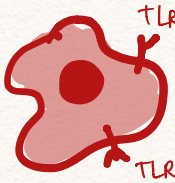
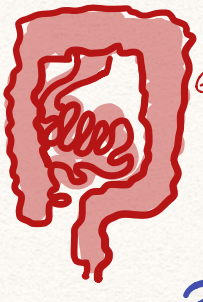
CONTENTS

PRR

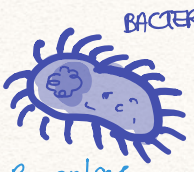
Pattern Recognition Receptor





membrane-bound

cytoplasmic



TLR 4

Toll-like Receptor 4

+MD2

+CD14

recognizes LPS (lipopolysaccharide)

TLR 1,2

for gram + bacteria

NOD like Receptors

contains **LRR**

bacterial cell wall peptidoglycan — Recognized

ACTIVATES:

NF_kB

transcription regulatory factor

- usually kept inhibited by I_kB

→ NOD activation → proteasome activation → I_kB removal

Inflammasome

- multimolecular complex
- assembled by NOD activation

↓

secretes inflammatory cytokines

IL-1 **IL-18**

LRR

contains

Leucine Rich Repeats

(mediate the recognition of PAMPS)

Pathogen-associated Molecular Pattern

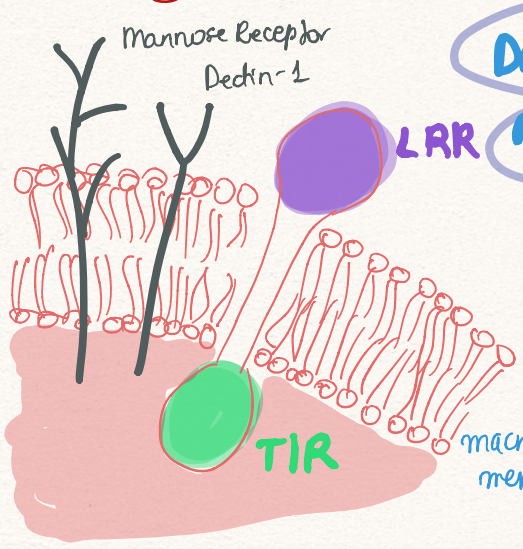
→ extracellular domain

① Mannose Receptor Dectin-1

② contains **TIR**

Intracellular domain of TLRS that signals the cell itself

③ gene transcription activated



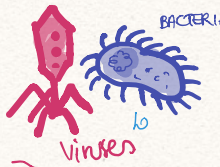
DECTIN-1

Mannose-receptor

- 2 types of C-type lectins
- activate phagocytosis

TLR4 on macrophage membrane

TLR 3,7,9



recognizes double stranded RNA = viruses

single stranded RNA = viruses (human wouldn't be found extracellularly)

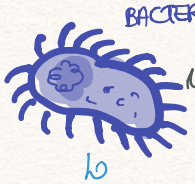
CpG DNA = bacteria & viruses

for endocytosed or phagocytosed microorganisms within these compartments

extracellular

CRP

C-Reactive Protein

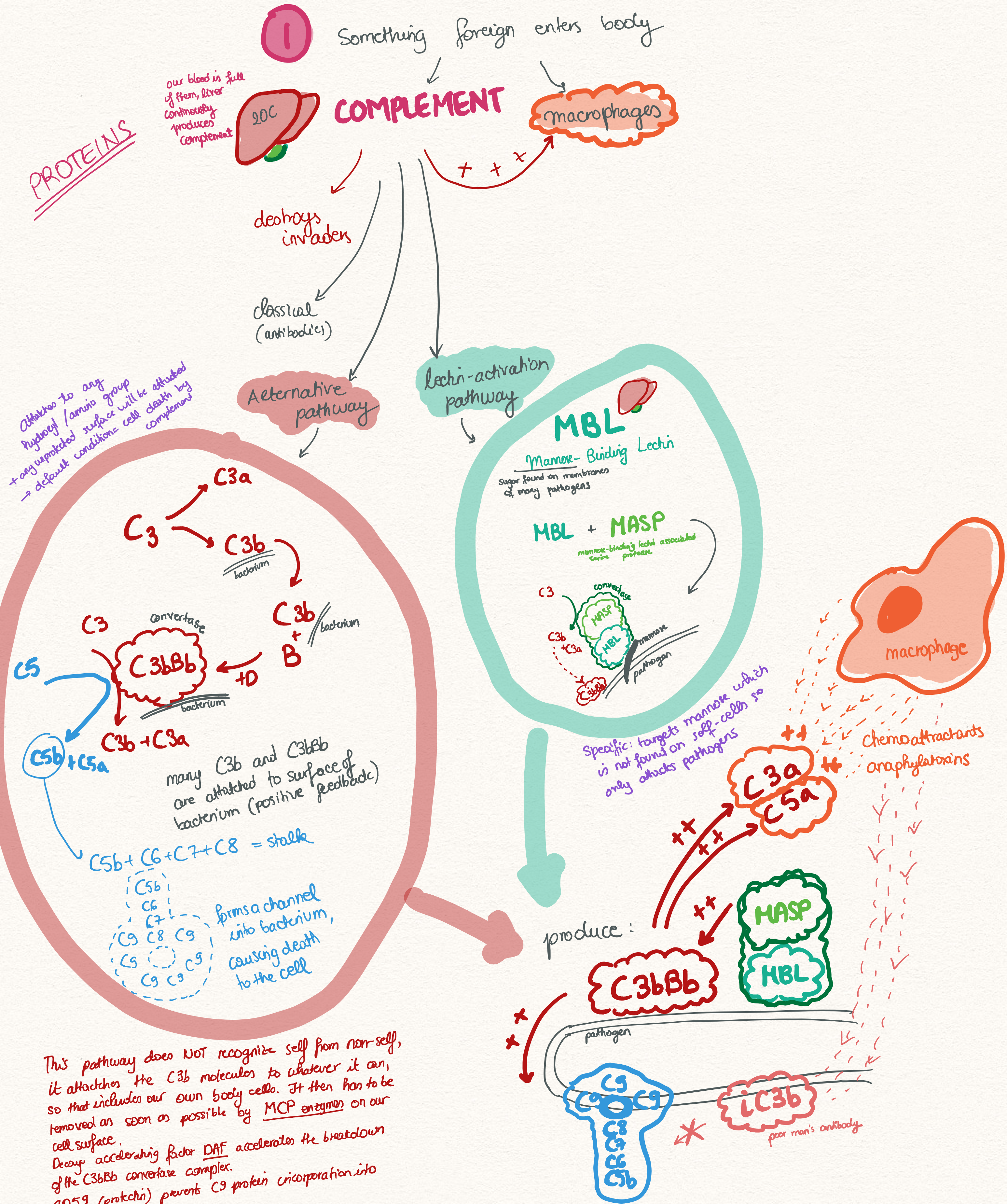


- appears in serum in hours after infection/damage
- binds to phosphorylcholine on bacterial cell walls

MBL

Mannose Binding Lectin

- binds mannose sugar
- serum protein
- binds to microbial surfaces to activate COMPLEMENT



This pathway does NOT recognize self from non-self, it attaches the C3b molecules to whatever it can, so that includes our own body cells. It then has to be removed as soon as possible by MCP enzymes on our cell surface.
Decay accelerating factor DAF accelerates the breakdown of the C3bBb convertase complex.
CD59 (protein) prevents C9 protein incorporation into MACs.

1/2

MACROPHAGES

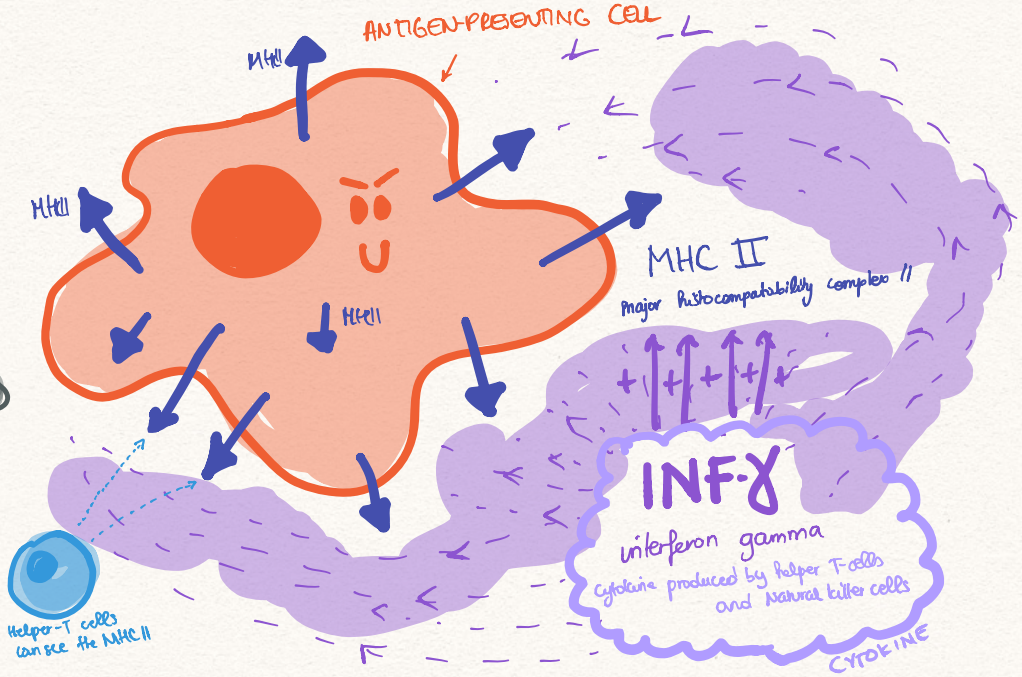
located just under most surfaces of the body ready to attack pathogens (lungs, gut) or to pick up cell debris. = long lived cells (months)

KILL OUR DEAD CELLS

Usually:

GARBAGE COLLECTOR

When they recieve signals INF-γ :

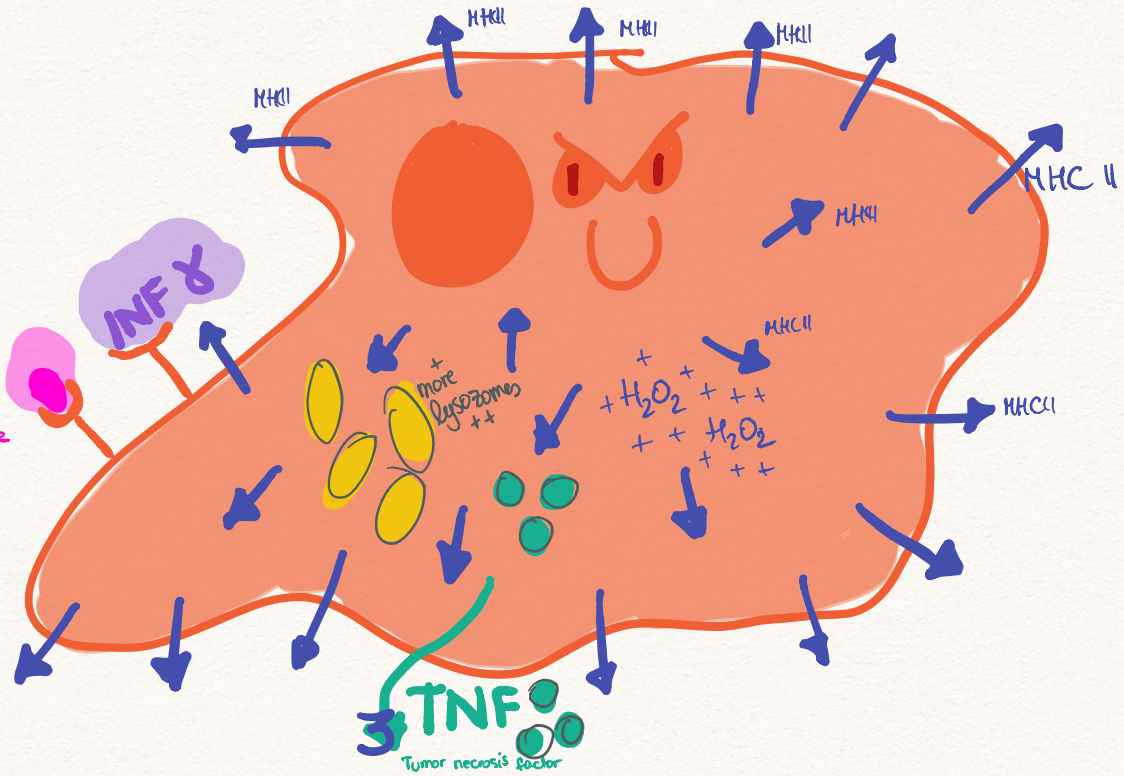


ANTIGEN PRESENTING CELL

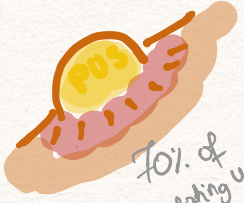
Hyperactivation:

direct signal from invader

LPS
lipopolysaccharide



KILLING MACHINE



70% of circulating WBC

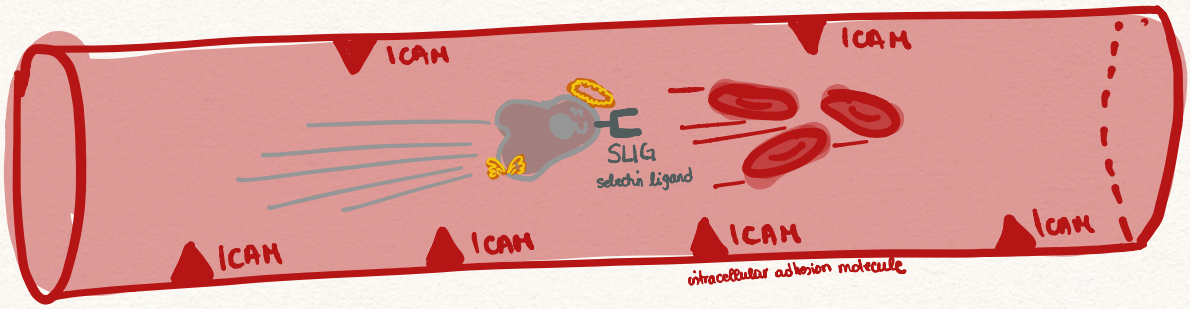
③ NEUTROPHILS

~30 min to be activated

Not antigen presenting cells. Natural killers "on call" = short-lived ~5 days

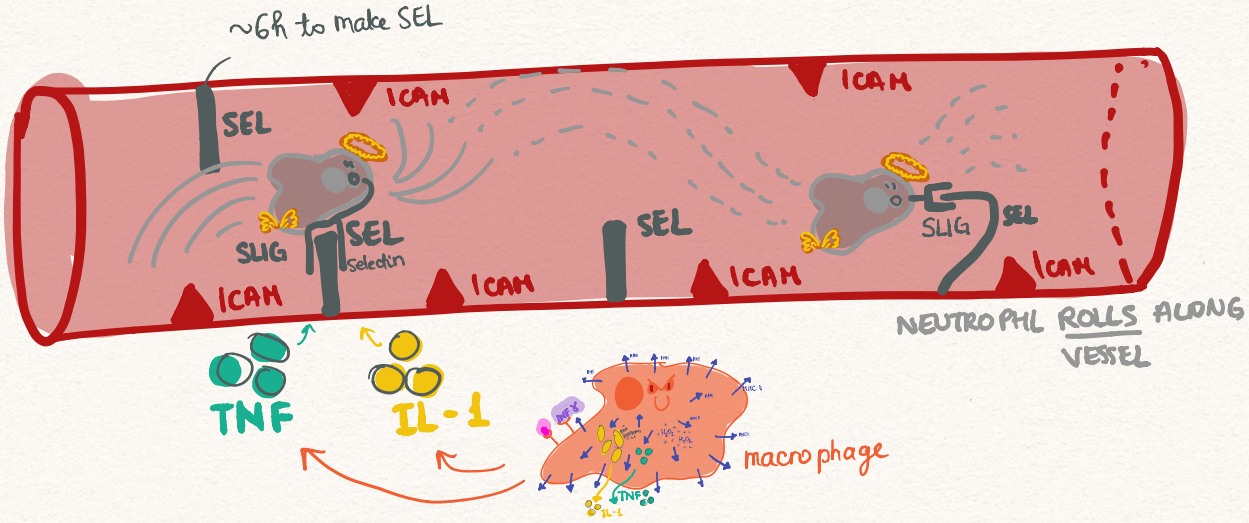
- incredibly PHAGOCYTIC
- produce TNF & other cytokines
- release chemicals that kill pathogens (and other cells) : the only immune system cells that can liquefy both cells and connective tissue

NORMAL TISSUE



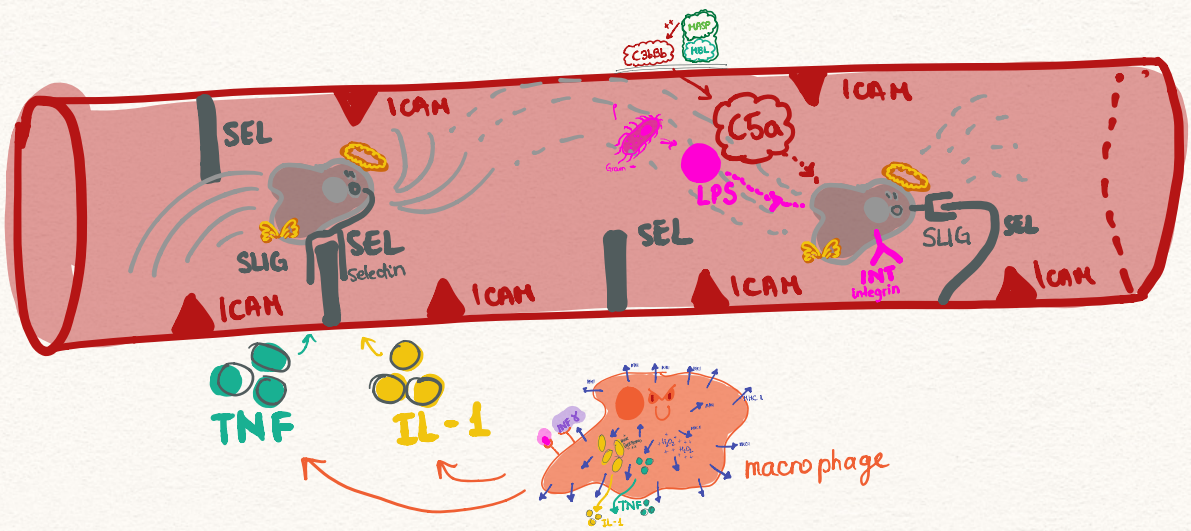
PATHOGEN-INVADED TISSUE

macrophage step



PATHOGEN-INVADED TISSUE

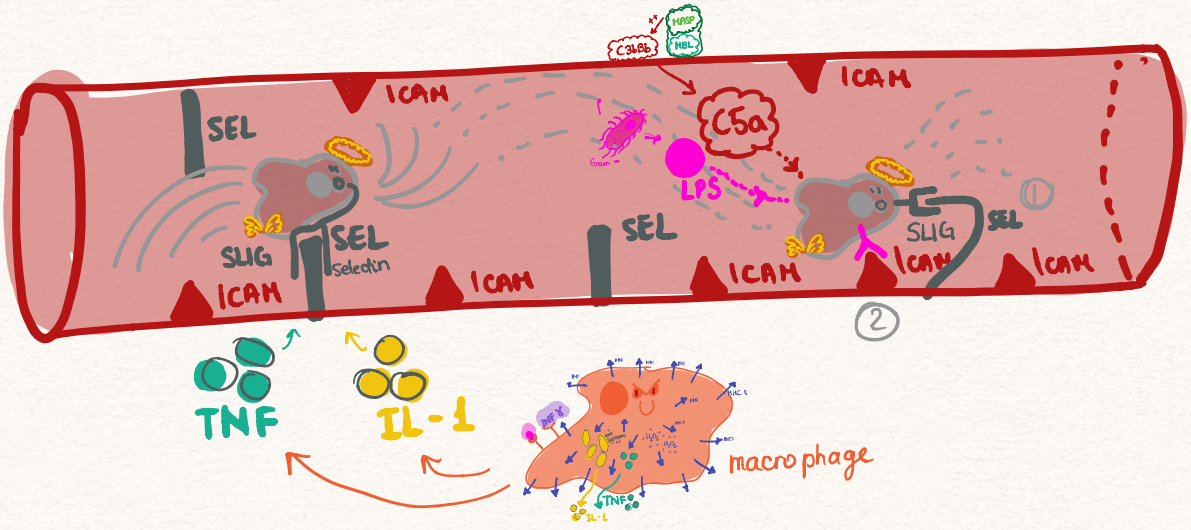
pathogen + complement step



NEUTROPHIL STOPPED

INT ICAM

SLIG SEL



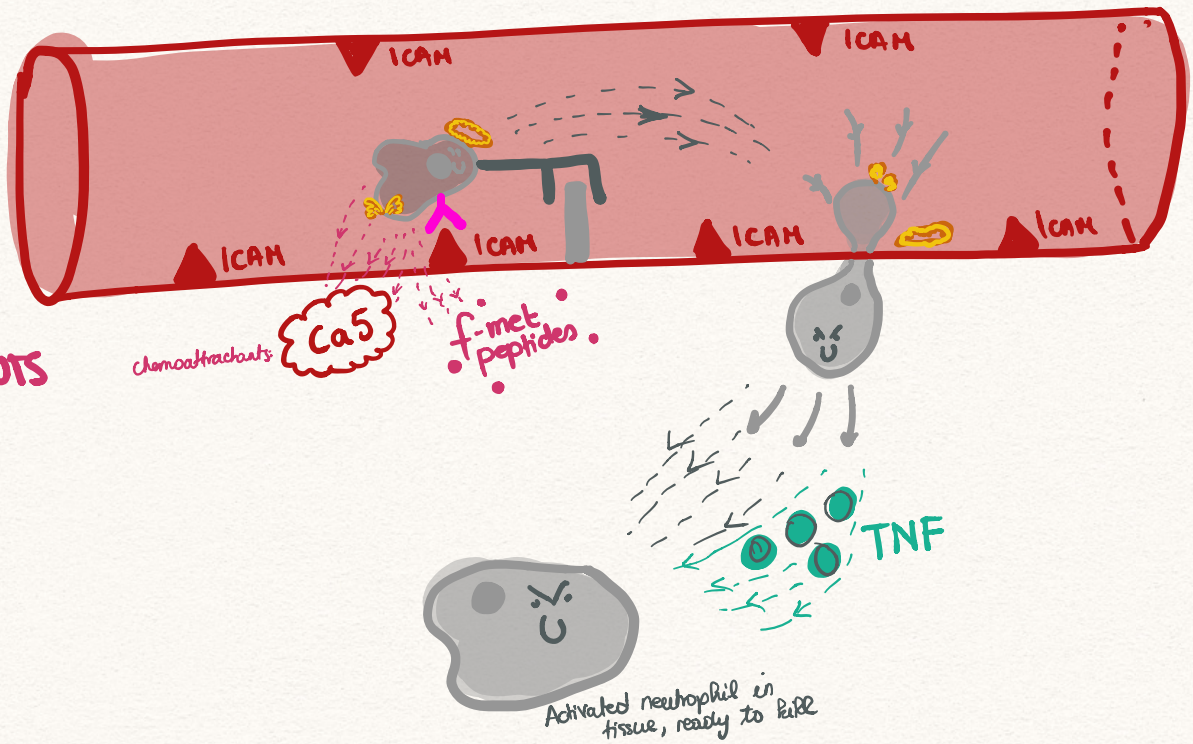
ESCAPING INTO THE TISSUES

INT ICAM

SLIG SEL

CHEMOATTRACTANTS

TNF



The same stopping mechanism is also used for

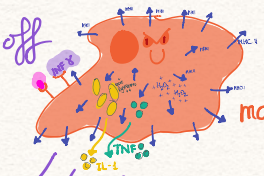
- eosinophils
- mast cells
- monocytes → macrophages
- activated T cells
- activated B cells

