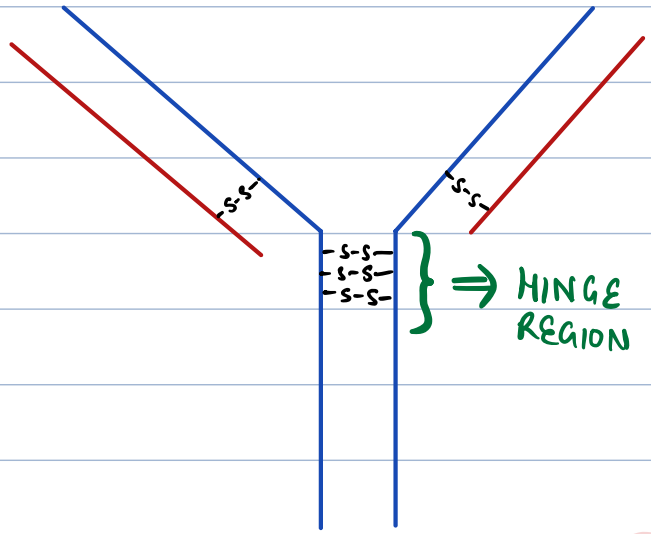
- → secretion of Ab
- → Export of memory & plasma B cells (with T cell circulation)
- → Apoptosis of low affinity GC B cells

recycling of GCB cells

Antibodies: glycoproteinaceous

↓

Constitute 20 - 25 % of serum proteins



⇒ HINGE REGION ⇒

- Each L is linked to H by 1 disulphide bond (DSB)
- The two H are linked to each other by 1-5 DSBs

→ Each Ab has: H_2L_2

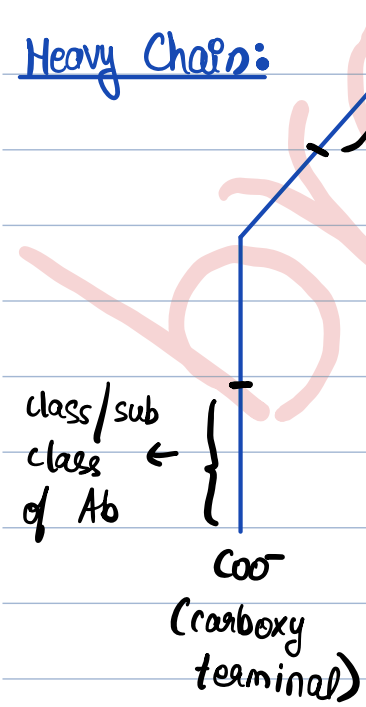
- 2 identical light chains $< \begin{matrix} k \\ \lambda \end{matrix}$
- 2 identical heavy chains ⟹ determines the class of Ab.

$(\gamma, \alpha, \delta, \mu, \varepsilon)$

4 types $(\gamma_1, \gamma_2, \gamma_3, \gamma_4)$

2 types (α_1, α_2)

Heavy Chain:



→ H chain :- 50,000 - 75,000 Da

- 446 to 576 $\bar{a}.\bar{a}$ with carbohydrate substitution

→ first 110 $\bar{a}.\bar{a}$ from amino terminal, determine the Ag binding

↳ V_H (variable part)

→ rest = C_H (constant)

→ first 110 ā.ā from carboxy terminal determine the class/subclass of heavy chain.

→ because of intrachain disulphide bonds, the heavy chain is folded into many globular domains.