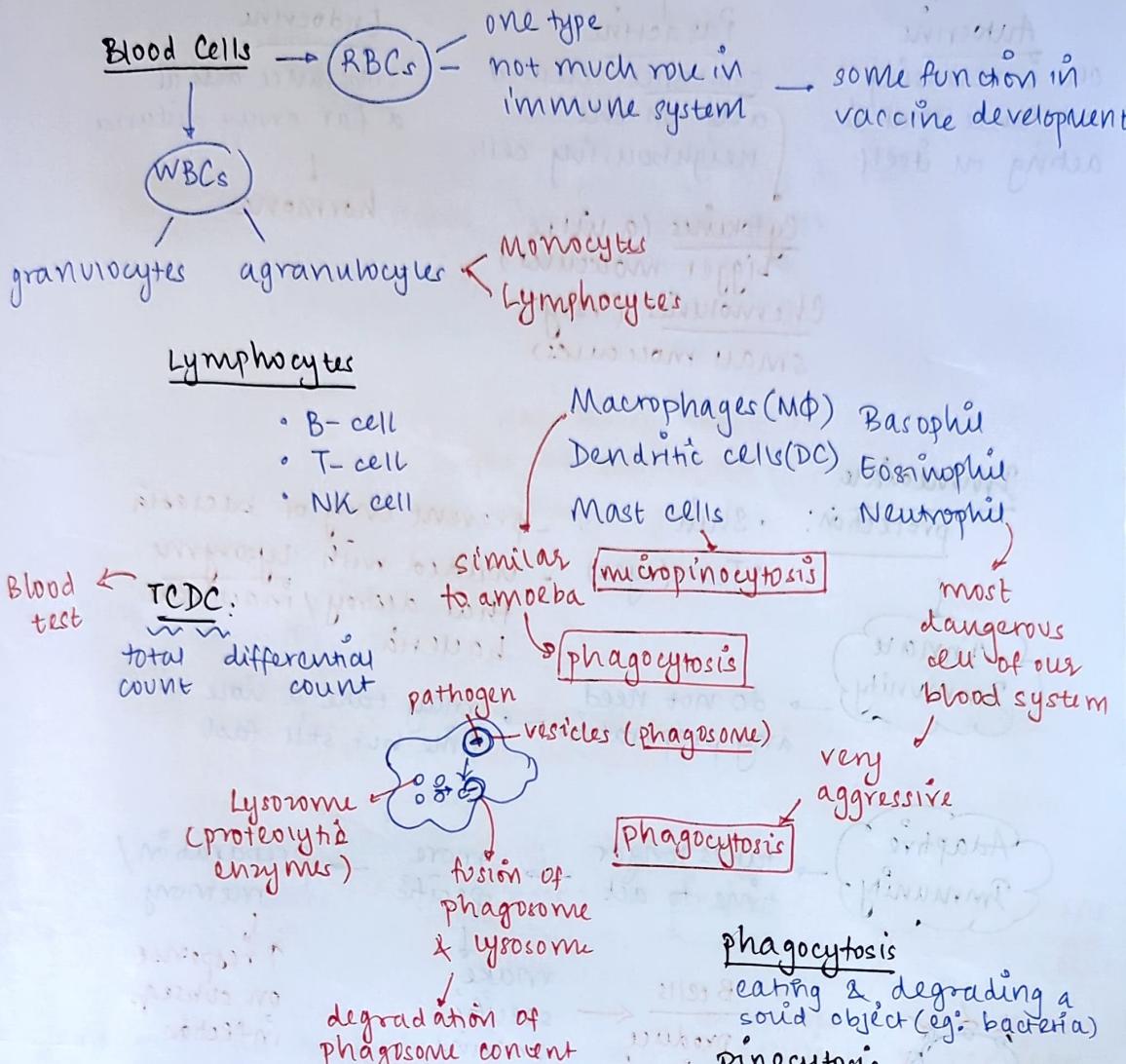
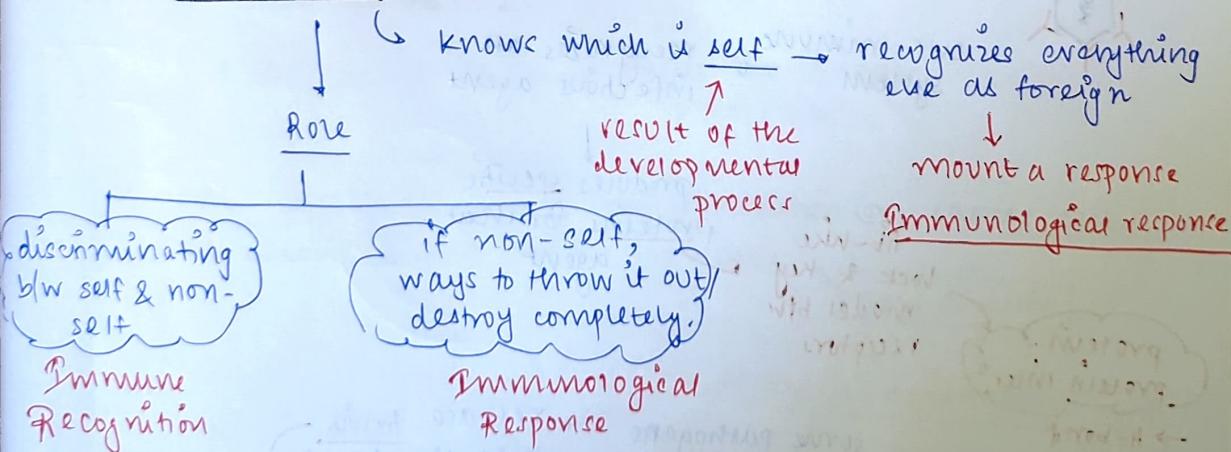


8/1/23



Immune system



Cytokine:

Signal Transduction

Autocrine
cell is releasing substance that is acting on itself

Paracrine

substance released acts on the neighbouring cells

Cytokines (a little bigger molecules)

Chemokines (very small molecules)

Endocrine

substance acts at a far away distance + hormones

Immediate protection:

• Skin → prevent entry of bacteria
• Tears(eyes) → loaded with lysozyme that destroy/inactivate bacteria.

Innate immunity

→ do not need any preparation → may take a little time but still fast

Adaptive immunity

→ takes longer time to act → more specific → preparation/memory

B cells → make specific proteins

very specific to diff. organisms..

↑ response on subseq. infection

our immune system → recognises an infectious agent

fit-like lock & key model b/w receptors
produces specific proteins for that agent

protein - protein inter²

- H-bond
- $\pi-\pi$ d.w.
- electrostatic
- hydrophobic

some pathogens

→ release toxins inside the blood/tissues

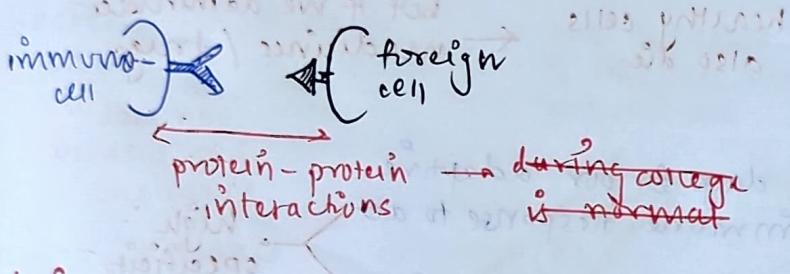
body creates antibodies to get rid of it.

non-living {
 metal substance → can induce the immune system even if no contamination on the metal substance
 glass substance

pavemaker/rod (bone) → made up of material that do not cause immunological power.

biomechanics, length & flexibility of the rod, etc.

artificial skin → needs a non-living base which might be destroyed by the immune system



when it is there, body knows something is there

learning about diseases & immunity

informⁿ from Mouse models

informⁿ from diseased patients

antiviral means killing our own cells

similar is the care with cancer treatment

✓ no antiviral medicine is possible → as viruses use our cellular machinery to replicate
✓ only immune system can kill viruses
✓ one virus/bacteria enters our body → they grow to a certain number → then cause the disease
↳ not enough to cause disease