→ Just the type of ICAM and SEL molecules are different in each case

INTERFERONS

= "interfere" with virus reproduction

Mainly against viruses → every virus has evolved a way to hold off the interferon system long enough to reproduce

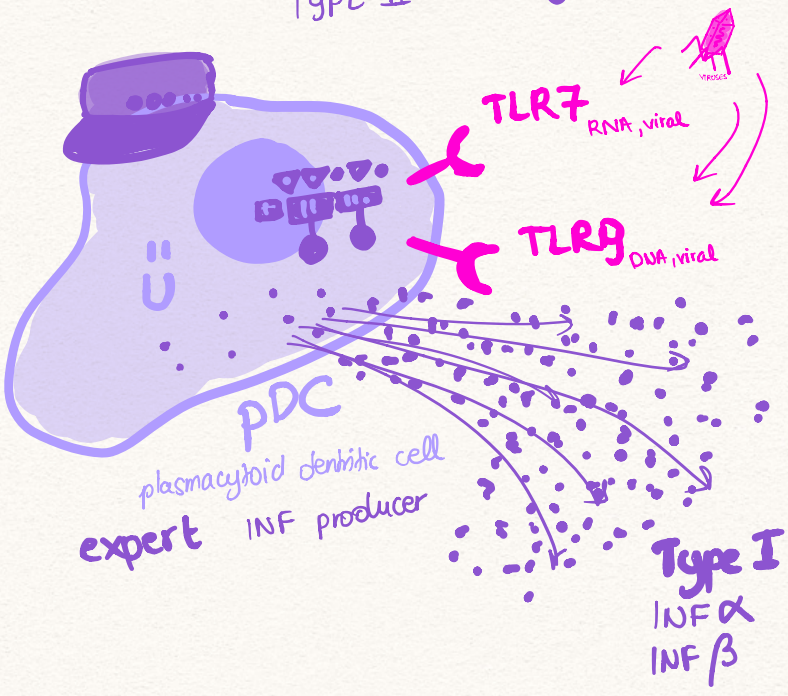


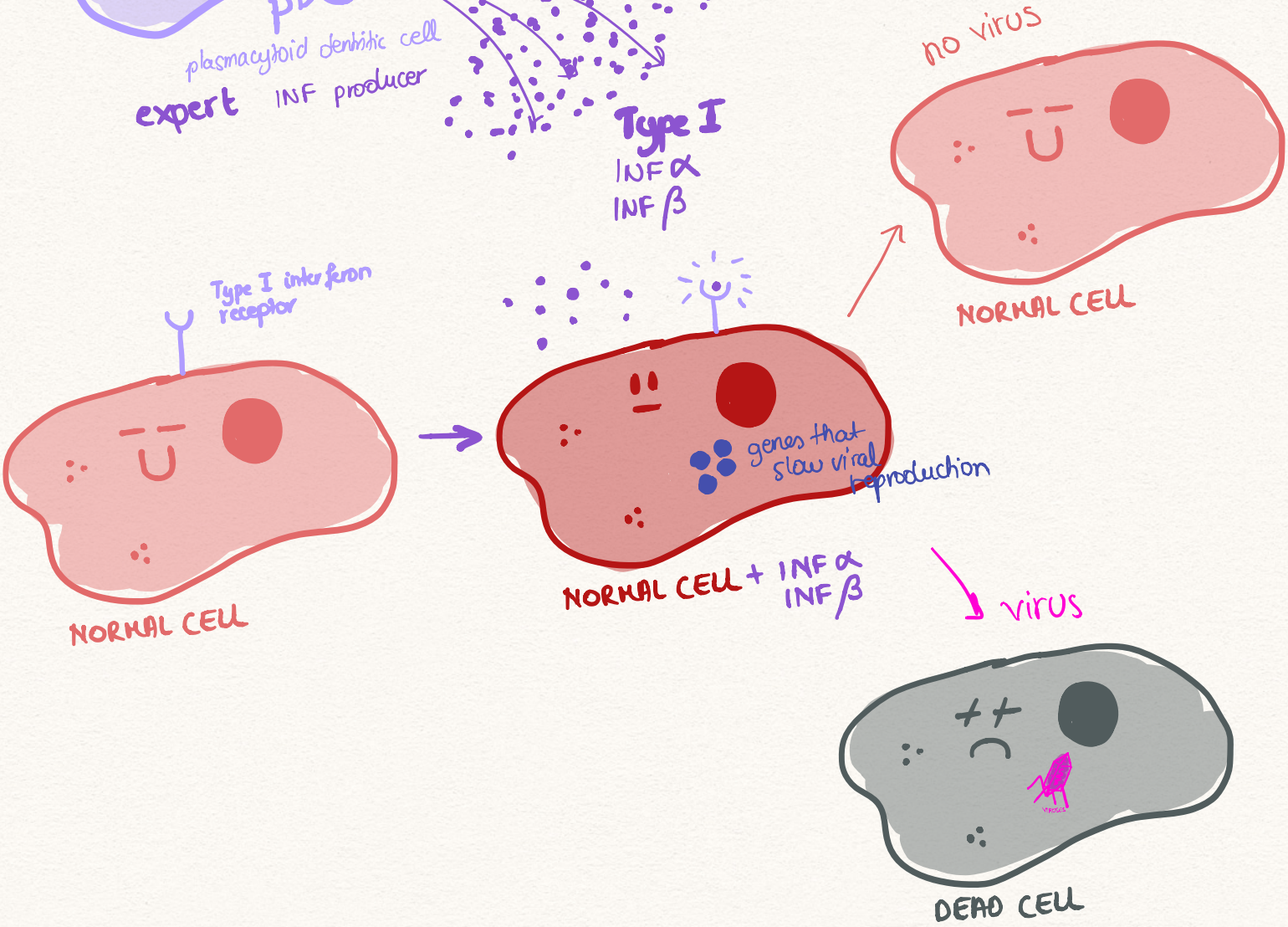
- produced by PRRs (pattern recognition receptors) macrophages
  * plasmacytoid dendritic cell

INFα
INFβ

TYPE I – INF α, INFβ

TYPE II – INF γ

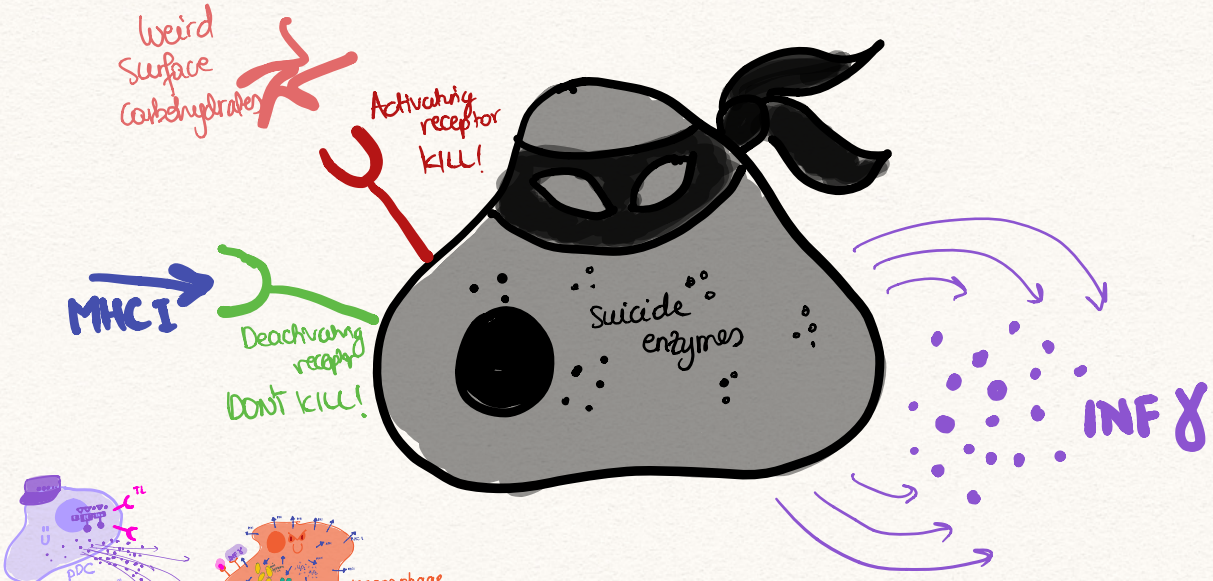


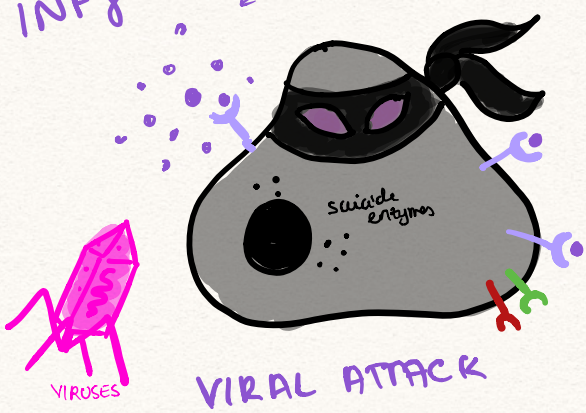


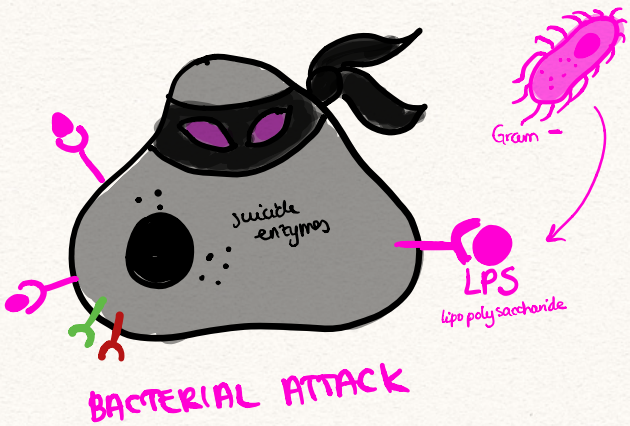
NATURAL KILLER CELLS

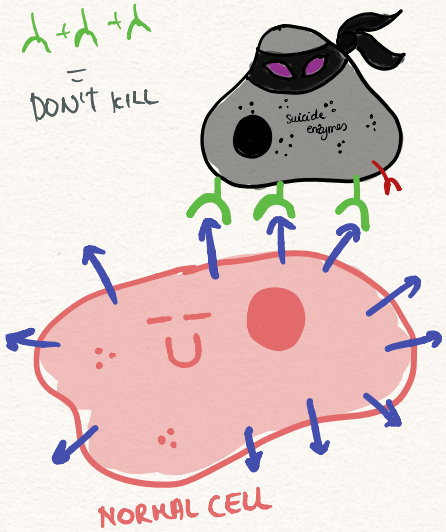
- short-lived ~ 1 week
- mostly in liver, spleen, blood
- roll, stop, exit, proliferate strategy

- inject suicide enzymes into infected cells NON SELECTIVELY!!!





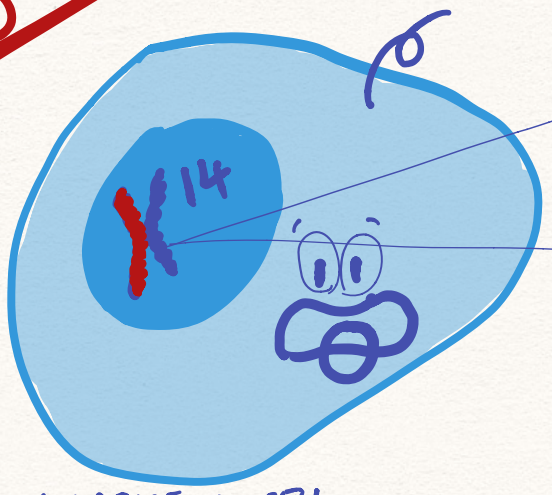




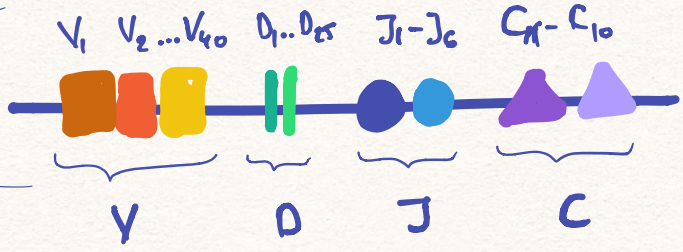
So it can kill cells that killer T-cells can't see b/c no MHC I complex

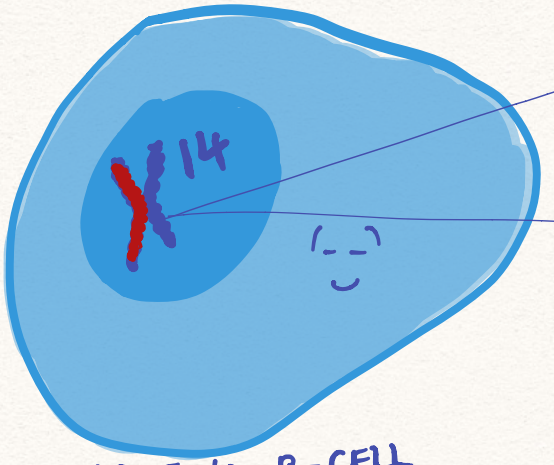
B-CELLS

① HEAVY CHAIN TESTS :



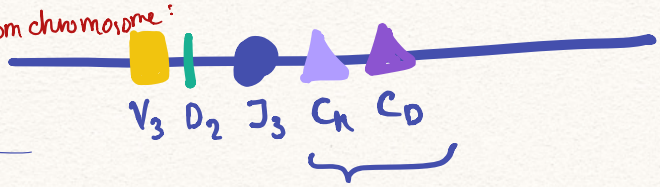
IMMATURE B-CELL





MATURING B-CELL

♀ mom chromosome:



constant region

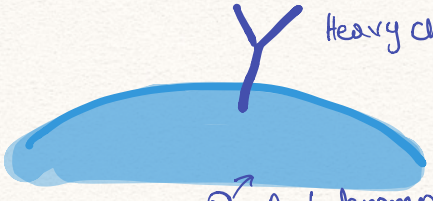
1/9 chance to be functional:

Test: Does it form a functional protein? (no stop codon?)

NO: DEATH

YES: productive rearrangement

↓



Heavy chain added to surface

♂ Dad chromosome off :)

② LIGHT CHAIN TESTS:

① CAN THE CELL PRODUCE A FUNCTIONAL LIGHT CHAIN?

YES ↓ NO : 

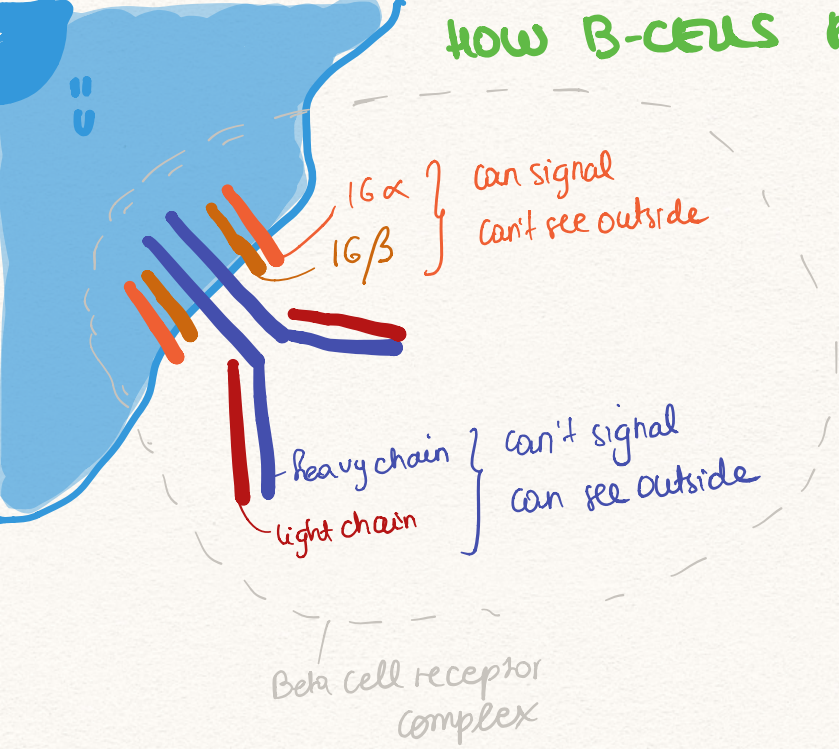
② DO THE LIGHT AND HEAVY CHAINS (H_2L_2) fit together?

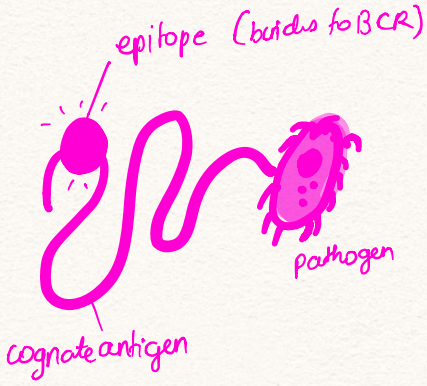
YES ↓ NO: 

(BCR)

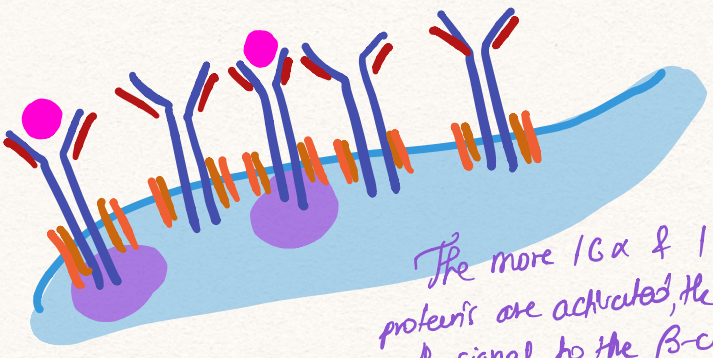
MATURE B-CELL PRODUCING ONLY 1 RECEPTOR TYPE ON SURFACE

HOW B-CELLS RECOGNIZE PATHOGENS:





B Cell Receptors need to be crosslited to work!