↑ the initial no. → faster the disease progression

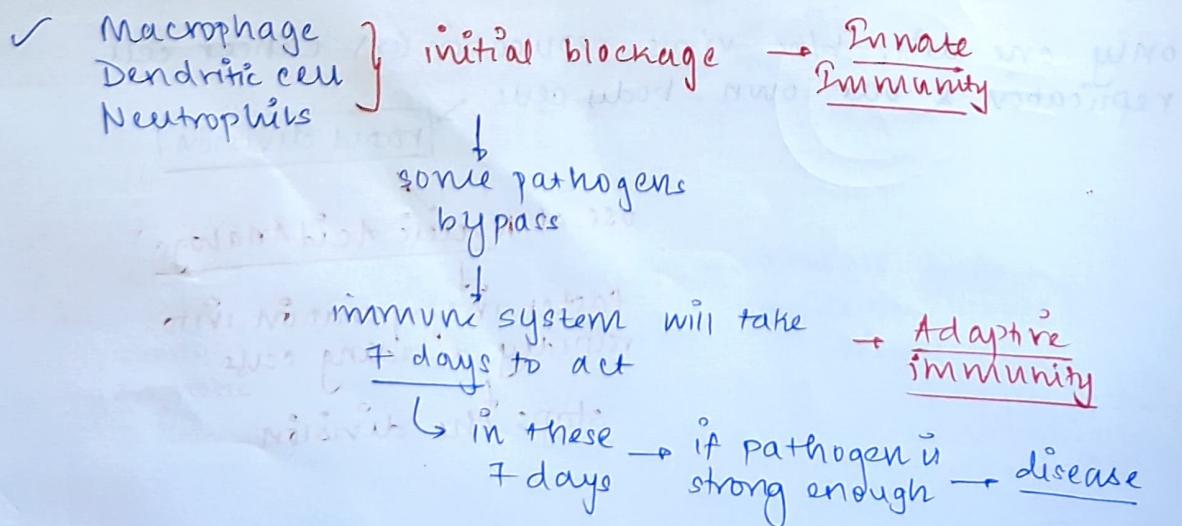
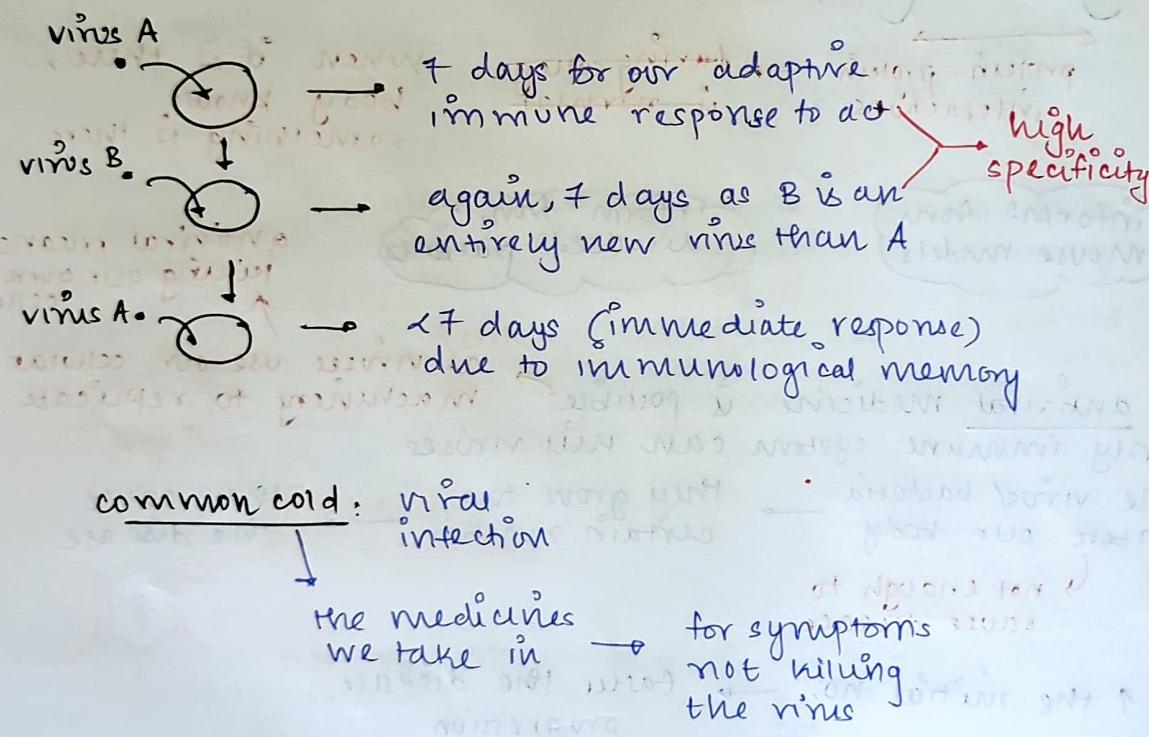
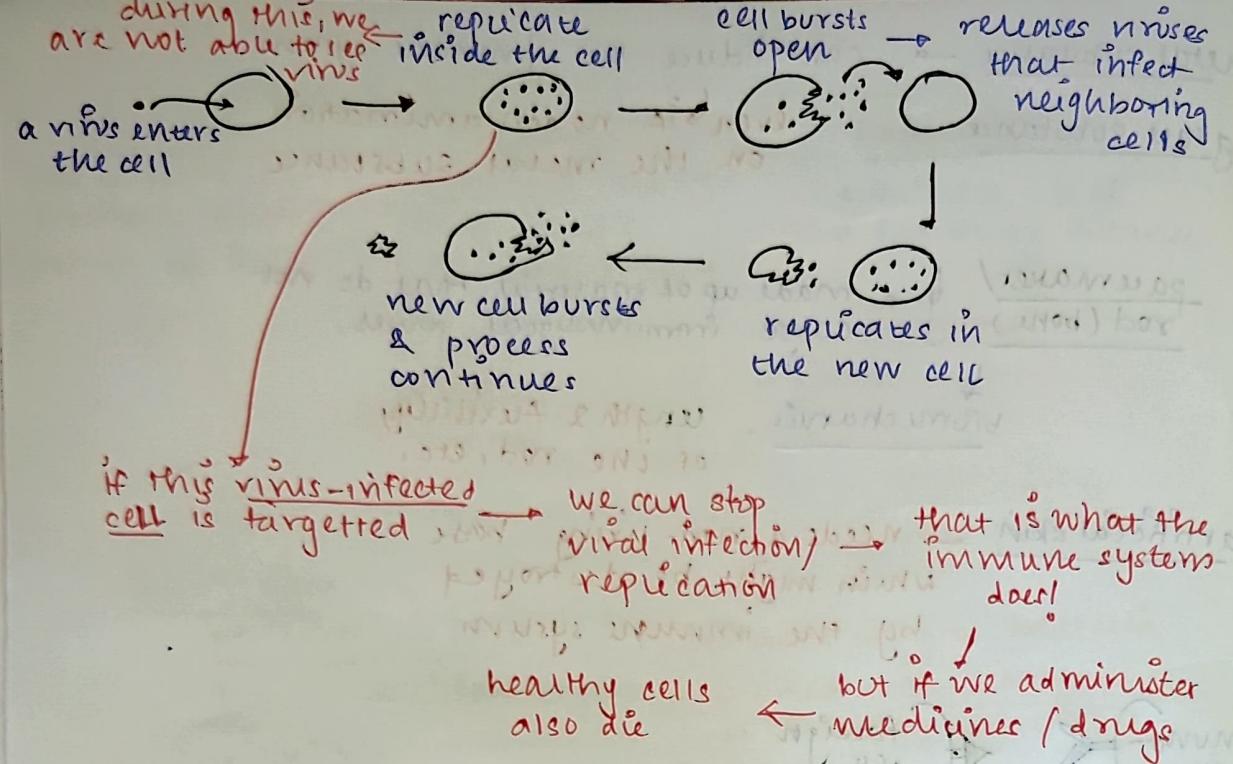
✓ only one diff. b/w virus replication (or) cancer cell replication & our own body cells

rapid division

use of Nucleic Acid Analogs

faster incorporation into rapidly dividing cells

stops the division



9/11/23

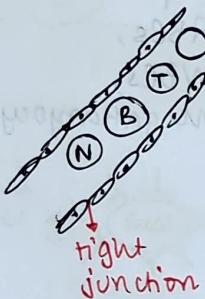
Innate

- barriers (skin)
- macrophages
- dendritic cells
- neutrophils

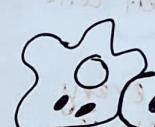
Adaptive

bacteria enter → through a cut site → goes to tissues & muscles allows around cut

↳ does not usually go to the blood
↳ if does
↳ sepsis



monocyte



macrophage phagocytose bacteria

immediately they are activated & realize that engulfed substance is foreign

TLR
Toll-like receptors

Cytokine
Chemokine → chemotactic

create small gap in tight junctions → bring in more neighboring macrophages

blood containing more aggressive neutrophils enter the tissue/site

→ phagocytosis

RBCs also infiltrate

swelling of the spot & a reddish ring

to make pathogen growth unfavorable

heat + pain

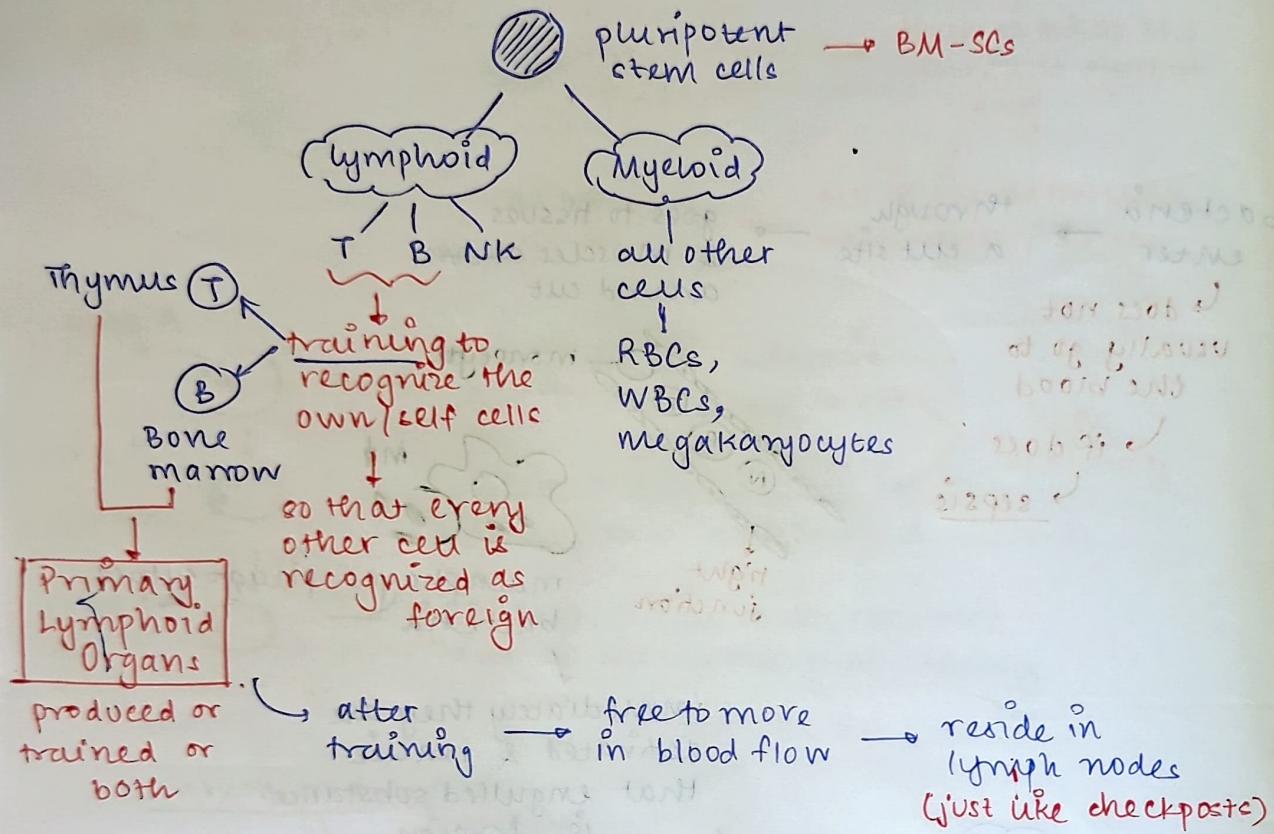
if no inflam' no infection

inflammation

there 4 things happen if there is an infection

✓ some of the macrophages & dendritic cells → travel to the nearest lymph node → through the lymphatic system
e.g. tonsils, adenoids

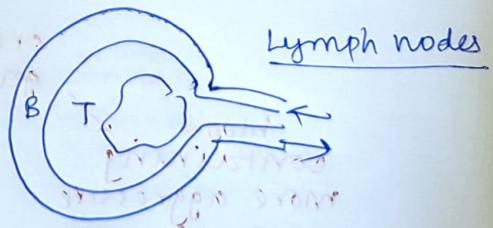
✓ all blood cells → bone marrow



✓ macrophages take up the bacteria & take them to the lymph nodes (just like arresting a thief, & taking them to the police station).