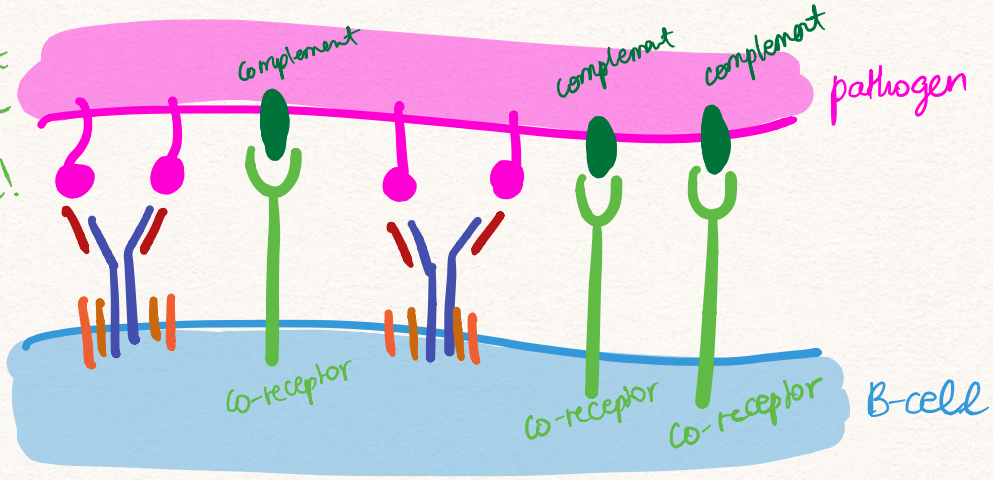


The more Ig α & Ig β proteins are activated, the stronger the signal to the B-cell

The presence of complement: opsonization of pathogen, amplifies the signal and reduces the amount of receptors needed for signal by 100 fold

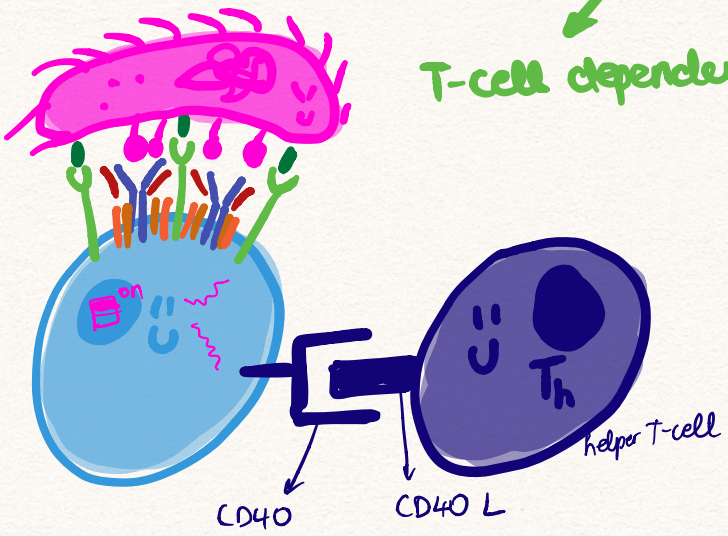
Co-receptors

*especially important initially allowing attack when not a lot of antigen is available!



HOW ARE B-CELLS ACTIVATED ONCE THEY RECOGNIZE A PATHOGEN?

T-cell dependent



co-stimulatory signal:

{IGα, IGβ, (coreceptor)} + CD40 = activation

(If no helper T-cells, T-cell dependent B-cell activation will not occur)

PROTEIN ATTACK

* **POLYCLONAL ACTIVATION**

=DISTRACTION

MITOGENS

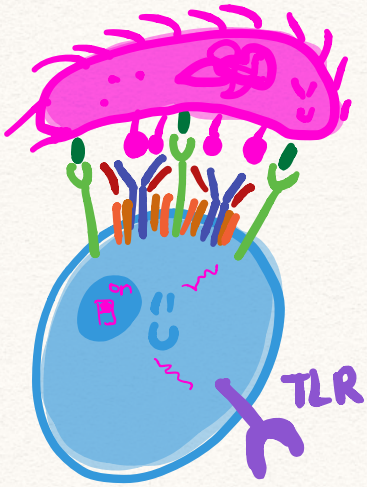
are antigens that drag the BCRs together through dragging other mitogen receptor proteins together

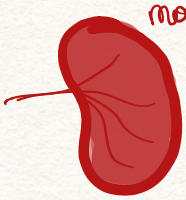
→ they can activate many T-cells non-selectively

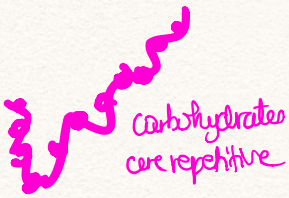
→ random, useless antibodies are made

=a diversion is caused, favoring the pathogen

T-cell independent pathway







① highly repetitive pathogen stimulation: many same epitopes clustered together.

+

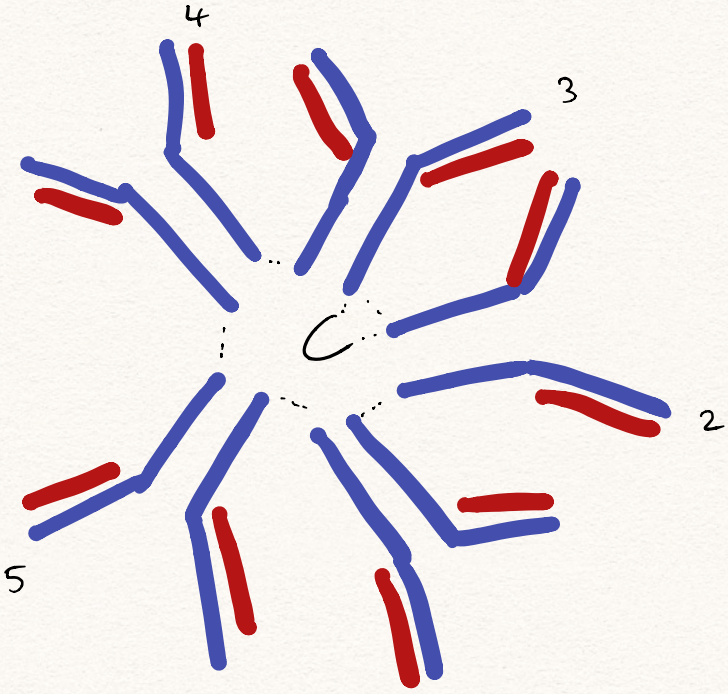
② a second signal from a toll-like-receptor

⇒ can respond fast, before T-cells kick in

⇒ but very specific, needs smth very repetitive for a strong signal in a cluster

* importantly, T-cells are activated by MHC II = amino acids/ proteins, these B-cells can also recognize carbohydrates

CARBOHYDRATE ATTACK

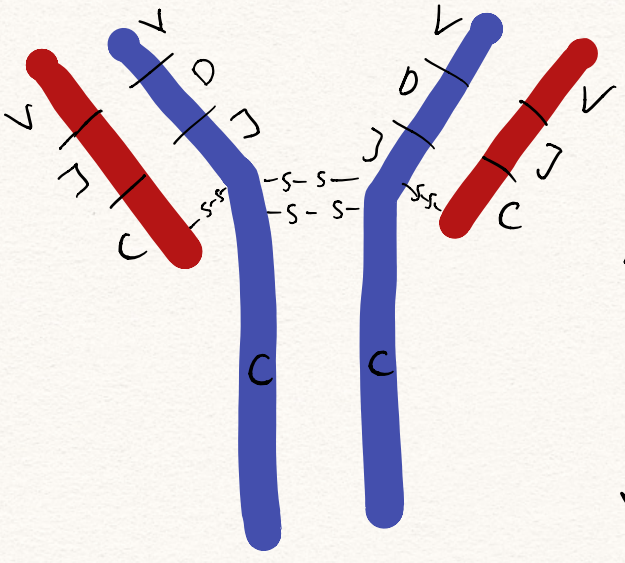


IgM ~1 day

"Ancient" antibody
First default type

1
→ Initially many C3 molecules come together to form a C1 complex, but it doesn't have activated convertases.
→ If 2 or more C1 complexes come together, inhibitory molecules fall off and convertases of C3 are made

C1 complexes bind to F_C of IgM → they are brought together
⇒ convertases are activated
→ extend the range of the complement system by attaching them to bacteria they couldn't possibly find.
→ specific complement binding b/c dependent on antibodies.



Antigen Binding Region
F_{ab}

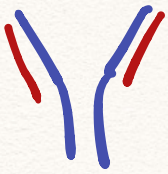
Constant region
F_C

- can also activate complement, depends on chance close proximity of two IgG antibodies, so quite weak

ANTIBODY
IgG ~3 weeks
= gamma globulins

"Classic" antibody
Most abundant in BLOOD

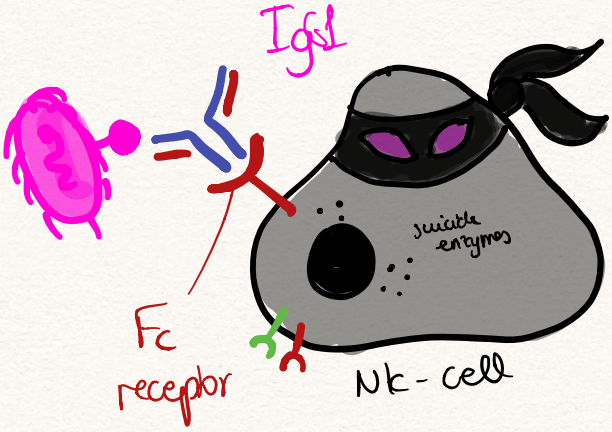
IgG-3



IgG3 = good complement fixer

C1 → C3

IgG-1

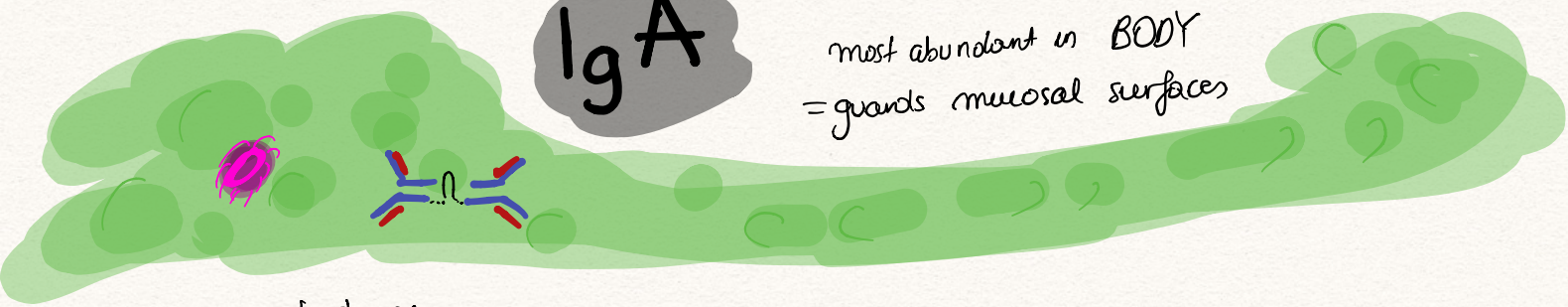


activates NK-cells by binding to both them and the pathogen

ADCC

Antibody Dependent Cellular Cytotoxicity

IgA



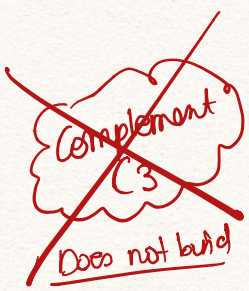
most abundant in BODY

= guards mucosal surfaces

clip shape:

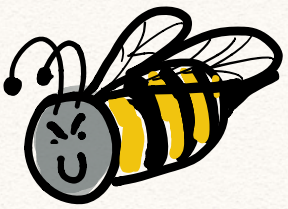
1) facilitates transport across intestinal wall
2) resistant to enzymes & acids
4) has 4 Fab regions instead of 2 → can clump & expell pathogens

Contained in nursing milk

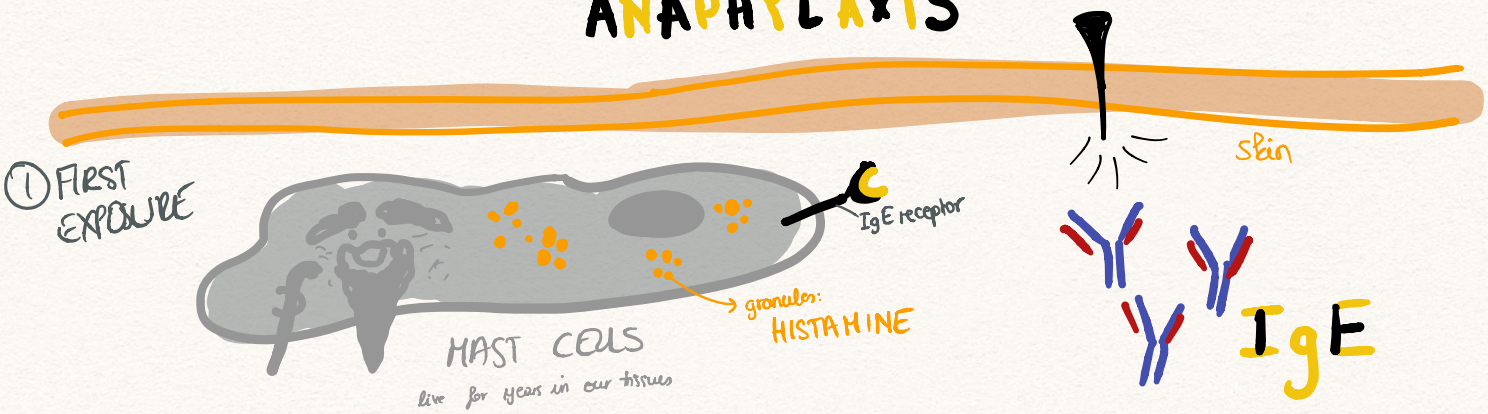


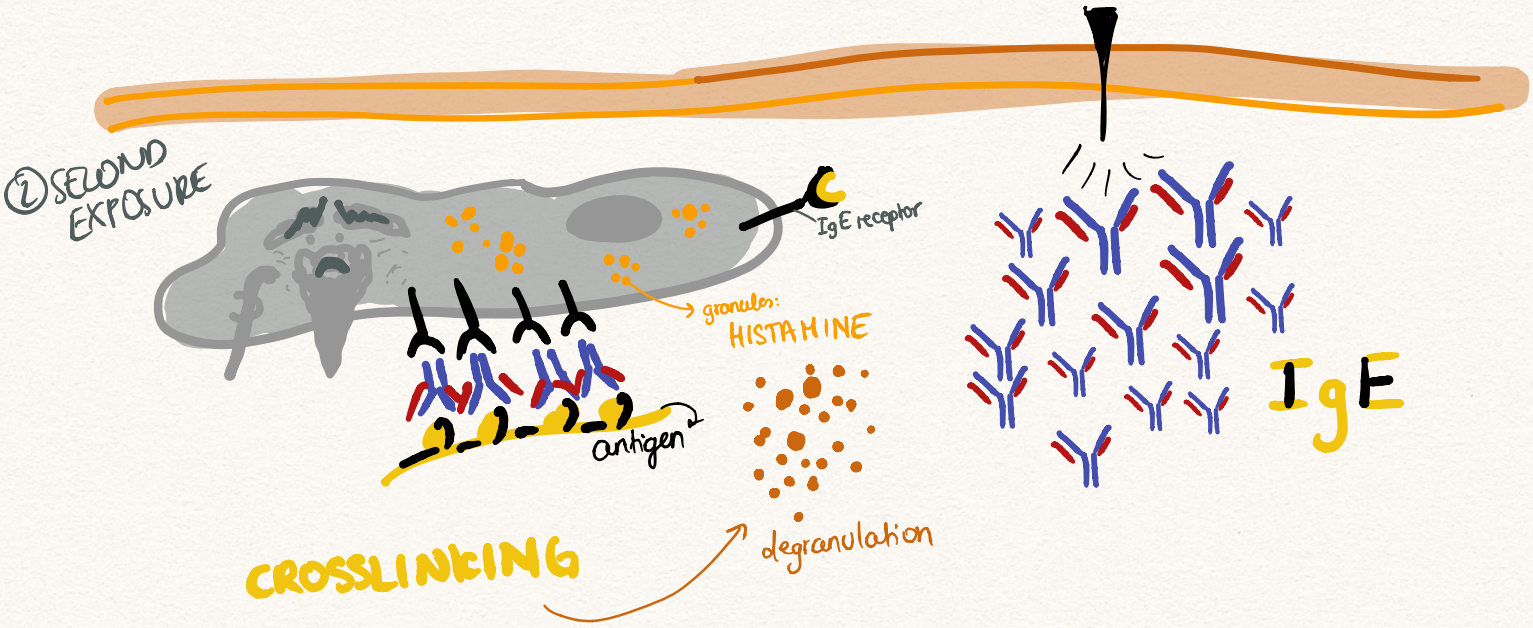
(to prevent constant gut inflammation)

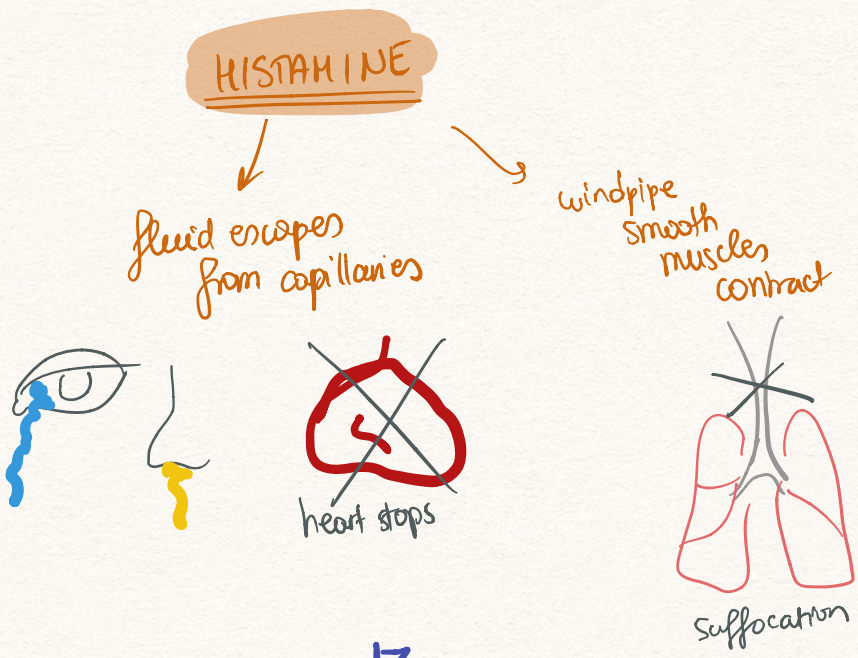
IgE



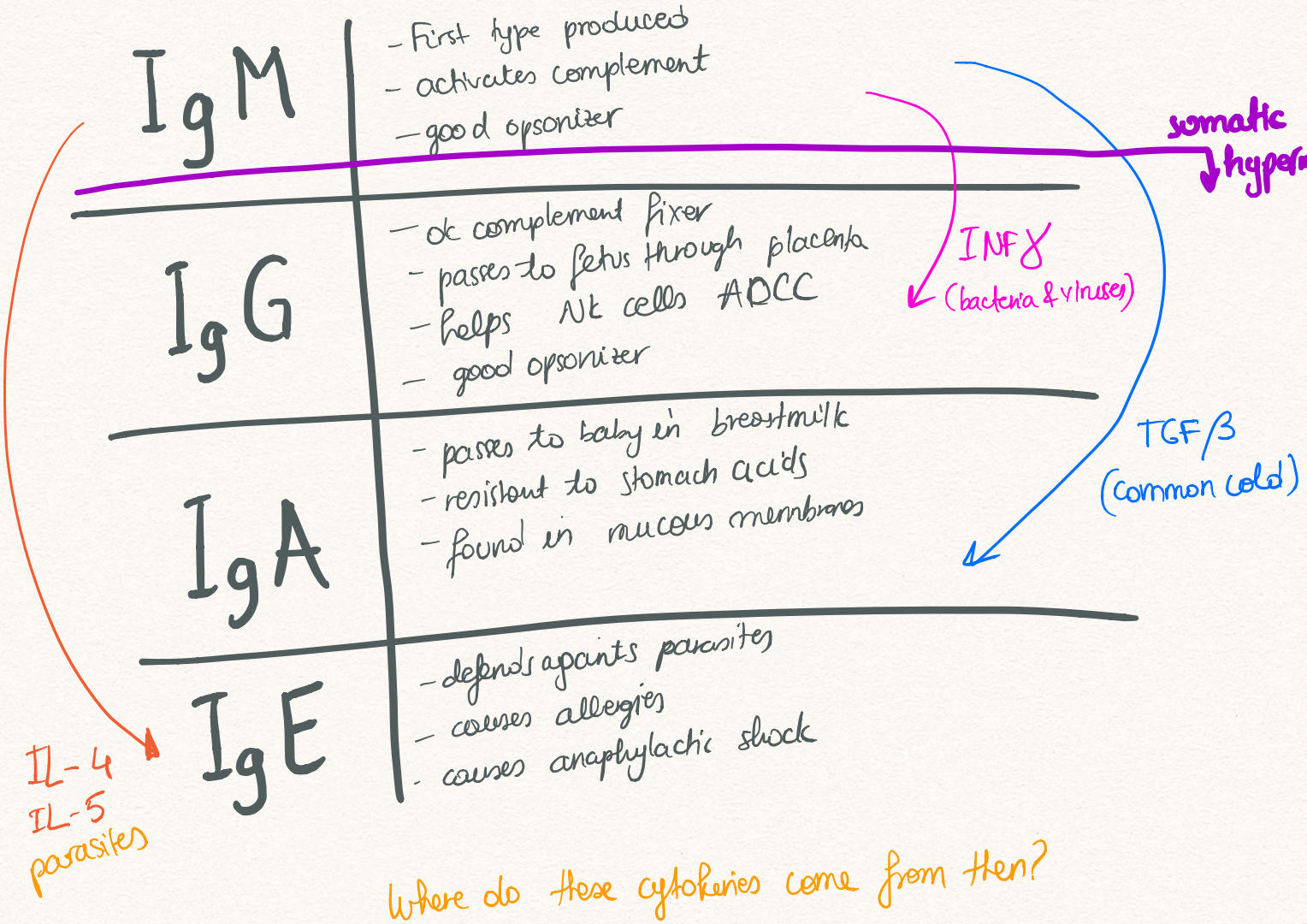
ANAPHYLAXIS







CLASS SWITCHING OF B-CELLS



Where do these cytokines come from then?

HELPER T CELLS

SOMATIC HYPERMUTATION

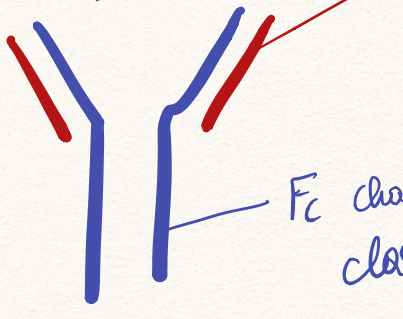
= the ability of the **V,D,J** regions of the DNA of selected B-cells, after their IgM stage to mutate their genes at a very high rate

- no change
- less affinity
- more affinity

= COMPETITION for antigens

= AFFINITY MATURATION

(IN THE PRESENCE OF HELPER T-CELLS)



Fab changed by somatic hypermutation

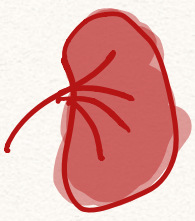
Fc changed by class switching

(if B-cells are activated without helper T-cells, they generally don't undergo class switching or hypermutation)

CAREER CHOICE?

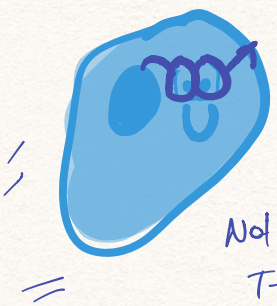
Plasma cell

memory B-cell

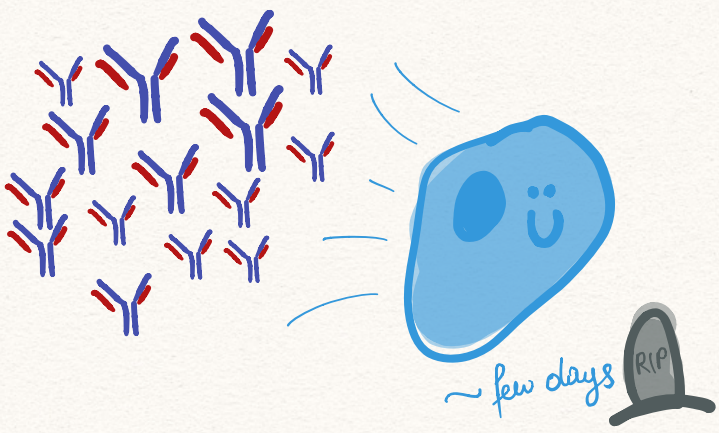


spleen

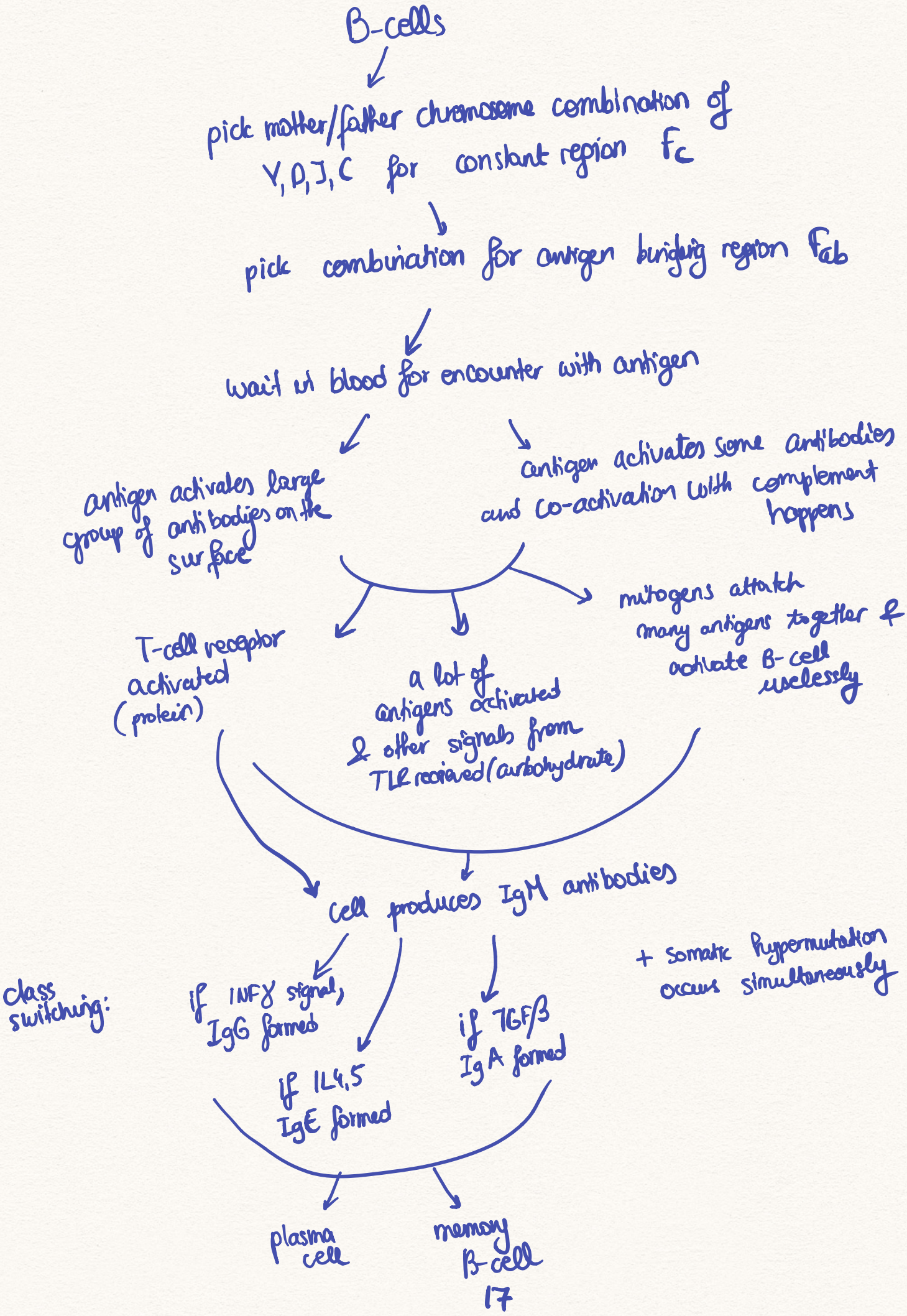
bone marrow



Not formed without T-cells though



~ few days


B-cells
pick matter/father chromosome combination of V, D, J, C for constant region Fc
pick combination for antigen binding region Fab
wait in blood for encounter with antigen
antigen activates large group of antibodies on the surface
antigen activates some antibodies and co-activation with complement happens
T-cell receptor activated (protein)
a lot of antigens activated & other signals from TLR received (carbohydrate)
mitogens attach many antigens together & activate B-cell uselessly
cell produces IgM antibodies
class switching:
if INFγ signal, IgG formed
if IL4,5 IgE formed
if TGFβ IgA formed
+ somatic hypermutation occurs simultaneously
plasma cell
memory B-cell

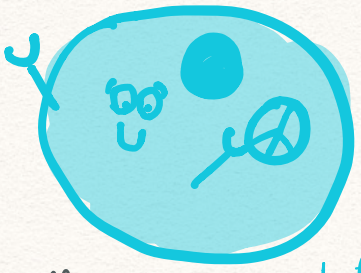
ANTIGEN PRESENTATION

MHC

MHC I

MHC II

Present to killer T-cells (CTLs)



Present to HELPER T-cells

- on all cells
- compatible part on edges of molecule
- ~9 aa
- random proteasome chopping: most can't be used on MHC I

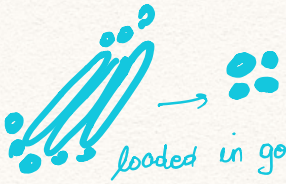
NORMAL CELL

- on immune system cells
- compatible region in middle of molecule
- fits more aas
- invariant chain = blocks the MHC II until a suitable exogenous peptide is found

ANTIGEN PRESENTING CELL

- proteasome chopping not random
- preferentially cut after hydrophobic/basic regions = more sticker

loaded in ER



loaded in golgi → endosomes

endosome + phagosome + MHC II + invariant chain

↓

presenter MHC II molecule to cytoplasm

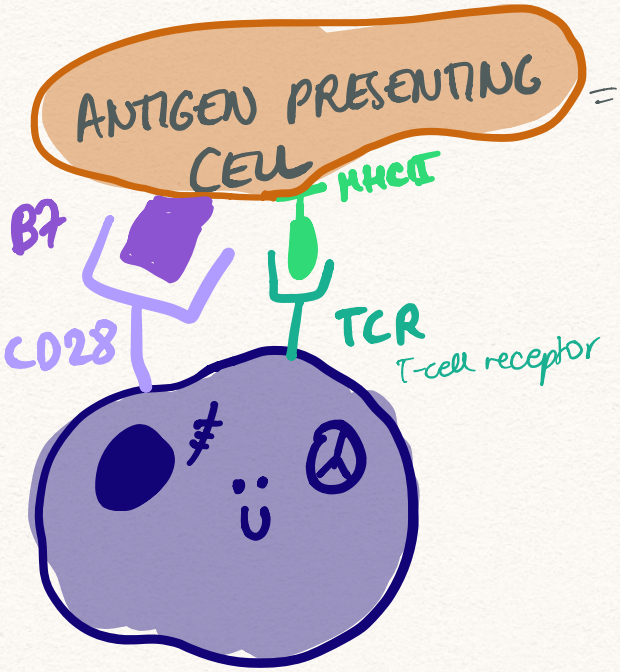
What is happening INSIDE cell

WHAT IS happening OUTSIDE cell

TO PRODUCE THEM:

1. proteasomes cleave old/unfoldable/misfolded proteins
2. peptide chain transported to the ER by TAP transporters
3. binding of the peptide to the MHC I molecule
3. transported to Golgi, to endosome, invariant chain removed, exogenous peptides added → formed MHC II molecule

= separate loading pathways for MHC I - MHC II



= a cell equipped to provide both MHCI - MHCII display & co-stimulation to activate a killer/helper T-cell

= T-CELL ACTIVATOR

(in contrast, a normal cell cannot activate a T-cell, it can just alert it)

- ☑ T-cell receptor connected to MHC II
- ☑ CD28 recieves a B7 co-stimulatory signal

1. Activated dendritic cells — 1st
2. Activated macrophages — 2nd
3. Activated B-cells — 3rd

DENDRITIC CELLS

Can't kill

photograph bullshit going on

! Distinguish from plasmacytoid dentritic cells: interferon α,β producers → these are very different cells !

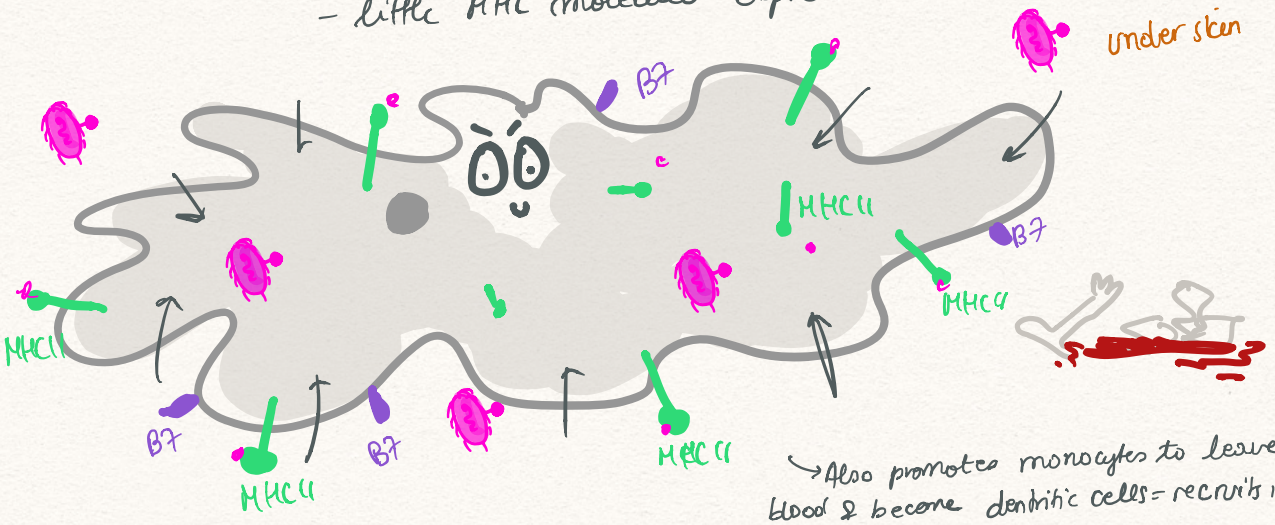
most important ANTIGEN PRESENTING CELL because they activate virgin T-cells (which need a lot of receptor cross-linking and stimulation to be activated)

1 when resting:

They are "wire" tasters. Sit just below the epithelium, first line of defence

- Take in 4 times their cytoplasm volume in EC fluid and just spit it out
- little MHC molecules expressed

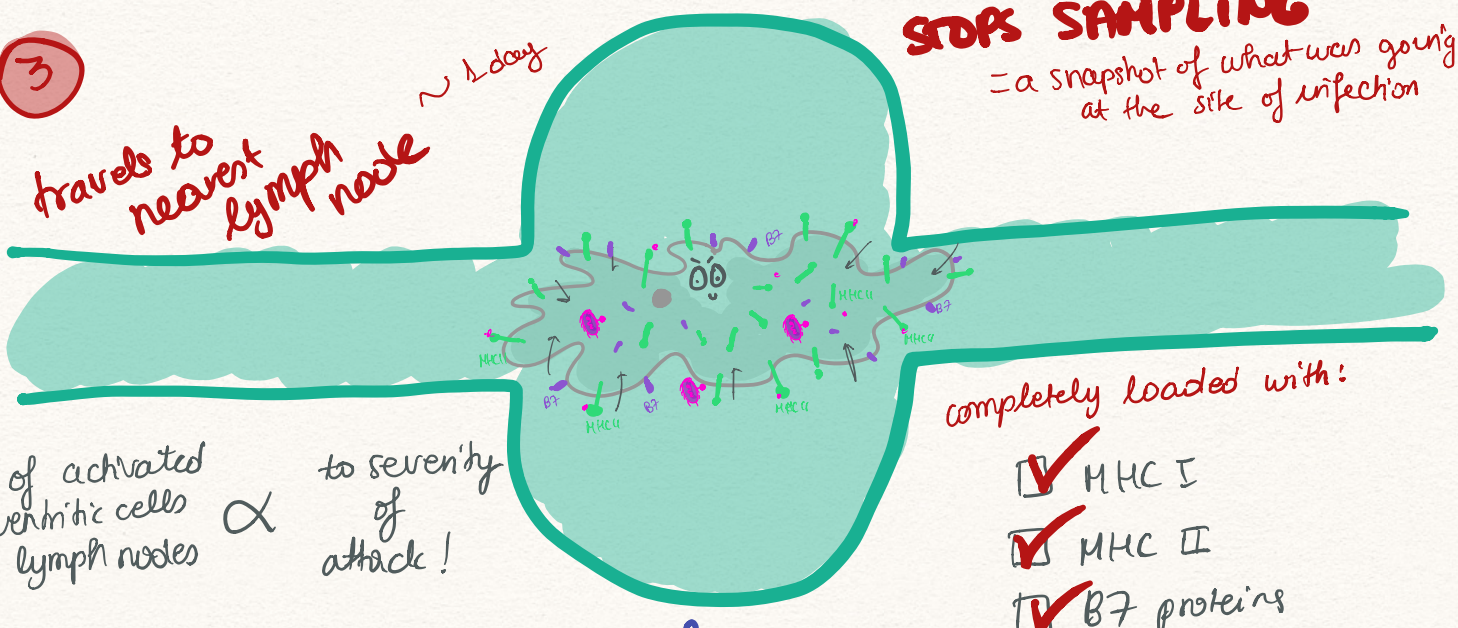
2 under attack ↓ activation



→ Also promotes monocytes to leave blood & become dentritic cells = recruits its replacements

3 travels to nearest lymph node ~ 1 day

STOPS SAMPLING = a snapshot of what was going on at the site of infection



completely loaded with:

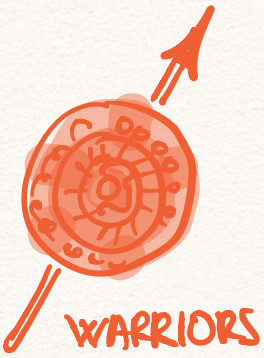
- [x] MHC I
- [x] MHC II
- [x] B7 proteins

nr. of activated dentritic cells in lymph nodes ∝ to severity of attack!

2o

can't travel

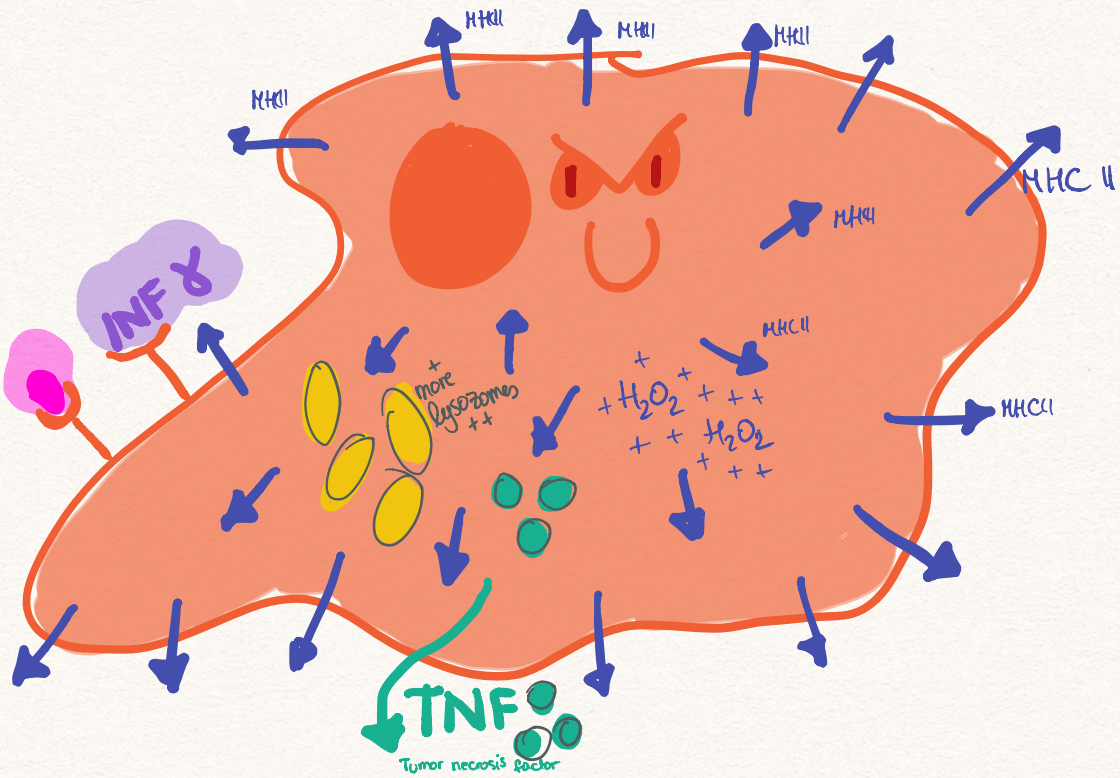
MACROPHAGES



~ to dentritic cells, but → depend on signals to start displaying MHC II molecules (INF γ)

Restimulate activated T-cells on site

(in contrast, dentritic cells activate virgin T-cells at lymph nodes)



B-Cells

Virgin ↙ Unactivated:
= few MHCII molecules

↘ experienced Activated:
= many MHCII molecules
+ B7 proteins

* THEY CAN CONCENTRATE ANTIGEN
— which the other cells can't do

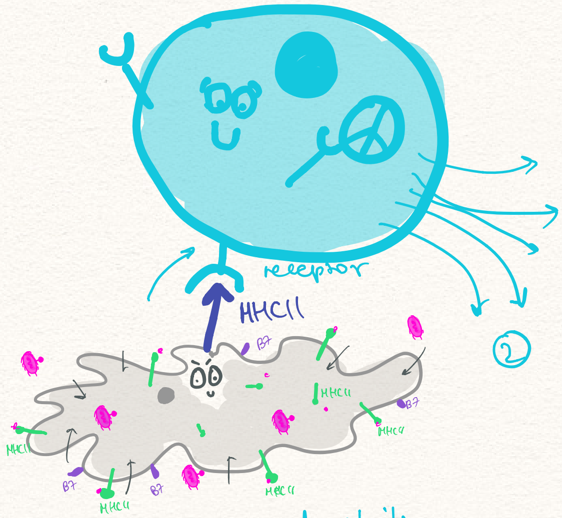
① DENTRITIC → first to encounter, be activated, and activate T-cells

② MACROPHAGES → are on the front lines so can keep T-cells activated

③ B-CELLS → later on (virgin) / early (experienced)
can activate <u>many</u> T-cells <u>fast</u>

HELPER T-CELLS

= secretors



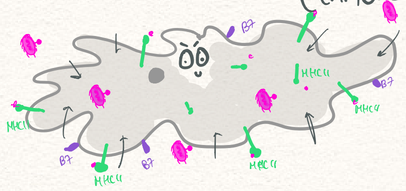
① activated dentritic cell activates helper T-cells from naive/resting → active