Secondary Lymphoid Organs:

- MALT - Mucosal-associated lymphoid tissues:** Found in mucosal membranes.
- GALT - Gut-associated lymphoid tissues:** Found in the gut.



Lymph nodes swelling → Indication of infection
e.g. throat infection → nearest lymph node (tonsil) swell

Spleen → Master 2^o lymphoid organ

B BCR
 (B-cell receptor)
 T TCR
 (T-cell receptor)

in Lymph node

→ MHC (major histocompatibility complex)

macrophage
 protein fragment
 (13-20 a.a.)
 proteolytic enzyme cleavage

T
 recognized by TCR
 cytokines

bacteria is no longer active

B → antibodies (very specific to the antigen)
 released in blood
 may stay in blood for months
 go to tissues

✓ (say): 10 B-cells were activated

after infection is taken care of

8 may die, but 2 remain

within 2-3 days, response is mounted

adaptive immunity will not take 7 days again

faster response on subsequent infection by the same pathogen

immunological memory

✓ memory to some infections are good

some are poor

eg: Chicken pox (lifetimne)

eg: Tetanus (1 year)

23/4/24

B & T-Cell

Plasma cells

produce antibodies

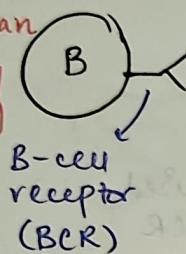
Helper

Cytotoxic

directly kill virus-infected cells & tumor cells

II

These nos. ~ 10^8
practically can handle any foreign body that enters our body



B-cell receptor (BCR)

~ 10^9



T-cell receptor (TCR)

G constantly scanning the body

different types

if it comes across a tumor cell, kills it

variations in receptors

* human genome has 25,000-30,000 genes
but 10^8 diff. B-cell BCR genes.

bone marrow produces ~ 10^{11} varieties of B-cells receptors

BM

bone marrow produces ~ 10^{14} varieties of TCR

receptors that recognize self-proteins die

the receptors that recognize self-proteins die

if no autoimmune diseases

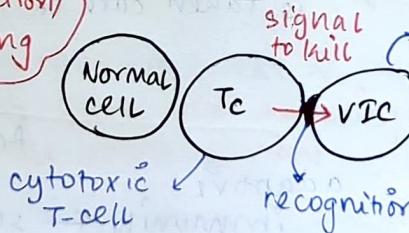
~ 10^8 remain that do not recognize our self-proteins

come into the peripheral blood

if it recognizes a foreign antigen/protein

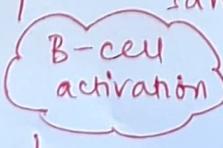
same cell multiplies & diff'ns into plasma cells

antibody prodⁿ as long as the threat is eliminated



This requires help by Th cells

T-cells that can recognize the same antigen



part of the receptor
that recognizes

Paratope

part of the antigen
that is recognized

Epitope

as only a small
region from the
entire protein
is recognized.

say there are 10
bacterial proteins

each on an avg.,
contain 3 epitopes

30 diff. B-cells!

✓ one human protein can be
an antigen to another individual. eg: Rh factor in RBCs.

✓ if B-cell recognizes but T_H cells do not, no immune
response. ↗ a safeguard against
self-recognition

✓ if both B & T_H cells make a mistake → autoimmune
diseases

✗ similarly T_c cells require signal from
 T_H cells to recognize VIC & tumor cells

safeguard against
autoimmunity

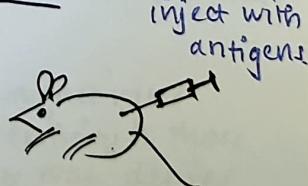
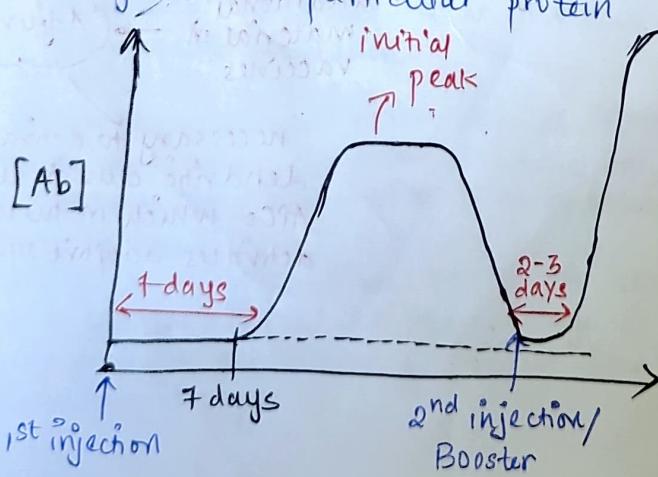
Much more Ab
produced

↑
Subsequent
infection

↑
higher
peak

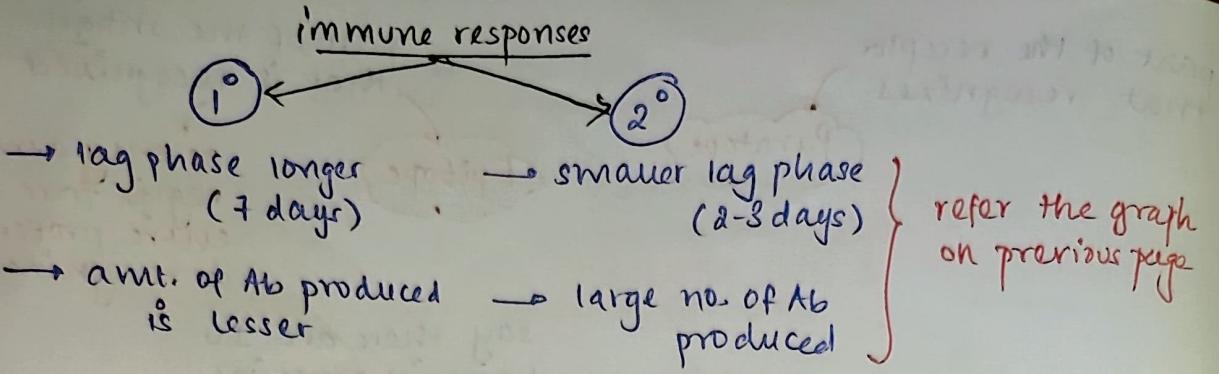
ELISA

used to measure specific antibody
against a particular protein

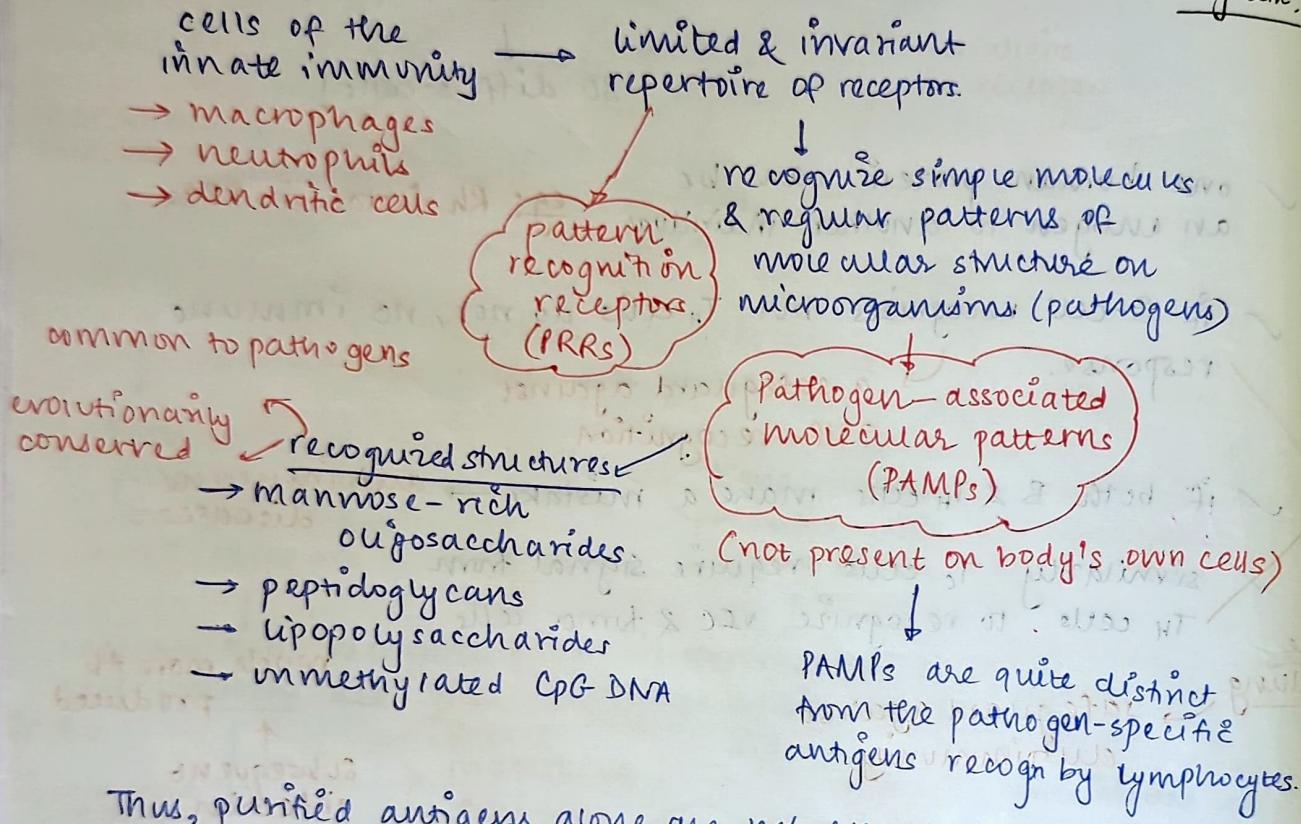


2nd injection/
Booster

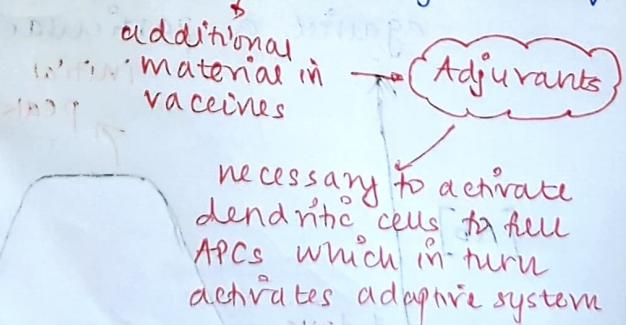
Principle of
immunization



Initial discrimination b/w self & non-self by the innate immune system:

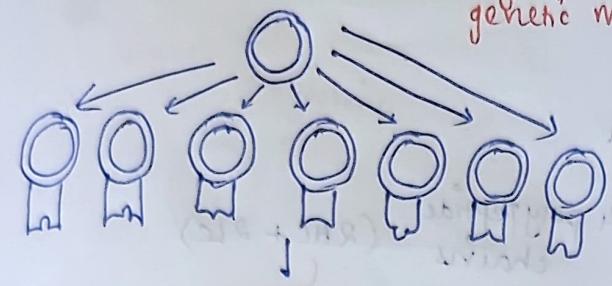


Thus, purified antigens alone are not enough to evoke an immune response. Bacterial components that can be recognised by PRRs are required to activate innate immunity & subsequently the adaptive immunity.

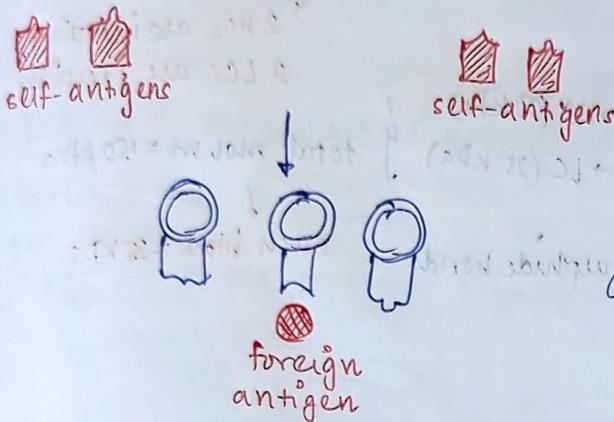


The Clonal Selection Theory of Lymphocytes : (Burnet, 1950s)

by a unique genetic mechⁿ



A single progenitor cell gives rise to a large number of lymphocytes, each with a different specificity



Removal of potentially self reactive immature lymphocytes

Clonal deletion

Pool of naïve lymphocytes (that is prior to activation)

Clonal expansion

Proliferation & differentiation of activated specific lymphocytes to form a clone of effector cells

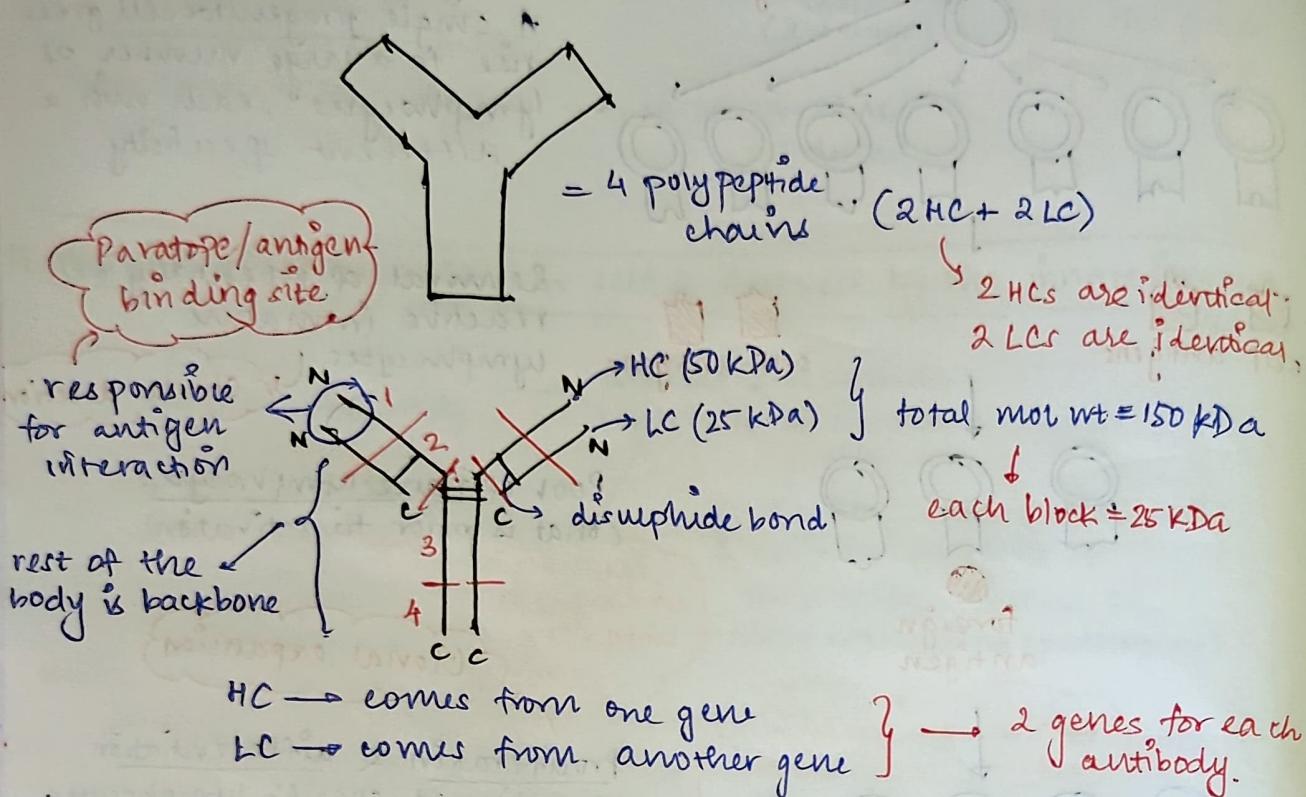


Postulates:

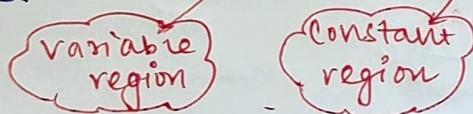
- ① Each lymphocyte bears a single type of receptor with a unique specificity.
- ② Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation.
- ③ The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity to those of the parental cell from which that lymphocyte was derived.
- ④ Lymphocytes bearing receptors specific for ubiquitous self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes.

29/11/24,

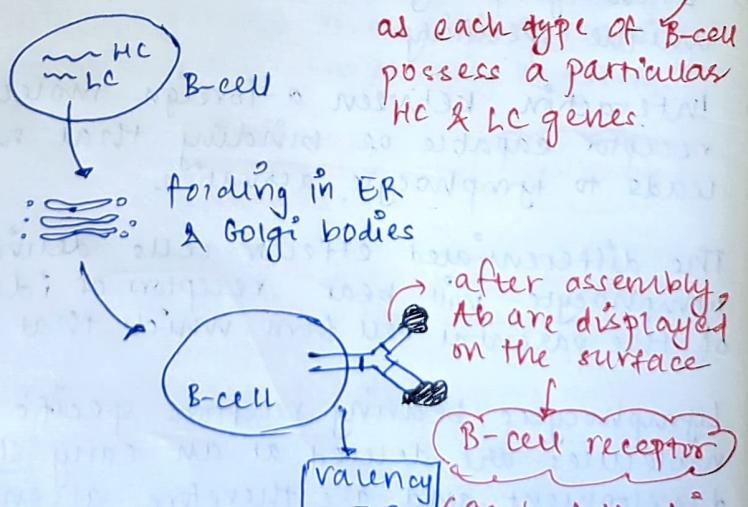
Antibody:



When we say there are 10^8 varieties of Ab in our body, the variation is in part 1. Parts 2, 3, 4 are same (almost) in all antibodies.

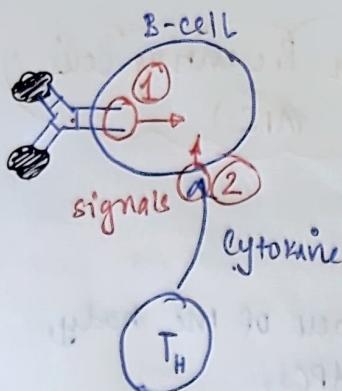


- binding arm site is identical on both the arms (naturally).
- by rDNA technology, we can have two different paratopes.

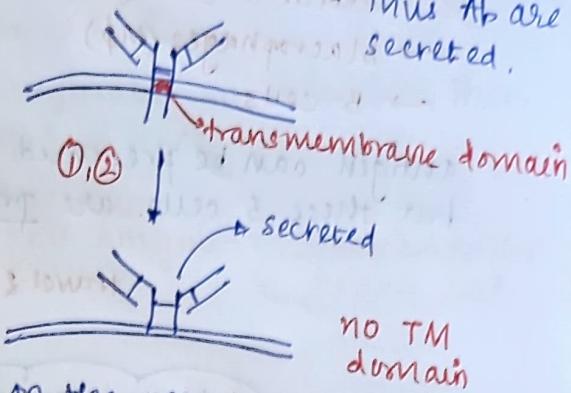


10^9 varieties of antibodies = 10^8 varieties of B-cells.