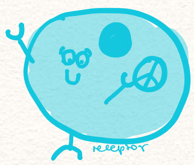
secretes

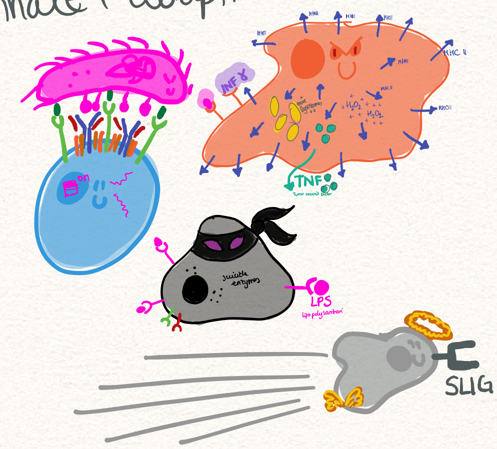
- IL-17, IL-21 — fungi Th17 cells
- IL-2, TNF, INF γ — virus/bacteria Th1-cell
- IL-4, IL-5, IL-14 — pathogen/bacteria in digestive tract Th-2 cell

} These are the cytokines which activate other cells and regulate the immune response

① dentritic (innate) → ② Th cell (adaptive) → ③ Nk-cells, neutrophils, B-cells, macrophages (innate + adaptive)

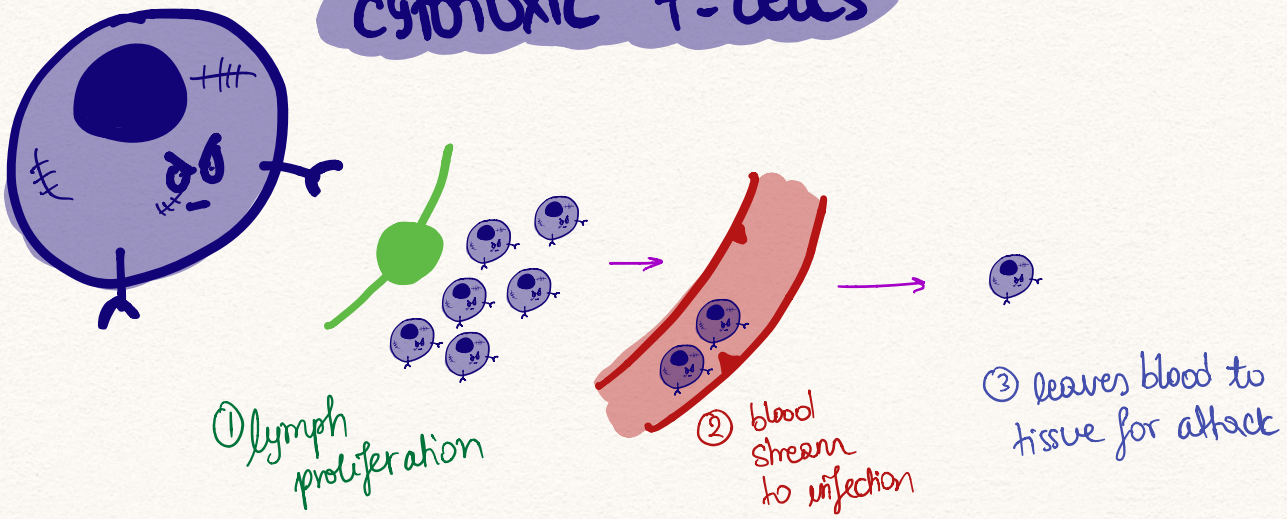






So the innate immune system recognizing a threat is essential to the adaptive immune system being activated: without this there will be no $T_h$cell activation and therefore, no response

CYTOTOXIC T-CELLS



① lymph proliferation

② blood stream to infection

③ leaves blood to tissue for attack

① identification by T-cell TCR

② binds to the cell via adhesion molecules

③ a mixture of perforin and granzyme B are given to the target cell

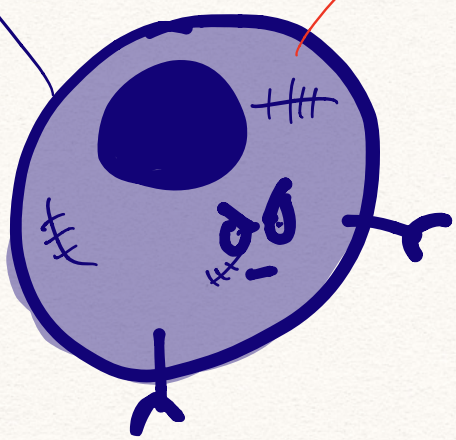
④ perforin forms holes in the endocytosed vesicle

⑤ GRANZYME B causes cell death by apoptosis

perforin

~C9 complement

TARGETED



FasL

Fas ligand L

① binds to FasL receptor on target cell

② causes target cell to die by apoptosis

Apoptosis VS. Necrosis

Apoptosis = controlled cell death, toxic substances packaged & then taken away by macrophages, no damage to other cells

Necrosis = UNcontrolled cell death, damage, inflammation inner cell parts leak out and cause damage to the surrounding cells

⚠ dangerous

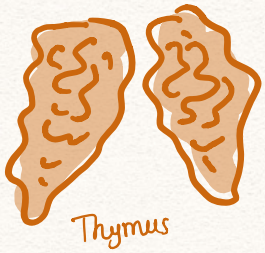
APOPTOSIS: any viral DNA is also killed with the rest of the cell by macrophages

→ highly controlled cell death

SECONDARY LYMPHOID ORGANS

① Primary lymphoid

Bone marrow

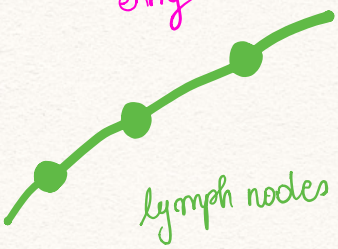


Thymus

1) production
2) maturation

Bring lymphocytes & antigen-presenting cells close together in an environment that maximizes the chance that the right B & T cells are activated

② Secondary lymphoid organs



focal pathogen entry

lymph nodes

breathed in pathogens

tonsils

blood-borne pathogen

spleen

→ no incoming lymphatics!
→ no high endothelial venules!

ingested pathogen

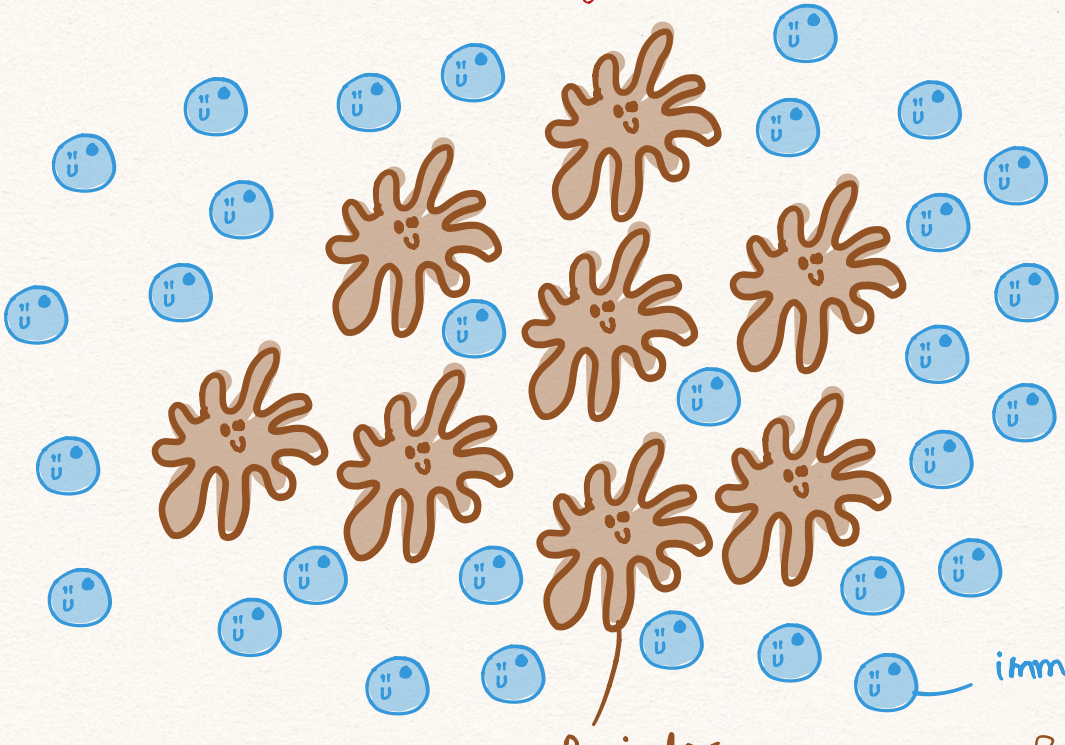
peyer's patches

~200 in body

MALT

mucose associated lymphoid tissue

What do they look like?



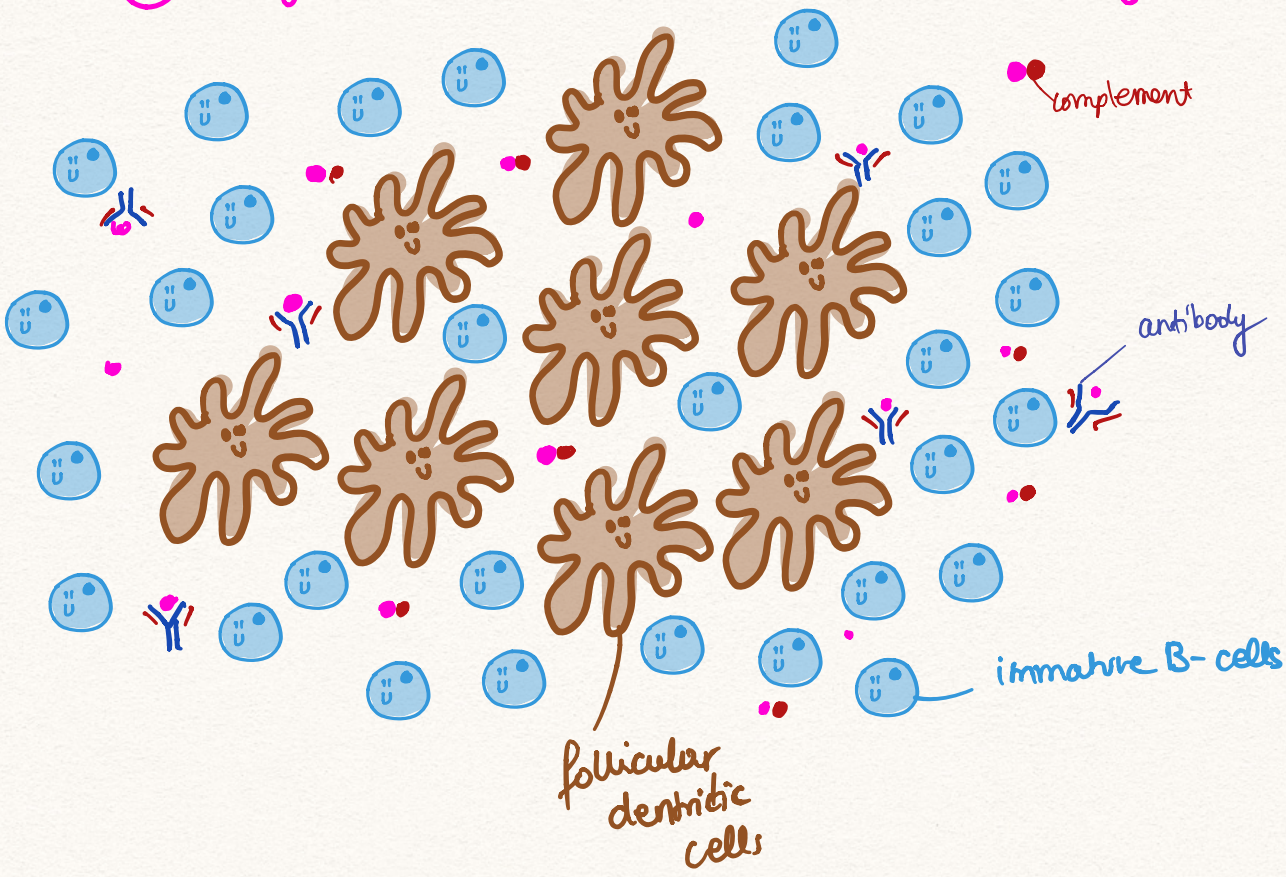
lymph node CORTEX

immature B-cells

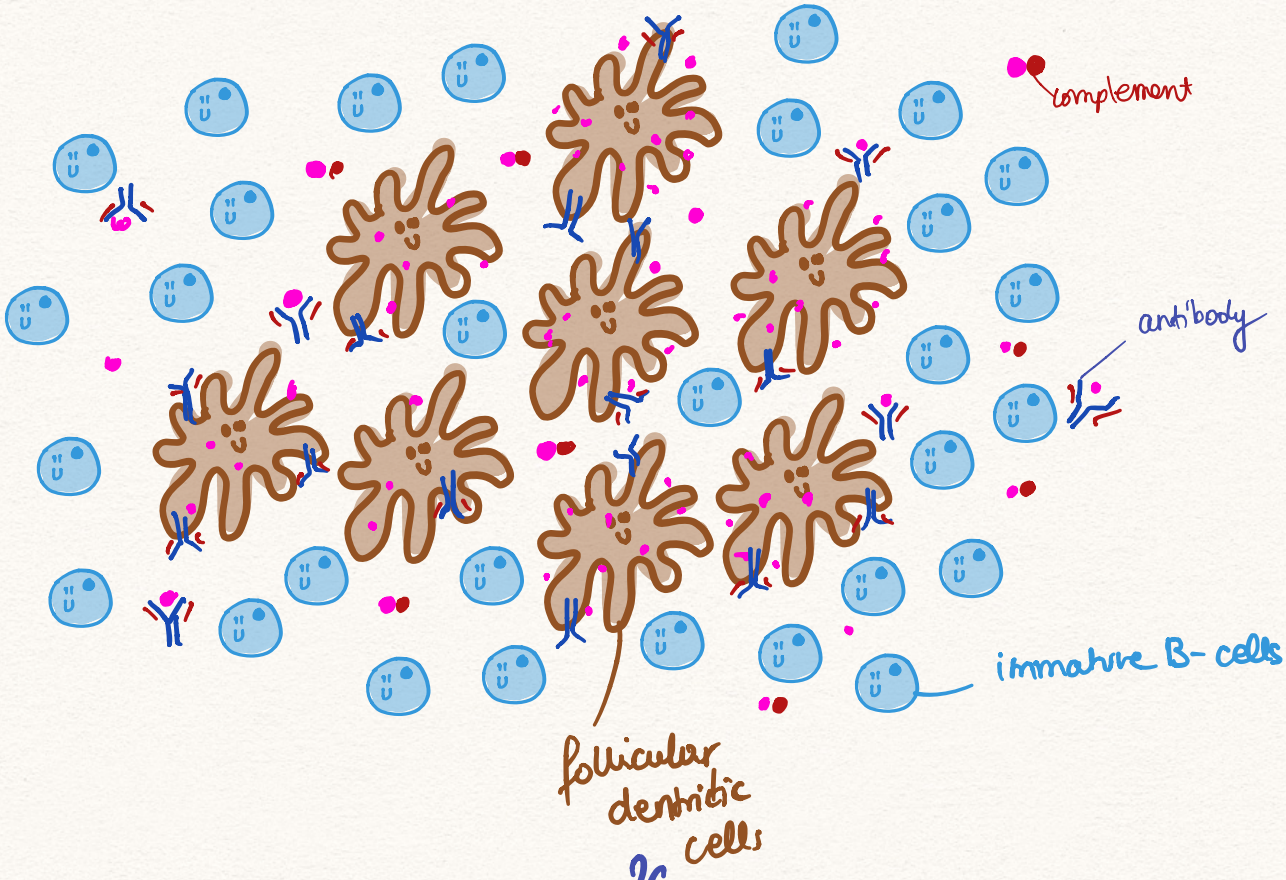
follicular dendritic cells

: always there, from early fetal stages, antigen presenters

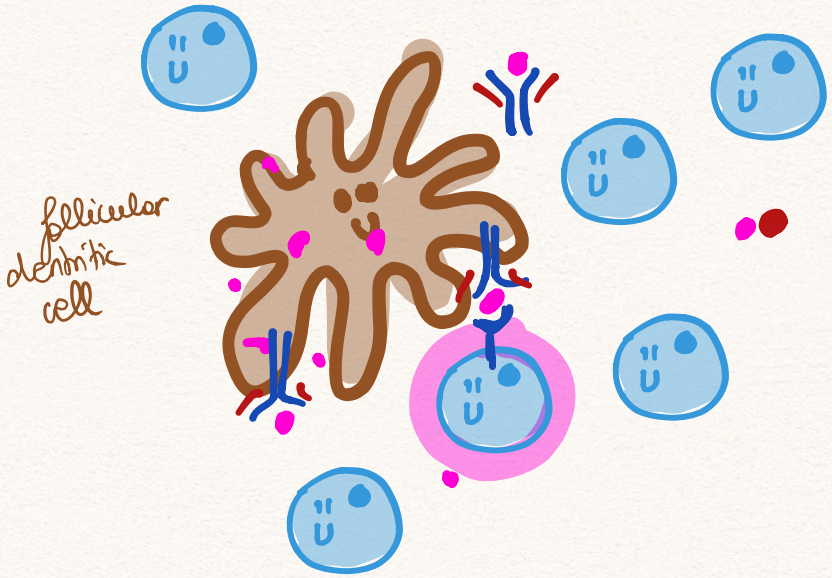
① Antigens pass through secondary lymphoid organs



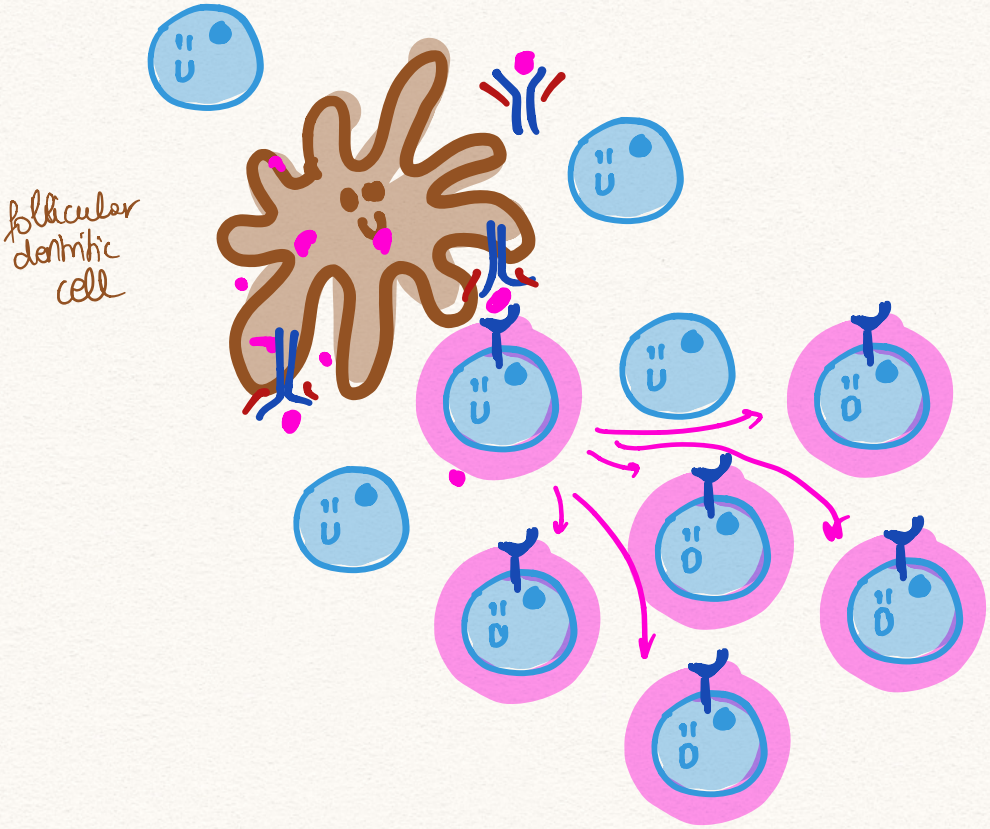
② Antigens can bind to follicular dendritic cells