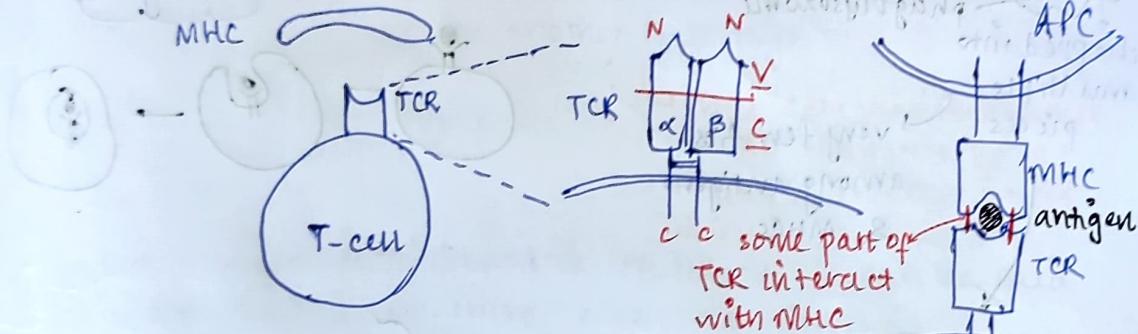
The Y-arm is flexible → 0° to 180° (\parallel , \perp)



These 2 signals cause some changes, such that the transmembrane domain of the BCR is not expressed.



- ✓ BCR → Ab that act as receptor on the membrane
- ✓ both B-cells & T-cells require two simultaneous signals to get activated.
- ✓ TCR → never secreted; remain on the surface.



BCR can react with free antigen

- ✓ T-cell receptor (TCR) never reacts with free antigen. It has to be presented → Major Histocompatibility Complex (MHC).

- ✓ TCR first interacts with the MHC, only then it can recognize MHC-antigen complex.

- ✓ An individual's MHC will interact with that person's T-cell only. The interaction is very very specific.

even blood-siblings have max. 25% chance of similarity

any foreign MHC

they are killed by the T-cells

MHC is the most polymorphic gene discovered in living world

organ transplant is thus complicated

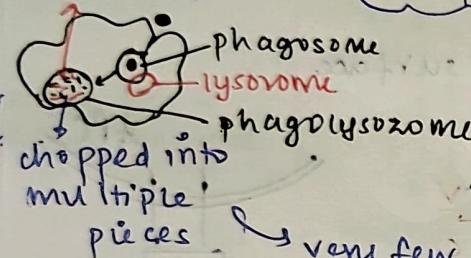
✓ only 3 types of cells which can present antigens

→ Antigen Presenting Cells (APCs)

- Dendritic cells (DC)
- Macrophages (Mφ)
- B-cells

antigen can be presented by any cell of the body, but these 3 cells are professional APCs.

MHC proteins

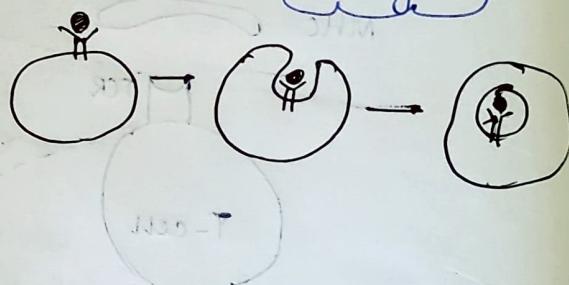


phagocytosis & macropinocytosis

travel & scan the entire body
if infection spotted,
DC, Mφ eat up the pathogen

B-cell receptors bind to antigen

(RME)
Receptor-mediated endocytosis



phago-lysosome

very few fit among antigens & MHCs

MHC displayed on the surface

Membrane of APC

✓ first stage of infection → inflammation

Mφ, DC eat up the pathogens

go to the nearest lymph node
& present antigen to T-cells

✓ ~200 MHCs can present almost all antigens.

✓ T-cell maturation → thymus → completed before puberty

↳ identical in BM

↳ in adults, the thymus is rudimentary

- ✓ training of T-cells in the thymus
 - ① recognise body's own MHCs
 - ② should not attack self-antigens
- ✓ MHCs are identical in identical twins.
- ✓ MHC production is ~~further~~ upregulated on infection. There is always a basal level exprⁿ of MHCs.
 - recognise self-antigens
 - but no action as TCR knows self.

After Elimination of Infection

- inflamm² goes down → antigen present stops → TCR interaction also stops
- even if infection is not there → Ab continues to protect us for another 15-20 days
 - Ab production will slow down
 - thus detection/diagnosis of Ab may not be a reliable indication of infection.
- but if antigen-Ab present in the blood, it can be said definitely there is or there was an infection.

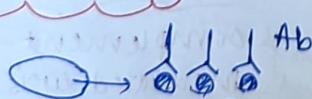
Plasma therapy:

- usually done for by viral infections
- a person's blood who just got cured from an infection → administer to a patient with same infection → strong response in the patient

Once Ab is secreted...

- spread all over the body → does not specifically reach the site of infection

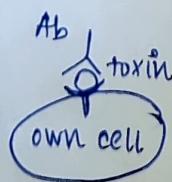
Effector mechanism of B-cells



eg: tetanus, Diphteria

each have a diff. mode of action

eg: transport channels



works on neurotransmitter

elong² factor

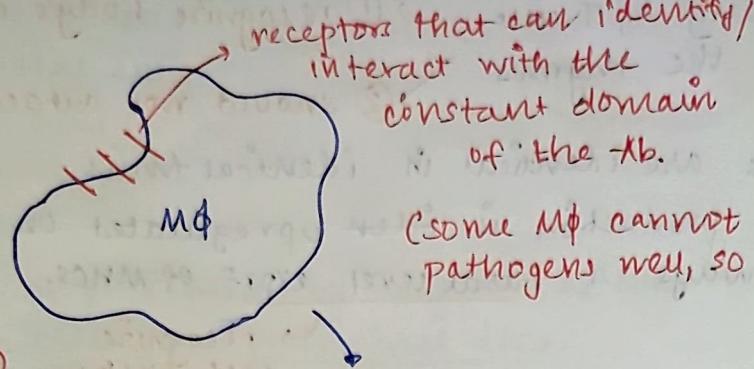
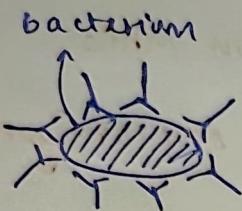
protein trans² is blocked.

when Ab binds to the toxin, the latter cannot bind to our receptors

no RME & effect

Neutralization

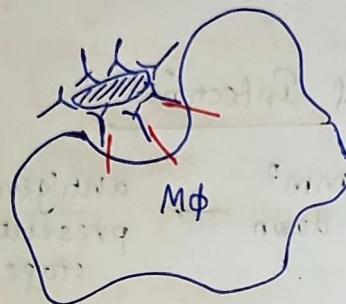
toxin
viruses



2.

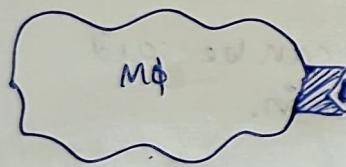
Opsonization

- bacteria
- parasite

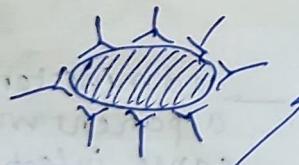


interaction

taken in into a phagosome



now Mφ presents the antigens normally



activated by Ab binding to pathogens

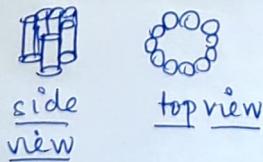
cascade series of activⁿ steps.

3.

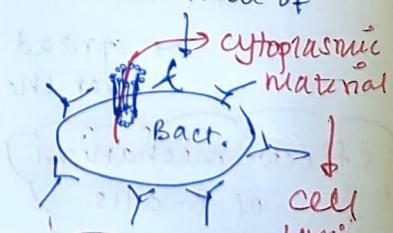
Complement

- ① Classical
- ② Alternative

20 complement proteins
part of the immune system



forms such a structure in the cell wall of



Complement-mediated lysis

- bacteria
- parasite

30/11/24

T-Cells



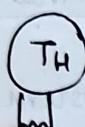
when it interacts with a cell (B-cells) it gives signal to proliferate

if it recognizes a cell, it will kill it

* both T-cells & B-cells recognize their antigens through their receptors

one of the most dangerous cells of the immune system

common T-cell → from BM to thymus → there they differentiate



recognize virus infected cells & tumors

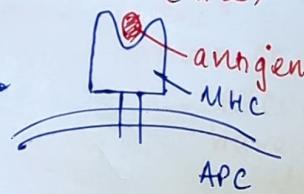
T-cell receptors

never recognize antigens in free cond.

only when presented (APCs)

✓ Mφ

✓ DC

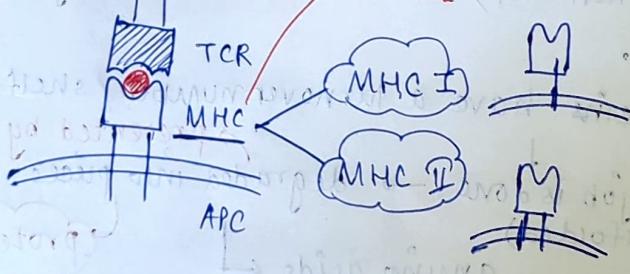


bacteria

chopped into many pieces

hugely diverse → 200 → sibling similarity ~ 20-25%

play a role in:
 ① recognition of
 ② self-non-self discrimination



one TM domain

two-TM domain

- ✓ T-cell from the thymus recognize only one's own MHC.
- ✓ Only antigens presented by own MHC can be recognized by T-cells.

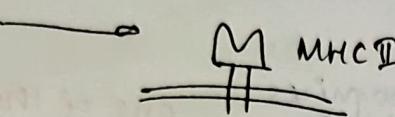
most successful transplants

- ① blood → we have to check only Rh factor.
- ② cornea → as our eyes have very poor immune system

T_c



T_H



any antigen presented by MHC I & recognized by T_c will kill the cell

any antigen presented by MHC II & recognized by T_H will produce Ab by B-cells.

tumors

cells that have lost the property of contact inhib

due to production of new/abnormal proteins

destruction of tumor cells

immune system finds it new

oncoproteins

Oncogenes
present in our chromosomes but inactive until triggered by a carcinogen

✓ MHC I, MHC II are continuously presenting antigens (both self & non-self) but BCR & TCR recognise only non-self.

✓ our self proteins have a turnover number / shelf-life:

after the job is done → degraded into pieces
(or misfolded)

amino acids ←
are recycled

proteasome-mediated lysis

→ (David Baltimore)
book

✓ during infection, by THRs, Mφ & DC are activated

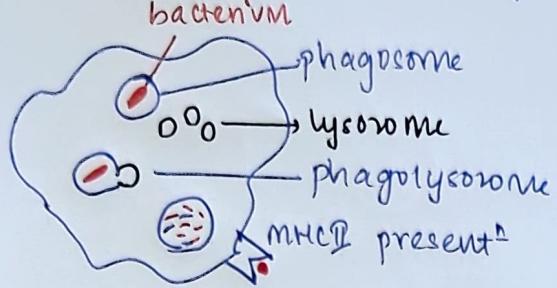
MHC I & MHC II production is upregulated

✓ proteins synthesized endogenously will be processed & presented by MHC I

in the cytoplasm of our own cells.

present when proteasome-lysis occurs → ER

✓ when a foreign cell (bacteria, for e.g.), is taken up by phagocytosis



- foreign antigens
- MHC II

∴ locations of MHC I & MHC II are very different.

✓ during a viral infection:

viral proteins produced endogenously will be presented by MHC I. Macrophages & dendritic cells which engulf a virus-infected cell by phagocytosis, the cell is degraded in phagolysosome & protein presented by MHC II. Therefore, viral proteins are presented by both MHC I & MHC II. Thus both Tc are activated to kill virus-infected cells and Th are activated to help B-cells to produce Ab against the viruses.

✓ MHC I is expressed by all nucleated cells. → RBCs do not have RBCs.
MHC II is expressed by only APCs

non-self protein presentⁱⁿ
present in ER only means either tumor protein or viral protein

MP
DC
B-cells

non-self proteins are mostly pathogen-derived

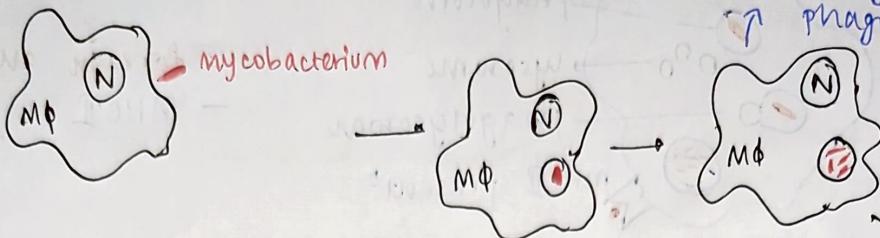
TH1

TH2

→ whatever discussed in previous day in Ab active

5/2/24

(air
borne) TB ← Lung
mf ← mycobacteria
multiply in the
phagosome



on mycobacterium infection, the macrophages do not kill or act on the phagocytosed mycobacterium.

do not cause phagosome-lysosome fusion. lysosomal vesicles

signal/warning to Mφ to cause lysosome phagosome fusion

helping B-cell to produce Ab

TH₂ response



TH₁ response
→ Leishmania
→ Tuberculosis
→ Leprosy.

helping Mφ to identify the pathogen

✓ most mycobacteria are extreme drug resistant (XDR).

✓ we can discover a molecule/drug that can induce the TH₁ response. To reverse mycobacterial suppression.

✓ before antibiotics, sulphur drugs and bacteriophages were used.

very dangerous in case of sulphur allergy. ↴ does not let bacteria to grow
eg: Ganga water

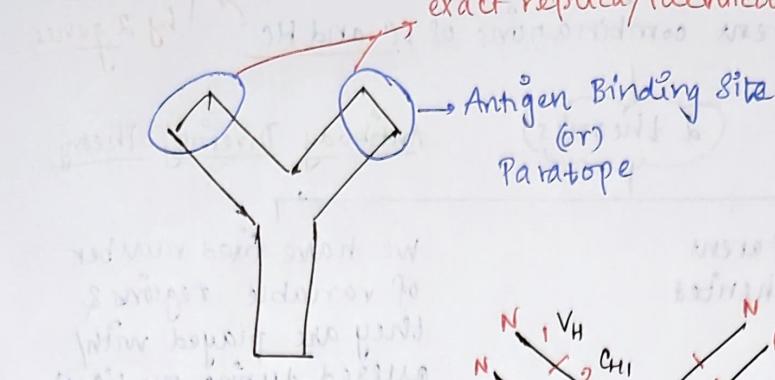
a. Immune response when there is a viral along with a bacterial infection?

✓ viral infection → suppress the immune system
✓ opportunistic bacteria → also infect

✓ throat infection with Staphylococcus. Can release Staphylococcus antigens that may cause joint pain.

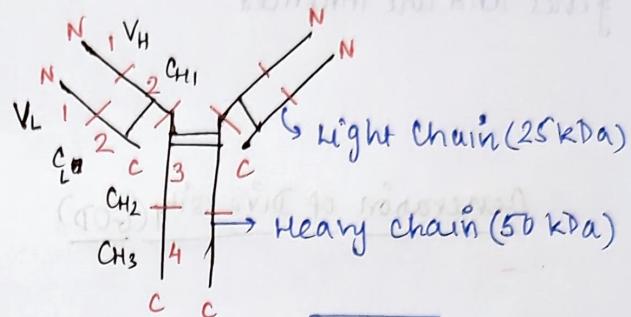
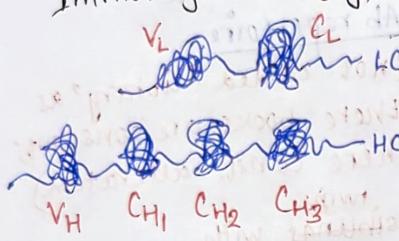
Structure of an Antibody:

exact replica/identical



2 LCs are identical;
2 HCs are identical

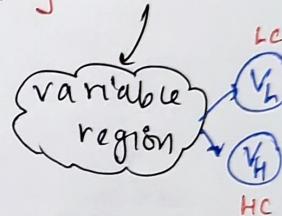
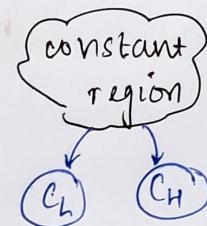
Immunoglobulin (Ig)



$LC \rightarrow 2$ regions $\rightarrow 1, 2$
 $HC \rightarrow 4$ regions $\rightarrow 1, 2, 3, 4$

150 kDa

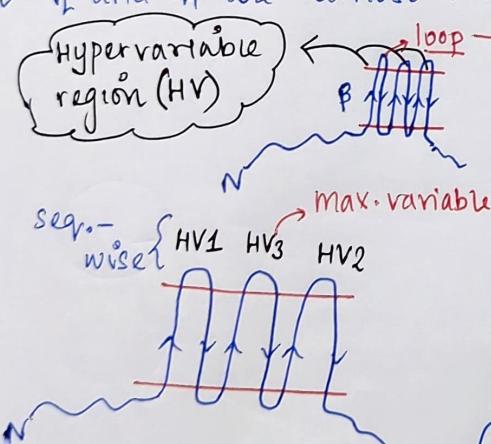
Ab specificity lies in 1



H.W.

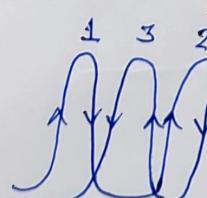
check crystal structure

✓ V_L and V_H are almost identical.



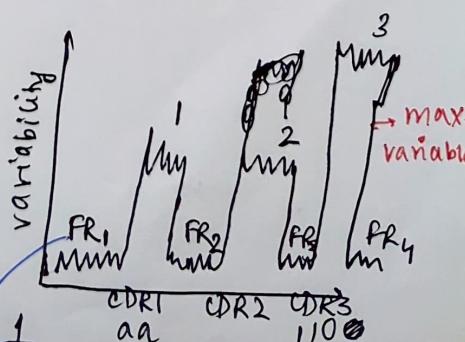
actually interact with the antigen
} antiparallel β -sheets
not taking part in antigen interaction
confers specificity

any β -sheet forming sequences would work



* $HV \equiv CDR$

complement determining region
 $CDR1/HV1$
 $CDR2/HV2$
 $CDR3/HV3$



Now $[FR_1/CDR1/FR_2/CDR2/FR_3/CDR3/FR_4]$ nc

framework region

V_L & V_H are similar in structure but in the two arms, same

✓ 10^8 different types of Ab in our body

10^8 different combinations of LC and HC.

produced by 2 genes

2 theories

Antibody Diversity Theory

all Ab have different genes and are inherited

we have fixed number of variable regions & they are played with/ altered during our lifetime & partly inherited