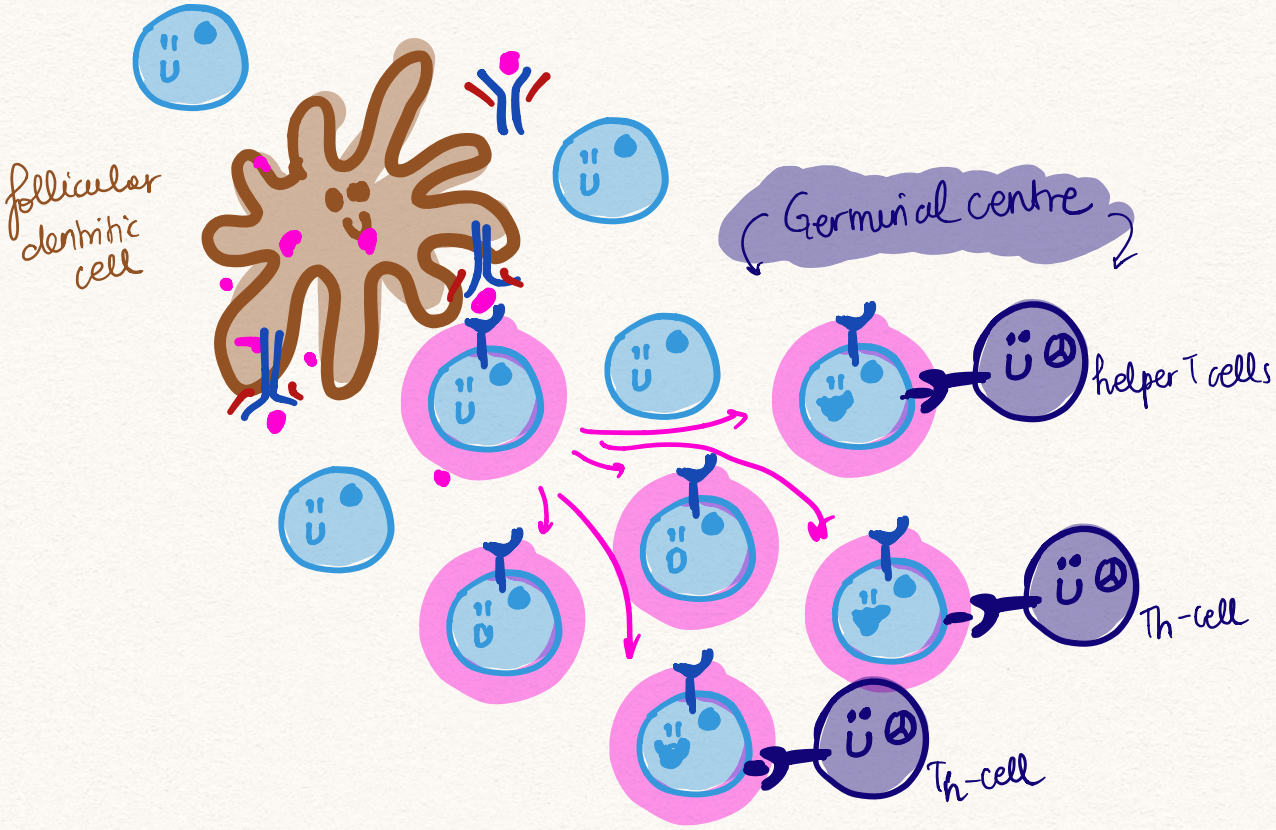
③ A B-cell which recognizes its antigen becomes activated



④ The activated B-cell will start proliferating, but it's B-cells would die

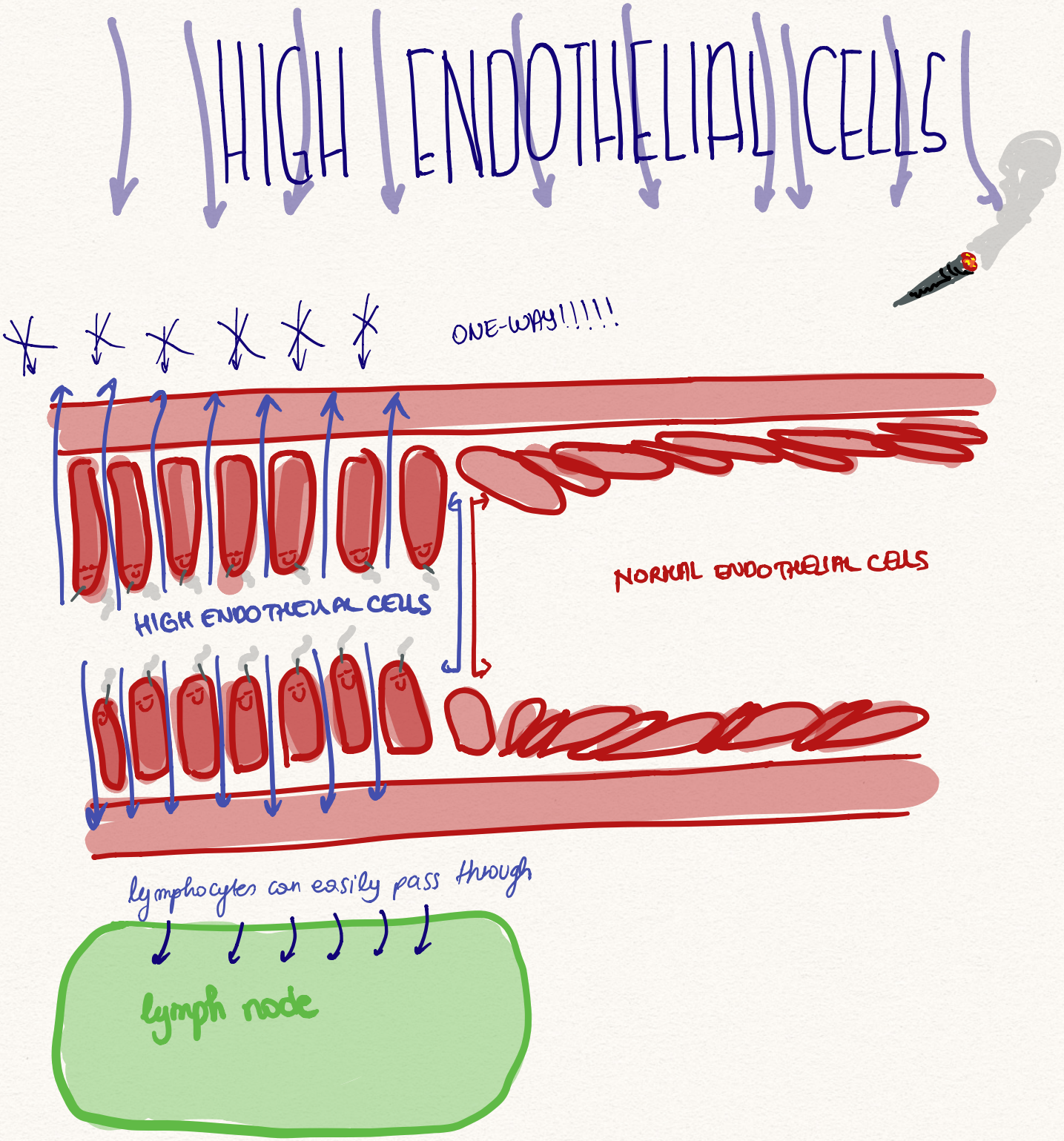


⑤ If the right T-cell comes along, it will bind to the B-cells, saving them from dying, and making them proliferate, somatic hypermutate, class switch

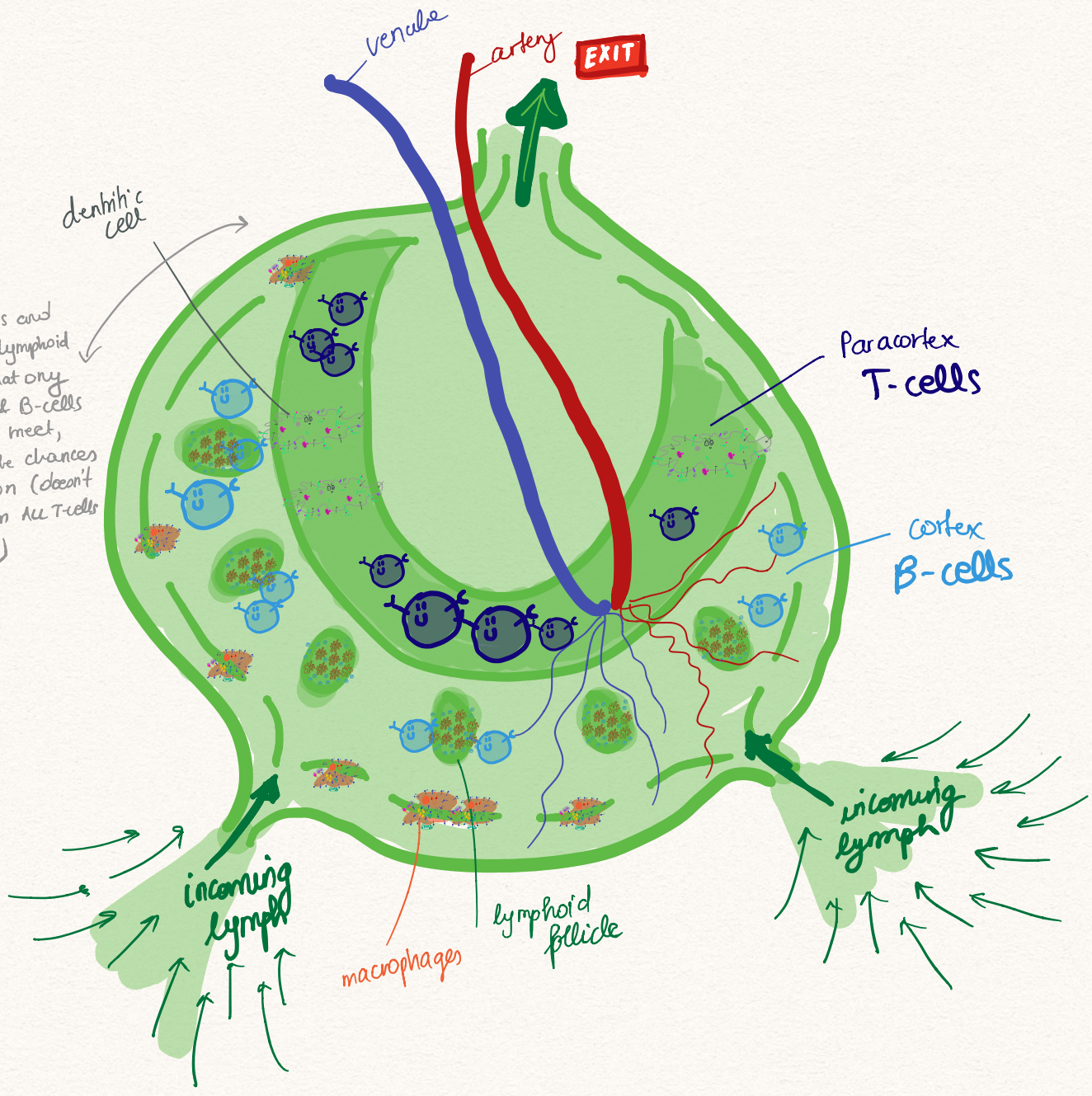


WHAT IS NEEDED TO PRODUCE ANTI BODIES?

1. APCs that display antigens to Th
2. Th cells which recognize that specific antigen
3. opsonized antigen displayed by follicular dendritic cells
4. B-cells that recognized that opsonized antigen


HIGH ENDOTHELIAL CELLS
ONE-WAY!!!!!
HIGH ENDOTHELIAL CELLS
NORMAL ENDOTHELIAL CELLS
lymphocytes can easily pass through
lymph node

LYMPH NODES



by keeping B-cells and T-cells apart, the lymphoid organ can ensure that only activated T-cells & B-cells (preselected ones) meet, greatly increasing the chances of mutual selection (doesn't randomly depend on ALL T-cells & B-cells meeting)

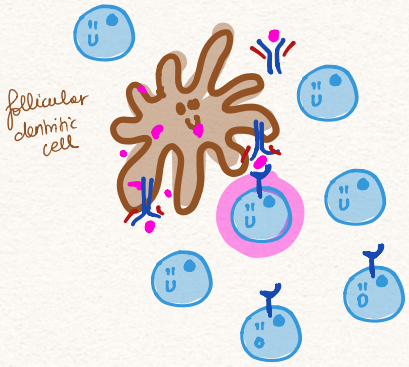
immune cells can enter via → lymph / → capillaries

but can only exit through the node!

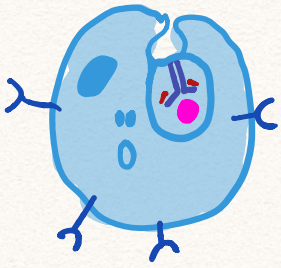
chemokines are produced (eg. by follicular dendritic cells) that attract cells to their locations (B-cells in this case)

B-CELL ACTIVATION

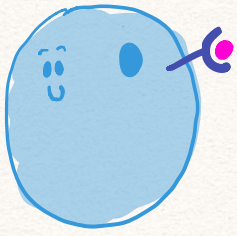
① B-cell receptor BCR recognises its cognate antigen presented on the surface of a follicular dendritic cell



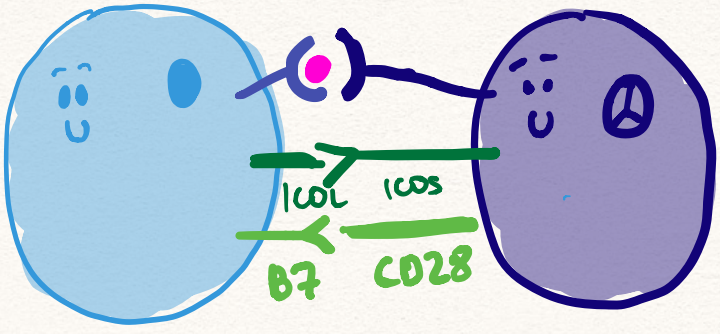
② B-cell takes in (pinocytosis) the antigen from the follicular dendritic cell and processes it



③ B-cell presents antigen on its MHC II molecules

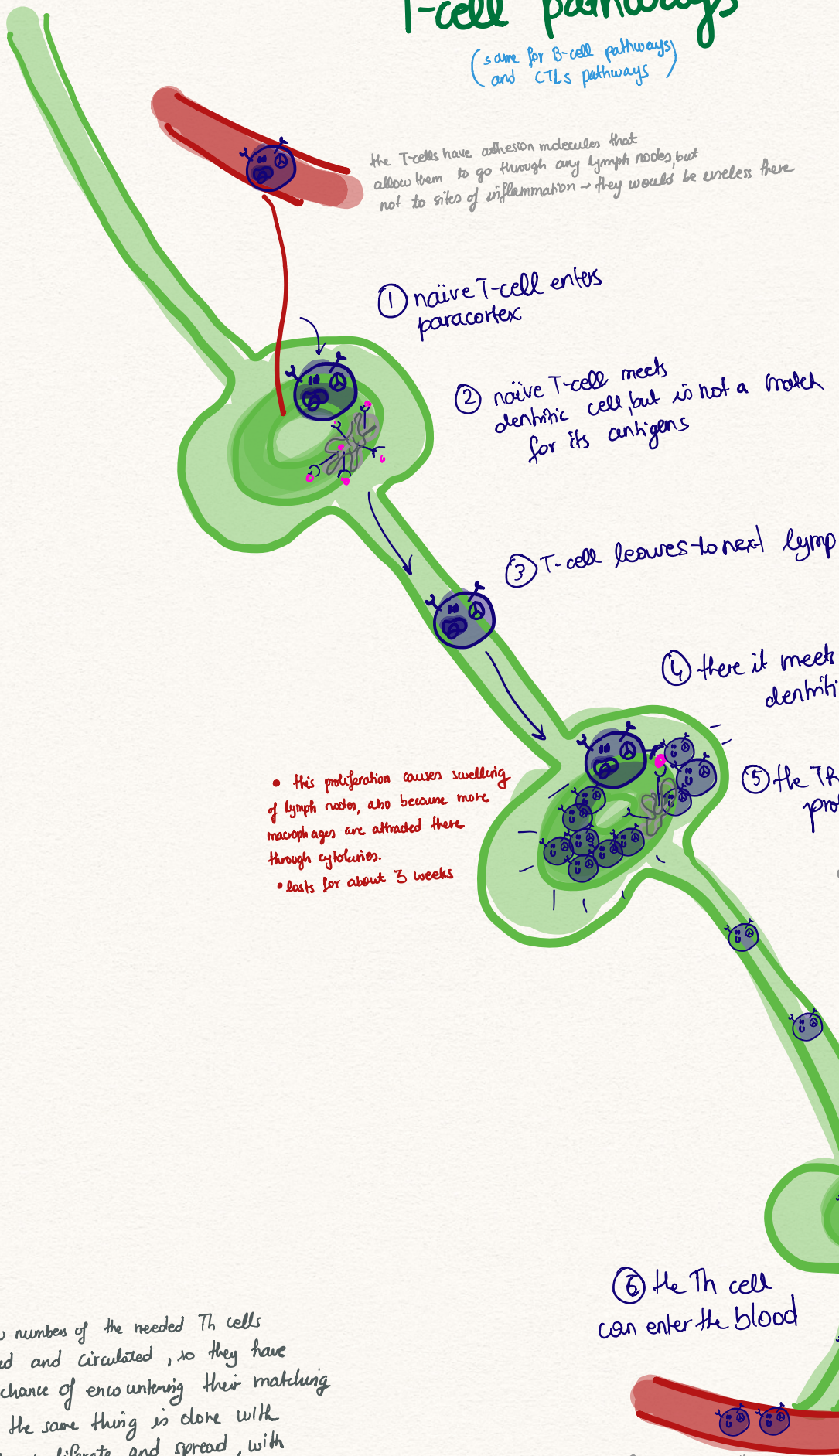


④ B-cell and Th cell co-activate each other



T-cell pathways

(same for B-cell pathways and CTLs pathways)



the T-cells have adhesion molecules that allow them to go through any lymph nodes, but not to sites of inflammation → they would be useless there

① naïve T-cell enters paracortex

② naïve T-cell meets dendritic cell but is not a match for its antigens

③ T-cell leaves to next lymph node

④ there it meets the right dendritic

⑤ the Th cell starts proliferating

- this proliferation causes swelling of lymph nodes, also because more macrophages are attracted there through cytokines.
- lasts for about 3 weeks

once activated, the T-cell expresses different adhesion molecules, so it can preferentially return to where it was activated: spleen, Peyer's patches etc.
→ have a higher chance of returning to where they are most needed / most likely to reencounter the antigen that activated them
→ more likely to be reactivated

→ B-cells, unlike T-cells usually don't leave, they settle in secondary lymphoid organs & let their antibodies travel

⑥ the Th cell can enter the blood

They can use the "roll, sniff, stop exit" method to leave the blood and enter tissues where needed

This is how numbers of the needed Th cells are increased and circulated, so they have a higher chance of encountering their matching B-cell → the same thing is done with B-cells to proliferate and spread, with follicular dendritic cells instead of dendritic cells

Why do mothers kiss their babies?

A baby does not efficiently produce antibodies yet.

IgG antibodies → given through placenta
IgA antibodies → given through breastmilk

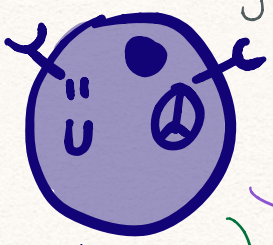
By kissing the baby, the mother samples antigens near the babies mouth → the same ones that the baby would ingest → so the mother starts producing IgA antibodies for those antigens → which are then passed on through the breastmilk

T-regulatory Cells

- Stop the immune reaction once battle won
- Stop unnecessary/too strong immune reactions

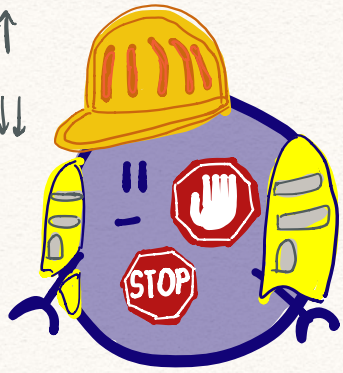
Th cells → induce immune response ↑↑

Treg cells → dampen immune response ↓↓



→ INFγ

Thelper cell → TNF

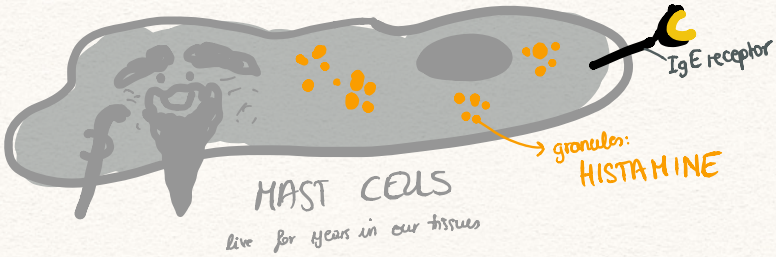


Treg cell → IL-10, TGFβ

keeps the immune system from overreacting

- **IL-10** → Blocks co-stimulatory signals (B7) and makes it harder for naive T-cells to be activated
- **TGFβ** → reduces T-cell proliferation rate → makes CTLs less potent killers

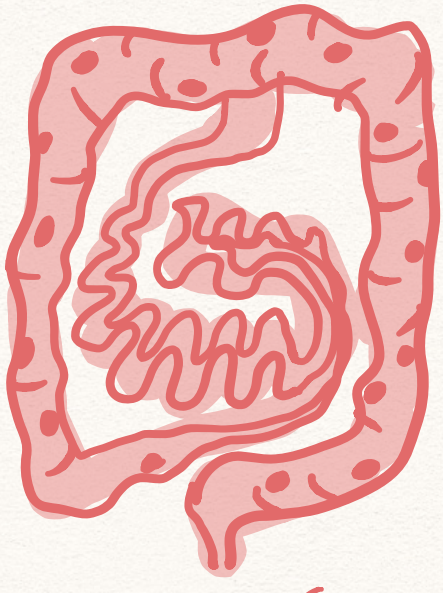
ESPECIALLY IMPORTANT FOR



live for years in our tissues

ALLERGIES

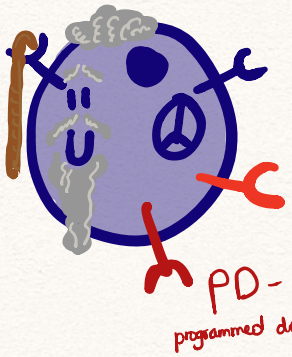
prevent mast cell degranulation



INTESTINES

prevents overreaction of immune system to helpful gut fauna

Important mechanism by which T-cells (Th / CTLs) are naturally deactivated:

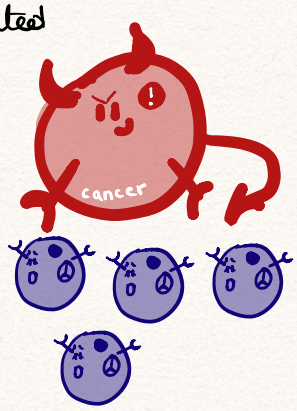


↙ competes with CD28 for B7 → instead of increasing the affinity for activation of the cell, there is a lower chance for it to be activated