Generation of Diversity (GOD)

maintain the Ab repertoire

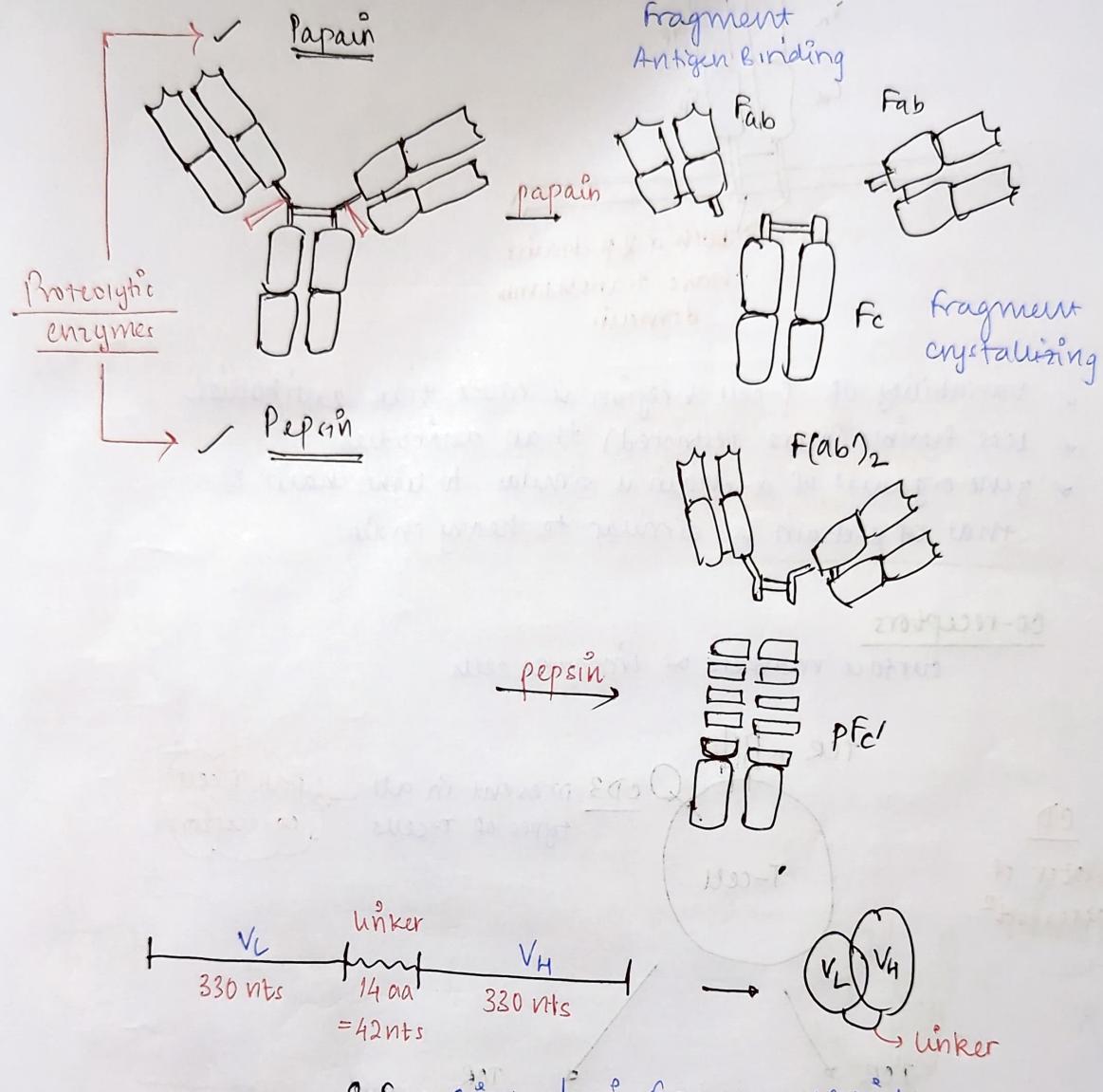
(not called 'library' as there books are constant; here const. alteration)

even two siblings with the same set of genes, have different Ab in their lifetime

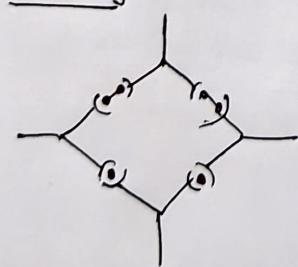
12/7/24

Yeast 22-T

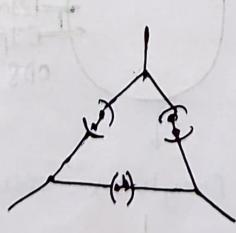
- proteolytic enzymes
- reducing agents



Flexibility:

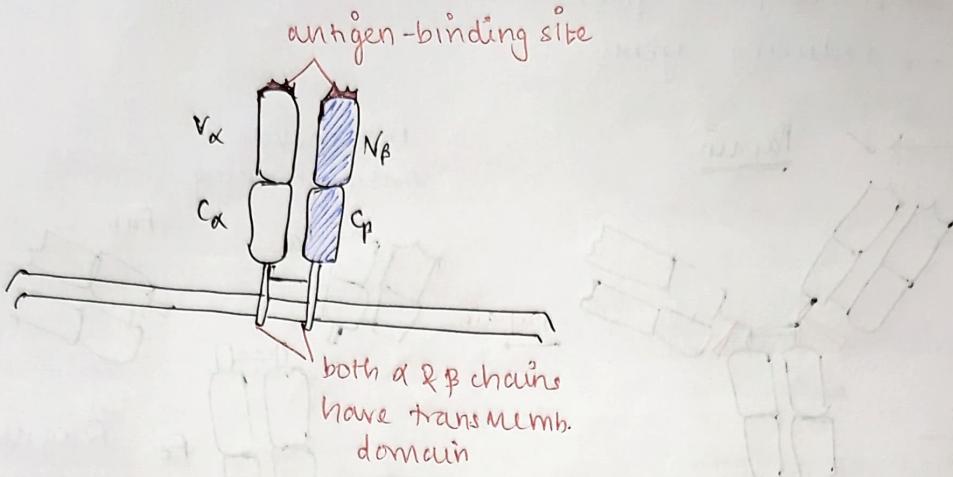


angle b/w arms = 90°



angle b/w
arms = 60°

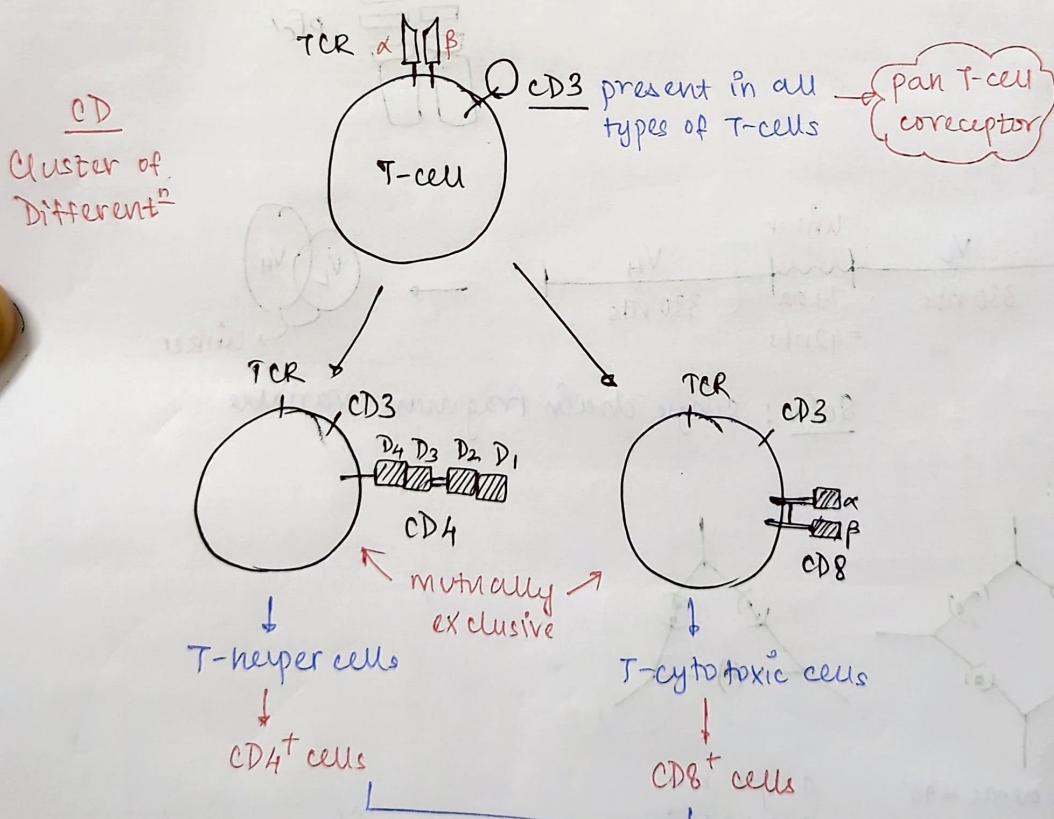
T-cell receptor



- ✓ variability of T-cell V region is more than antibodies,
- ✓ less flexible (more restricted) than antibodies,
- ✓ gene organization of α -chain is similar to light chain & that of β -chain is similar to heavy chain

Co-receptors

surface markers of immune cells



Monoclonal Antibodies:

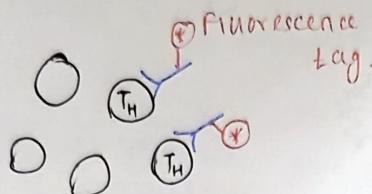
on infection → our body produces polyclonal antibodies → if one type of B-cells are chosen

Monoclonal antibodies ← proliferated ←

Anti-CD4 antibodies

commercially available → to test for HIV-AIDS.

if $\text{CD}4^+$ cells ↑ → indication of AIDS.
↳ TH cells



→ counting → Flow cytometry (or FACS)

10-30 sec to count
100,000s of cells

NK cell no.↑

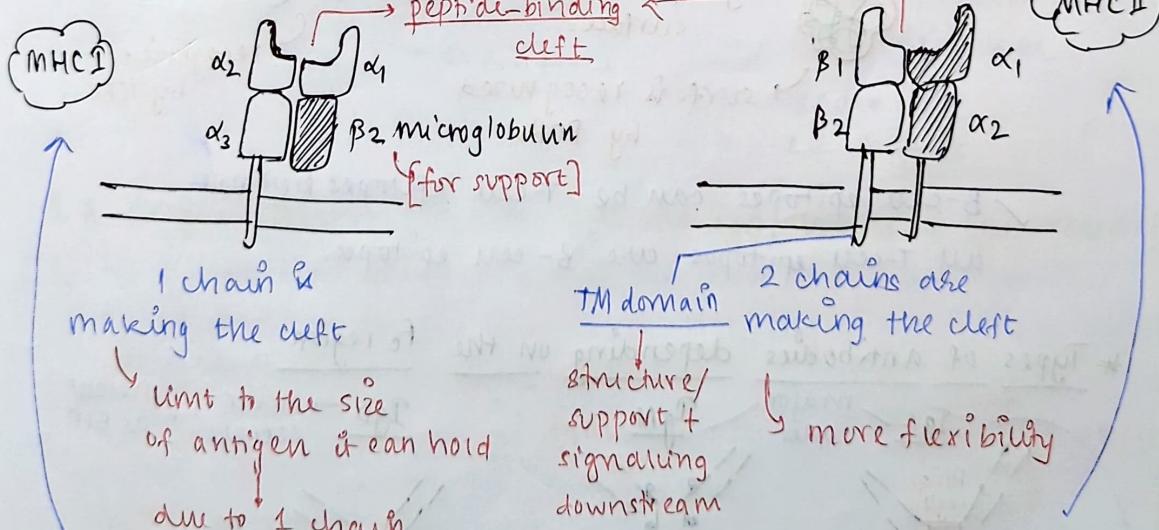
↳ either virus infection or presence of tumors → detection by its specific surf. marker antibodies.