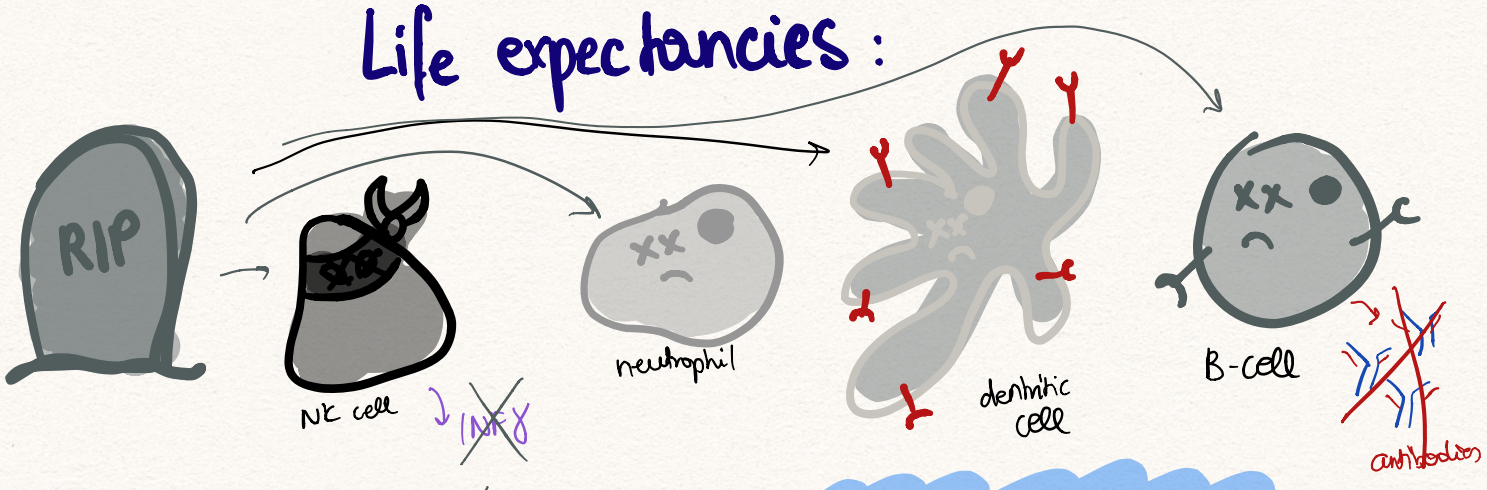
← inhibits proliferation of activated T-cells, activated by PD-1 ligands,

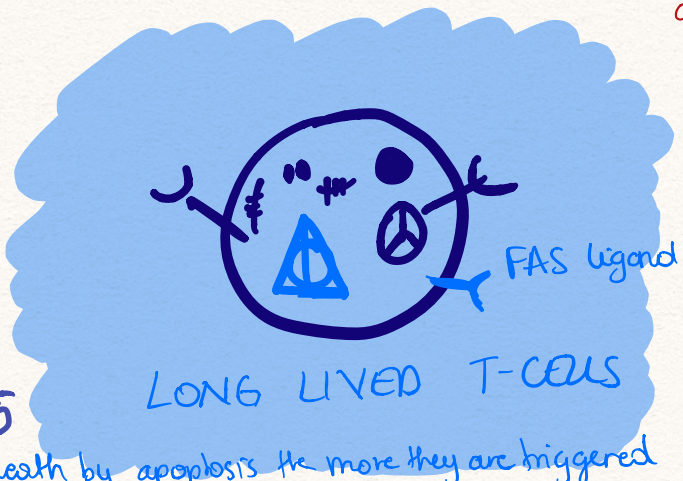
The older T-cells get, the more they express CTLA-4 and PD-1 molecules on their surface, and the higher the chance they become deactivated

⚠ cancer cells also express ligands for these two receptors, so they deactivate cells



Life expectancies:

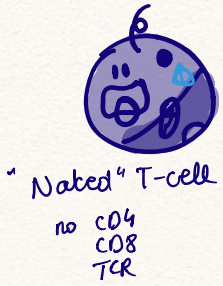




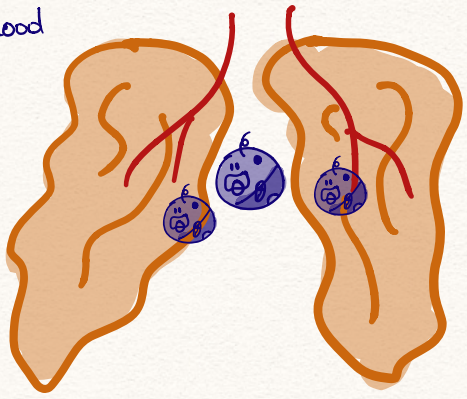
→ cell death by apoptosis the more they are triggered

T-cell Maturation

① T-cells enter Thymus from blood



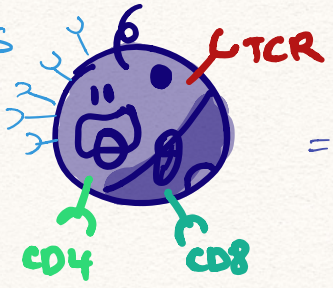
"Naked" T-cell
no CD4
CD8
TCR



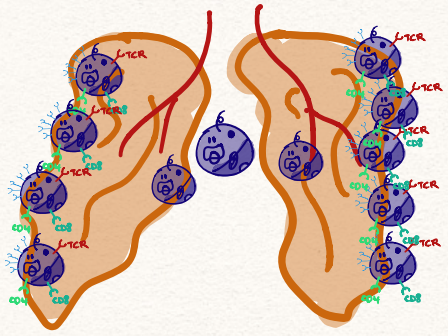
no incoming lymphatics

Immortal cell because no FAS expressed!

② a sucessful T-cell produces both a functional TCR, and CD4 and CD8

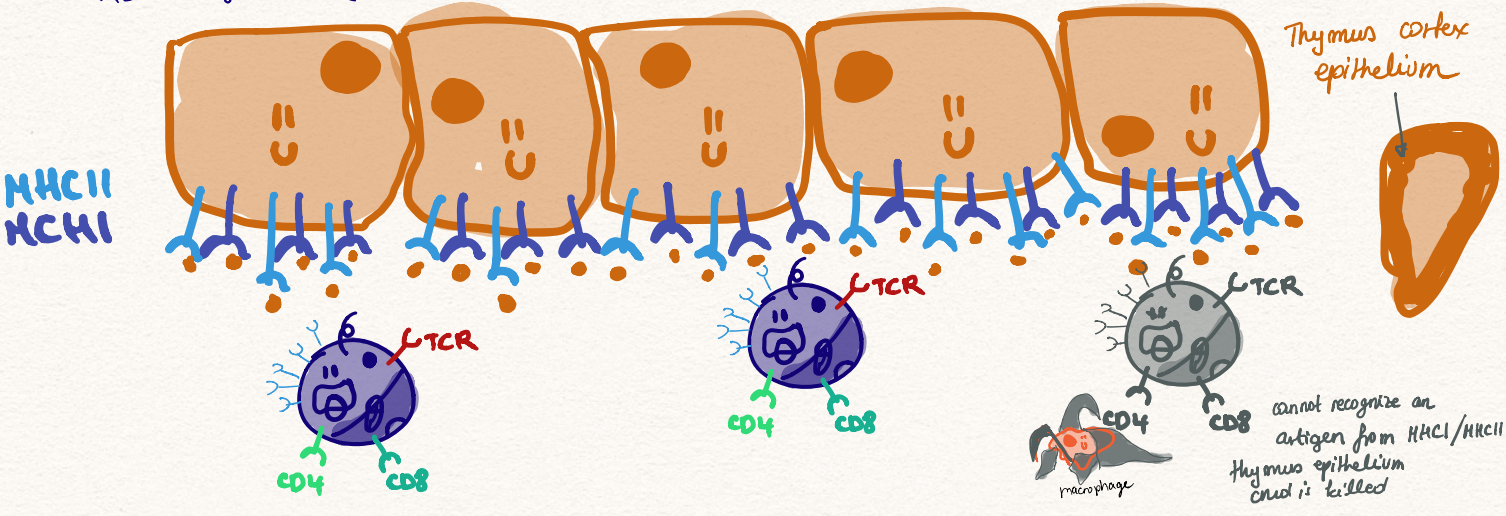


= double positive cell
DP cell



Proliferation of T-cells in CORTEX of thymus

③ Thymus cortex epithelium displays both class I and class II MHC molecules on its surface (MHCII are parts of the own cells cytoplasm processed by lysosomes)



POSITIVE SELECTION
CORTEX

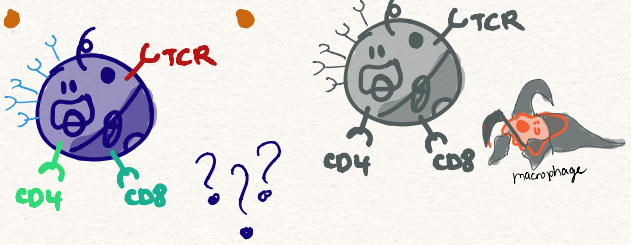
POSITIVE SELECTION?

Can you recognize class I and II MHC molecules?

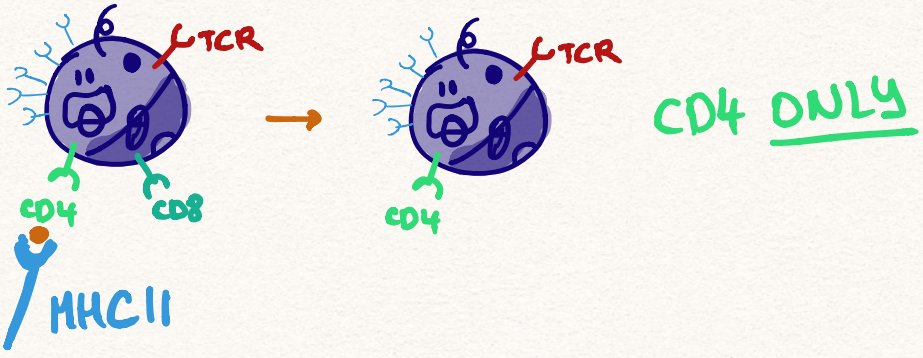
What is the importance of positive selection?

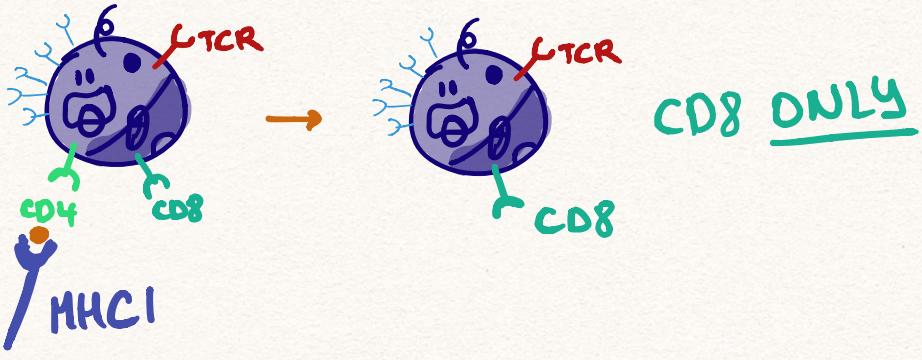
TCR are made like BCR → so some will be able to recognize unpresented antigens → we don't want these

→ so the point is to select for T-cells which are able to FOCUS only on PRESENTED antigens by MHC molecules



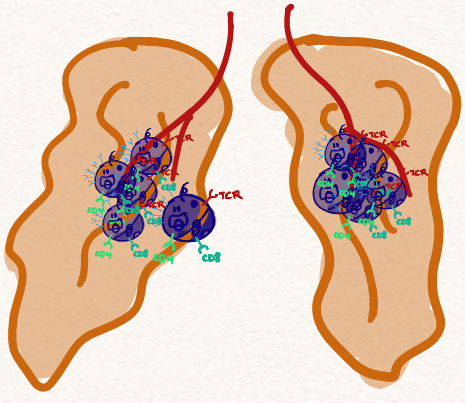
(4) The selected cells ☑ TCR ☑ CD8 ☑ CD4 and able to recognize ☑ MHC I ☑ MHC II start to change





(5) Now a test to recognize self is done: **NEGATIVE SELECTION**

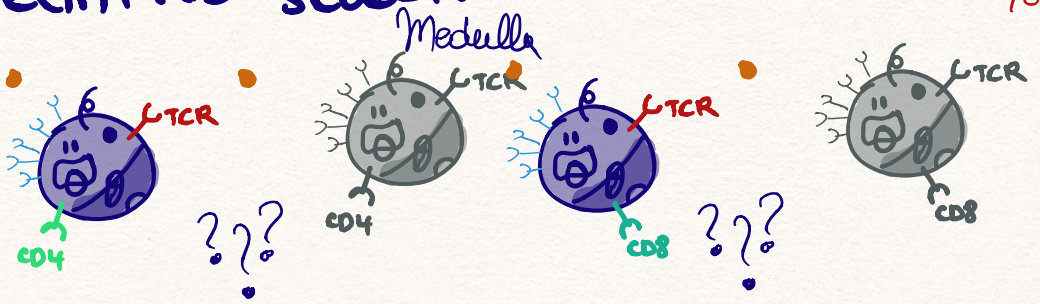
Medulla



in MEDULLA

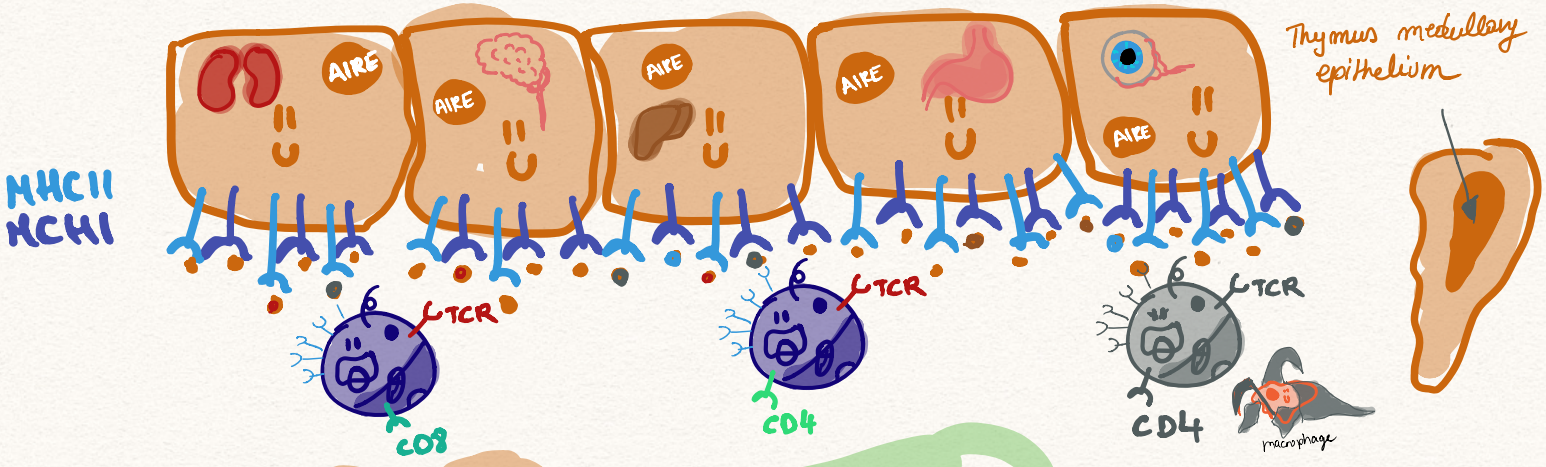
NEGATIVE SELECTION

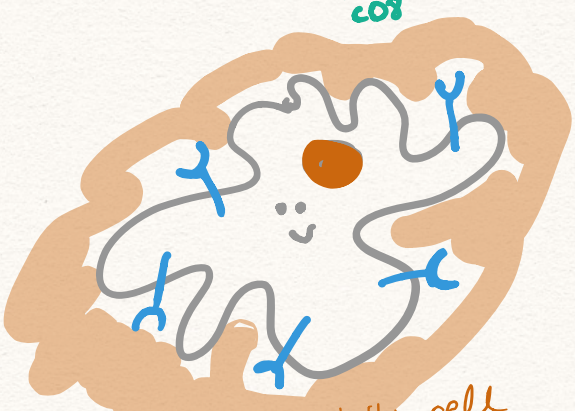
Can you recognize self peptides on the MHC molecules?
Yes? → Death.



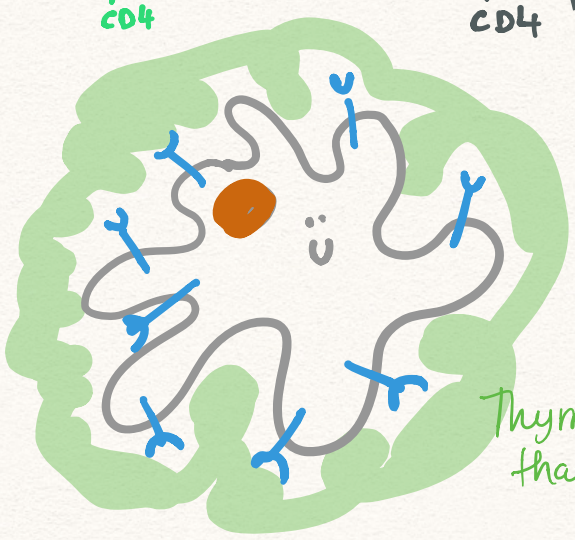
Prevents autoimmune disease through CTLs or Th cells which would attack own body as though it were an antigen.

⑥ Thymus medullary cells display not only the protein fragments of epithelial cells, but they also express those of cells from specialised tissues all around the body, due to a special transcription factor, AIRE → displaying them on both MHC I and MHC II proteins





Thymic dendritic cell → Resident in thymus

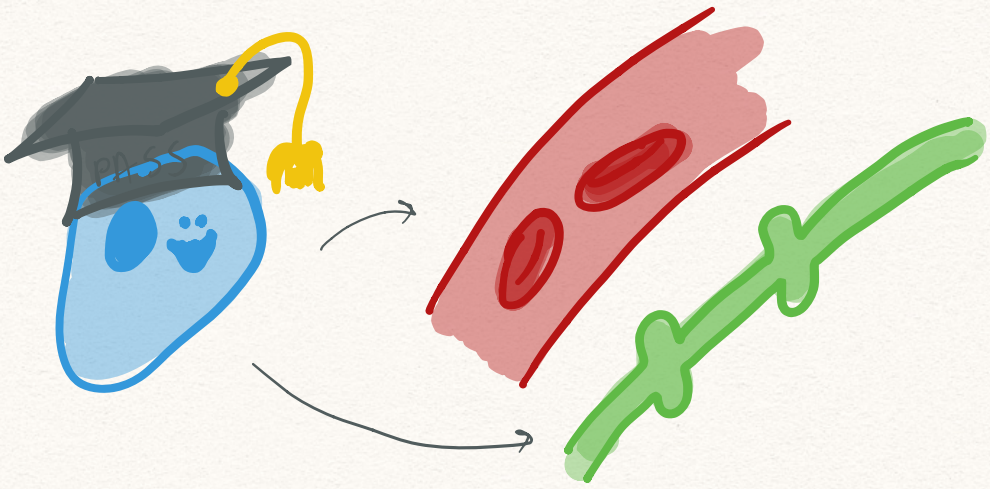


Thymic dendritic cell that travels around body

B-cell training

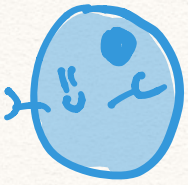
= receptor editing

can try to rearrange their light chain again if it recognizes self, and only if it isn't ok again is the B-cell killed off



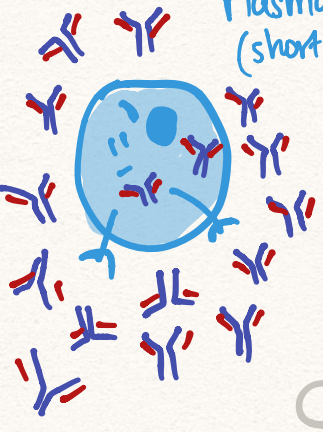
death mechanisms ≈ to those of T-cells for B-cells that recognize self as an antigen to be killed off