MHCs: ② only in APCs & epithelial cells of thymus

① present in all cells except RBCs

endogenous antigens

flat β-sheet where antigen can sit



proteasomal degradation

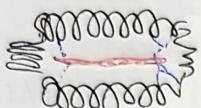
product is

9-11 aa ↴ not a problem for the smaller peptide cleft of MHC I.

- ✓ Isolating MHC w/o the peptide bound is almost impossible.
- ✓ Isolating memb' proteins is a challenge. not stable

↳ do not dissolve
in agr. phase ↳ distinctive
in lipids

MHC I

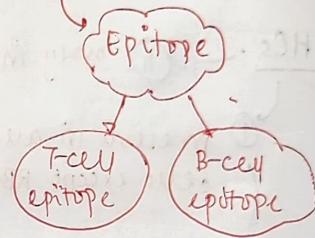
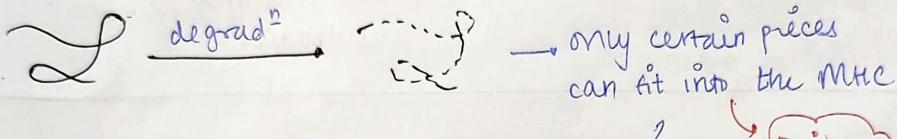


- smaller
- interactions only at ends
- ↑ no. of inter^a

MHC II



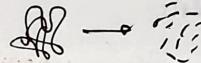
- larger
- interactions all over
- ↑↑↑ no. of inter^a.



- ✓ antibody → interact with an intact antigen molecule

hydrophilic surface.

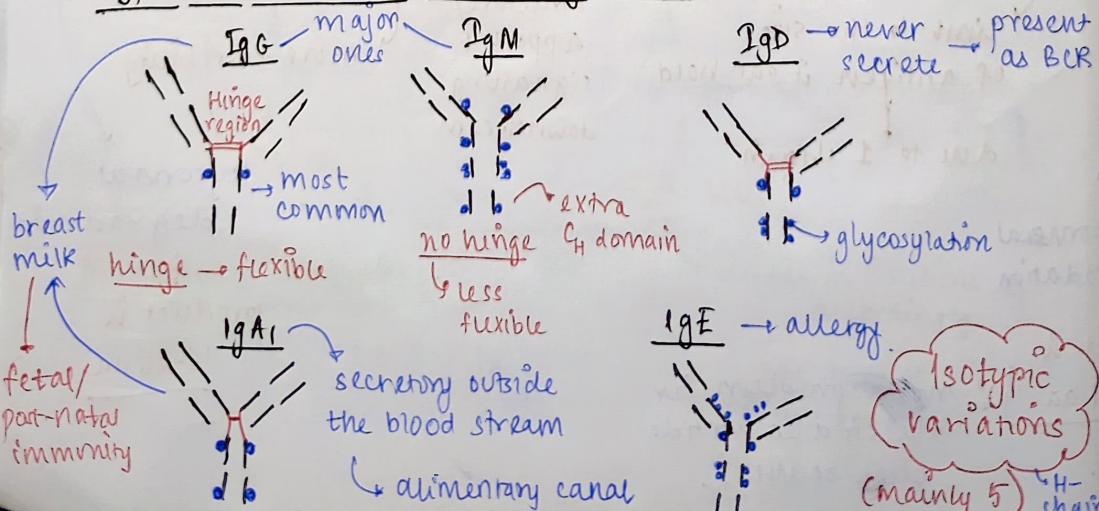
surf. is recognized by BCRs

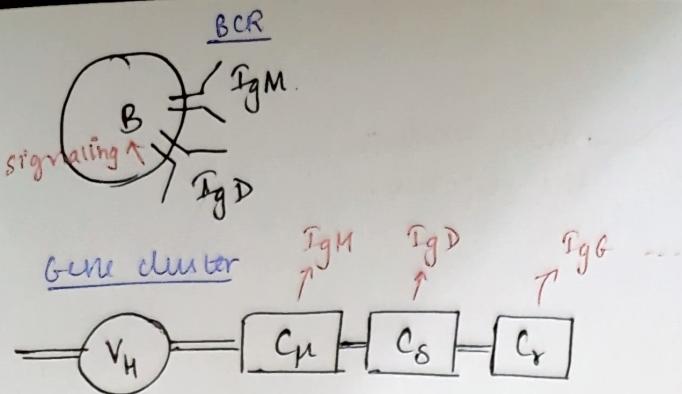


recognition by TCRs

- ✓ B-cell epitopes can be T-cell epitopes but not all T-cell epitopes are B-cell epitopes.

Types of antibodies depending on the Fc region





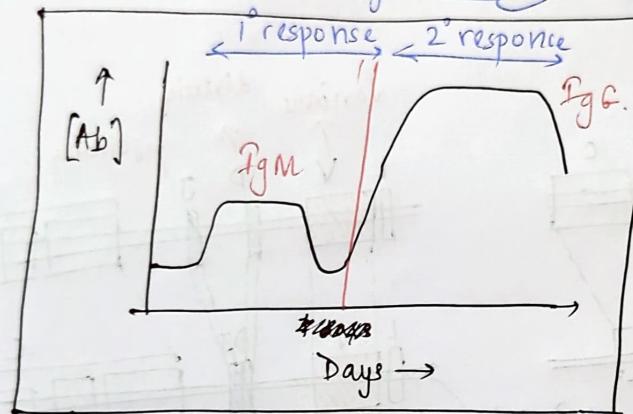
first → on infection immediately

closest in the gene cluster
IgM antibodies are produced

on closer inspection of the infection

T-cells release cytokines

decide the isotype



Diagnosis → IgM in blood → this might be the first infection in an individual
→ IgG in blood → the disease has occurred before

Q. A dengue patient has both IgM and IgG. What is the reason?

Ans: The person had dengue before but now the strain causing dengue is different. The new strain has the original characteristics along with some mutations.

↳ IgM
(new antigens)

↳ IgG
(prev. encountered antigens)

Whether vaccine worked

If we administer a vaccine, but on actual infection, we find IgM, it means the vaccine did not work.

IgE: in case of allergy
↳ always ready to act

→ sneezing to throw the dust out of body

allergen

object

peanut

allergenpeanut
agglutinin

dust

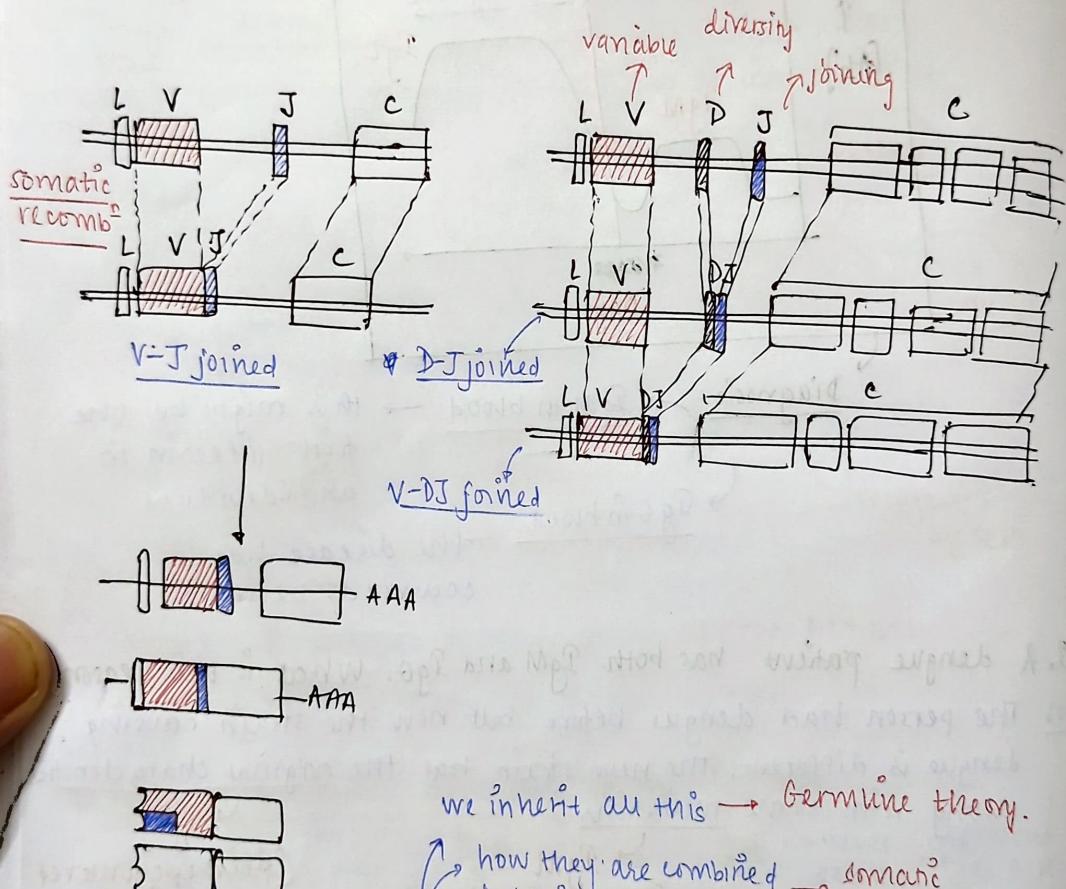
faeces of
dust mitethese produce
the response.Germline Theory

separate gene for each different antibody chain & the antibody repertoire is largely inherited.

Somatic Diversification Theory

a limited no. of inherited V-region sequence undergoes

both theories
are partially
correct.



No. of functional gene segments in human Ig loci

segment	light chains		Heavy chain H
	K	λ	
V	40	30	65
D	0	0	27
J	5	4	6

$$= 200 \text{ comb}^2 = 120 \text{ comb}^2 = 10,530 \text{ comb}^2$$