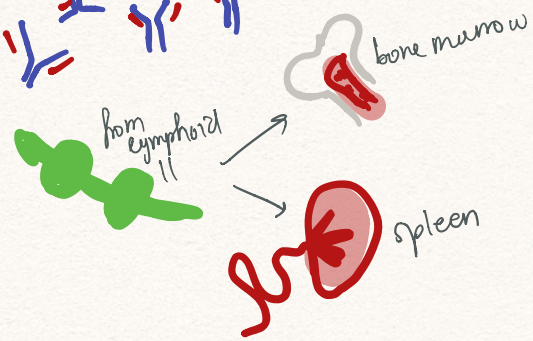
Immunological Memory



Virgin B-cell
Activated

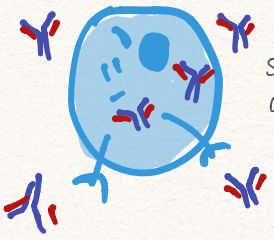
Plasma cell
(short lived)
~ few days



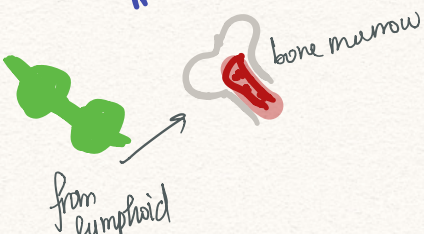


① sudden attack defense

Memory cell I
Long lived
plasma cell

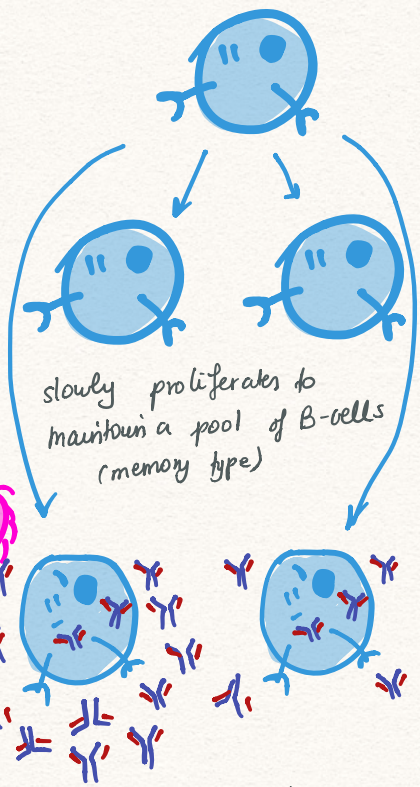


small amounts of antibodies over LONG time



③ In between immunity maintainance

Memory Cell II
Central Memory
B-cell

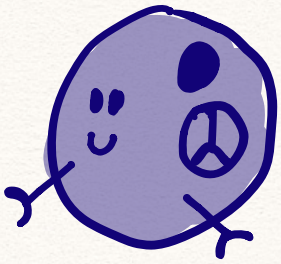


In the presence of an antigen, can also produce long and short lived plasma B-cells

② re-attack defense
→ in secondary lymphoid organs

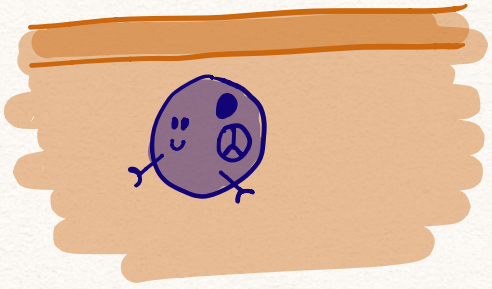
Can remain for a lifetime → not dangerous because B-cells only produce antibodies, so even if the antigen never appears, the antibody will be harmless

T cell after infection



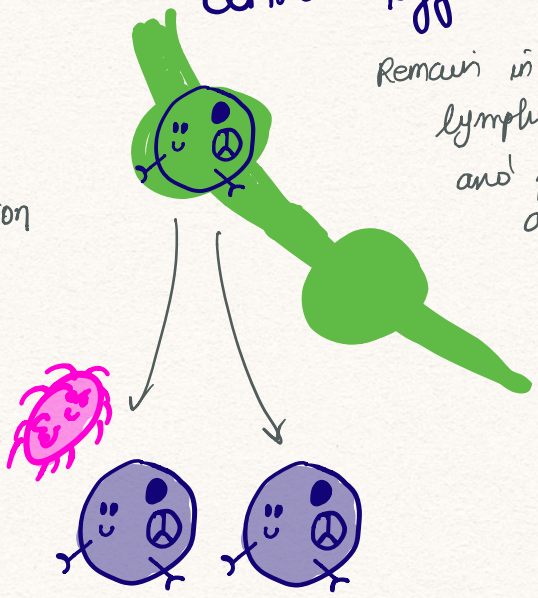
90% die by apoptosis

Memory effector T-cells



Remains in tissues near site of infection

Central effector T-cell

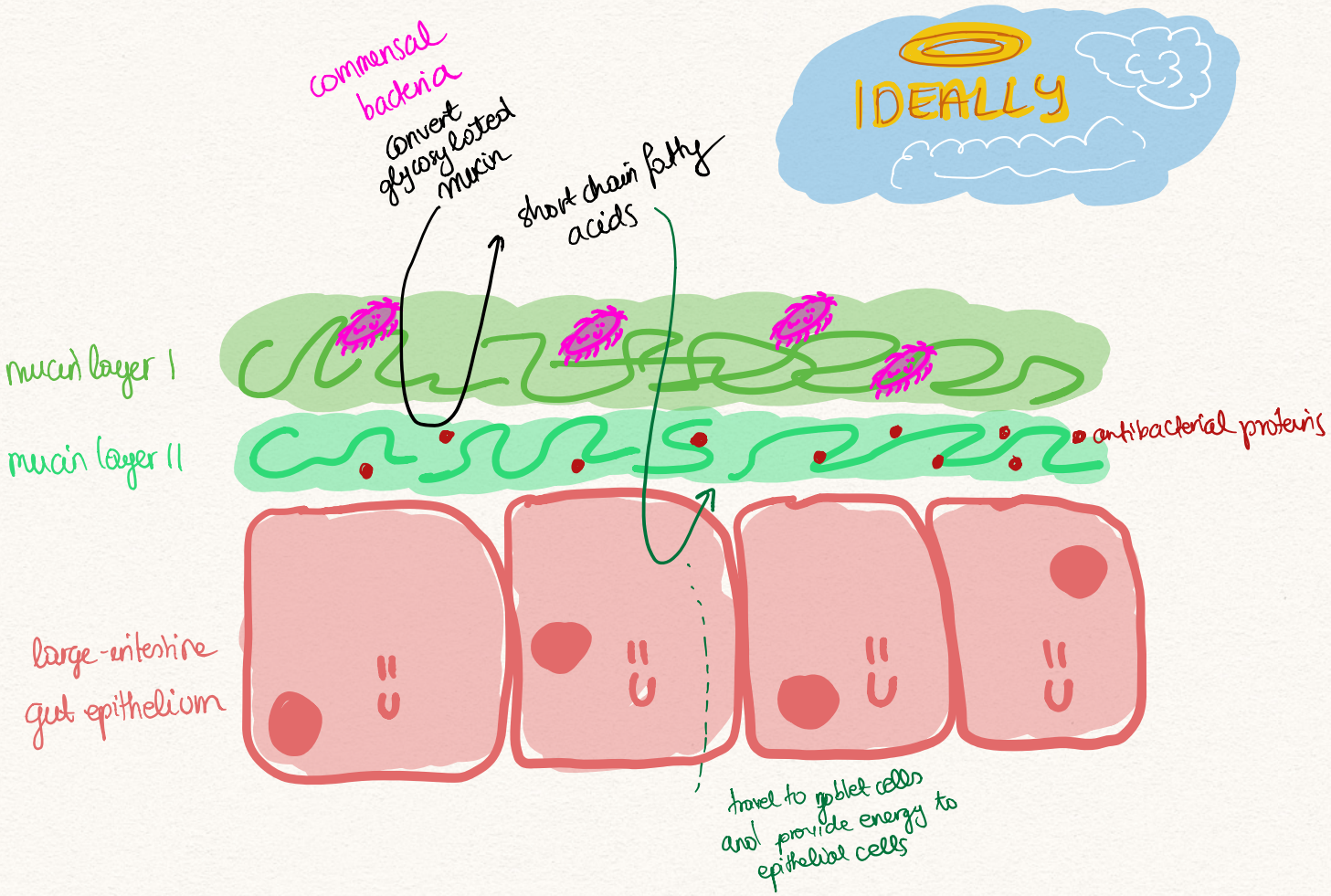


Remain in secondary lymphoid tissues, and proliferate and travel when needed

There are no T-cells that remain for a lifetime (like B cells can) This is because T-cells can produce cytokines = non-specific immune system activators (B-cells only produce antibodies, which are harmless even in absence of antigen) so we cannot risk long-long living T-cells!!

→ long lived T-cells need to go DORMANT

THE LARGE INTESTINE

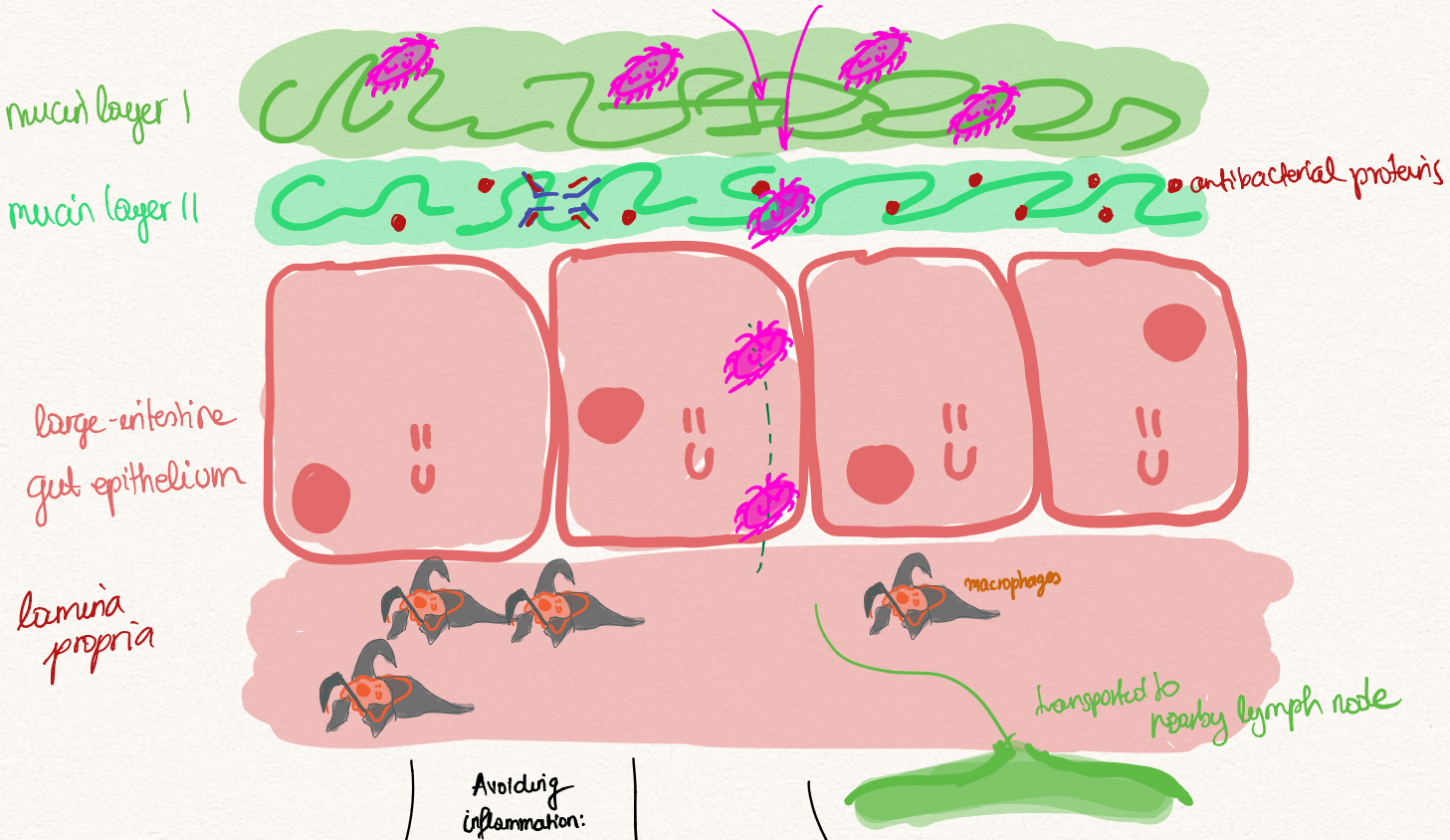


A SEPARATE immune system is away to the rest of the body:

- the cells (dendritic eg.) only travel to their local lymph nodes and not beyond
- the activated macrophages, T-cells, B-cells remain in the lamina propria and do not travel around the boo

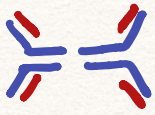
REALITY

UNDER CONSTANT ATTACK from bacteria breaking through gaps in the mucin layer



Avoiding inflammation:

non-inflammatory macrophage
=cannot produce cytokines



IgA antibodies

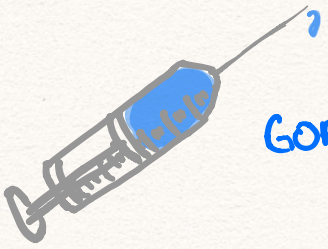
- ☑ clump antigens for removal from gut
- ☑ cannot initiate an immune response like IgG antibodies b/c their Fc region doesn't bind
- ☑ bind to invaders and prevent them entering gut lamina propria

non-local exit of cells:
unlike a splinter, where cells can be made to leak out exactly where they are needed, they are allowed to leak throughout the intestine. This is because:

1. it is likely that the same pathogen can leak anywhere in intestine
2. the intestinal immune system is always prepared, doesn't need such an alarming local response as elsewhere
   → massive inflammation avoided

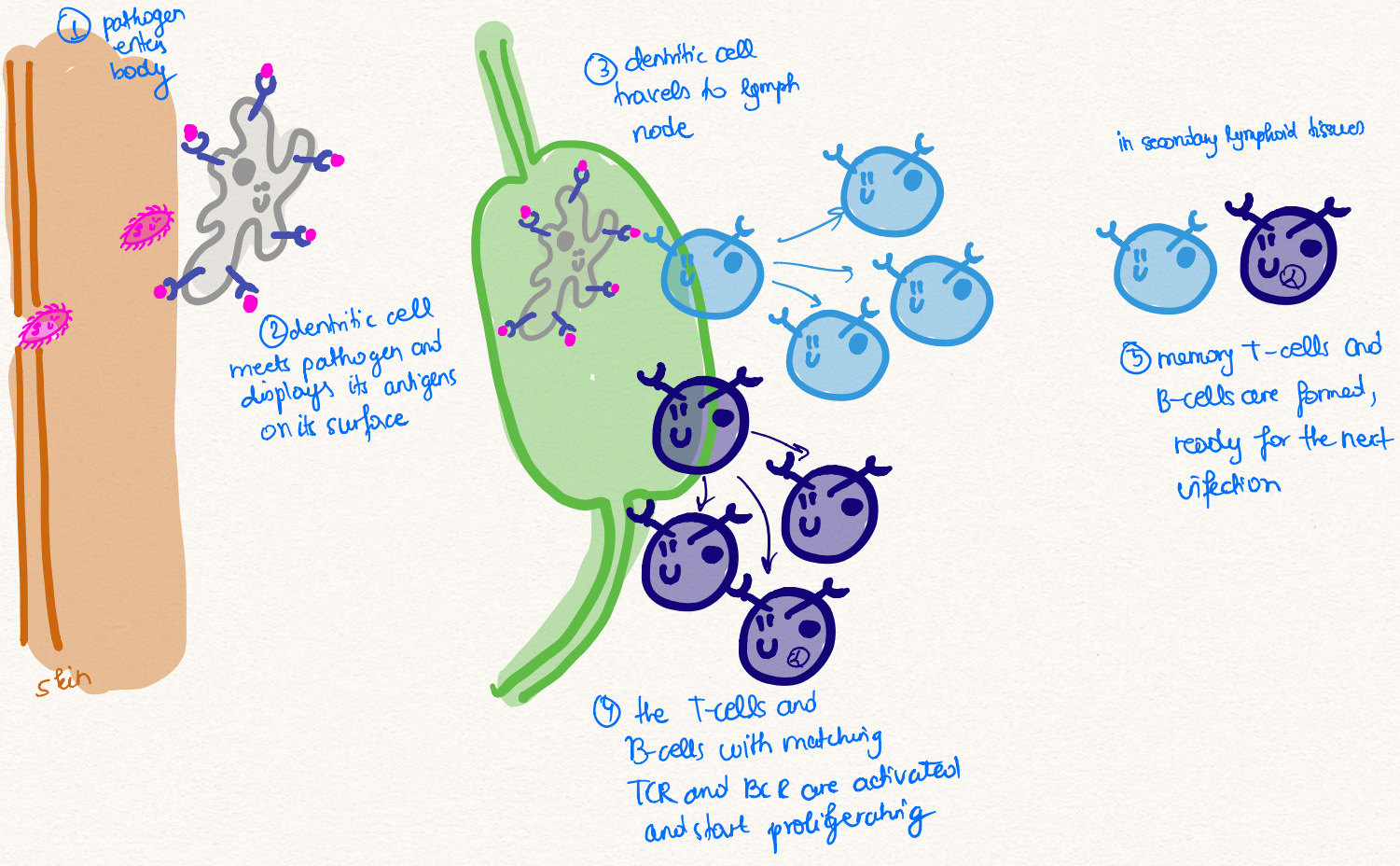
GOAL: TO AVOID INFLAMMATION: THE DEFAULT OPTION FOR THE GUT'S IMMUNE SYSTEM IS ANTI-INFLAMMATORY

VACCINES



GOAL? To produce memory T cells and memory B cells which can be there to initiate a fast immune response when their pathogen is introduced without having to put the body through the danger of actually being infected by that pathogen first

HOW? How are memory T-cells and memory B cells formed?



→ so this process can be exploited → instead of waiting to / introducing the whole pathogen, only the antigens are introduced → enough for the dendritic cell to become activated and memory T-cells and B-cells to be produced.

killer T-cells cannot be produced without the APC being actually infected by the pathogen, because it needs MHCI molecules, so memory CTLs will not be formed by this mechanism

Types of vaccines

FORMALDEHYDE TREATMENT

will "glue" proteins together, so the virus will look like one, but will be completely non-functional
= like "boots" to a wheel of car

⚠ is not guaranteed to be 100% effective on all of the viruses:
- not a big issue for the flu virus
- a HUGE issue for the HIV virus

acellular vaccine

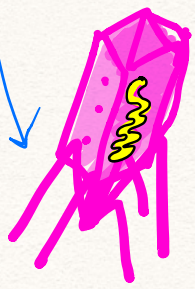
isolation and purification of only some part of bacteria
pertussis bacterium

diphtheria
tetanus

TOXINS

TOXOID

toxins produced by some bacteria are isolated, treated with **ALUMINIUM SALTS** and **TOXOIDS** are produced, which can activate B-cells and create memory B-cells

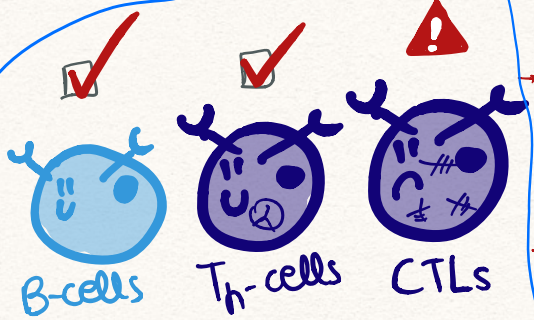


GENETICALLY MODIFIED

genetic engineering used to generate non-infectious viruses
→ no danger

hepatitis B
papillomavirus

NOT PRODUCED ☒



B-cells | T_h-cells | CTLs

→ not an issue for pathogens which do not activate CTLs anyway:
eg. extracellular bacteria which do not cause their MHCI production anyway

→ and the B-cell, Th-cell is usually good enough extra protection despite no CTLs

- but killed virus v accines do not work against either
- measles
- mumps

because of this!

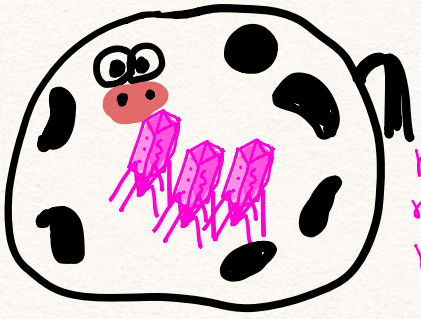
CARRIER VACCINES

Trojan horse

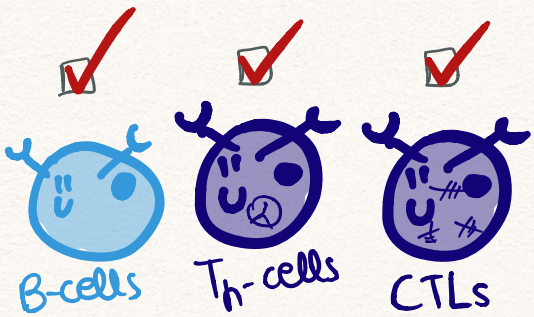
- a single gene that doesn't cause disease inserted into a virus capsule
- can "infect" host
- can certainly not cause disease

→ vaccines are grown in their non-normal host cells, so they accumulate mutations that weaken it

ATTENUATED VACCINES



measles
rubella
mumps



B-cells | T_h-cells | CTLs

⚠ SAFETY ISSUES

① can reproduce and spread to other
→ HERD IMMUNITY - but this is dangerous to some weaker immunity ppl

② virus can mutate and reactivate itself

IMMUNITY GONE WRONG

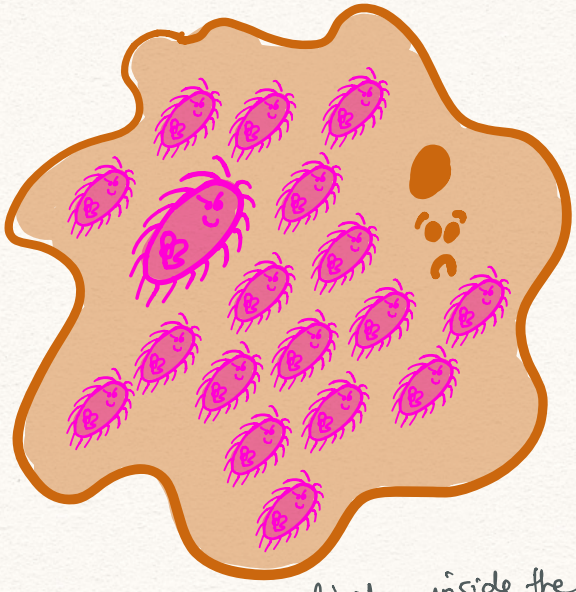
When the immune system does what its supposed to do

- TUBERCULOSIS -

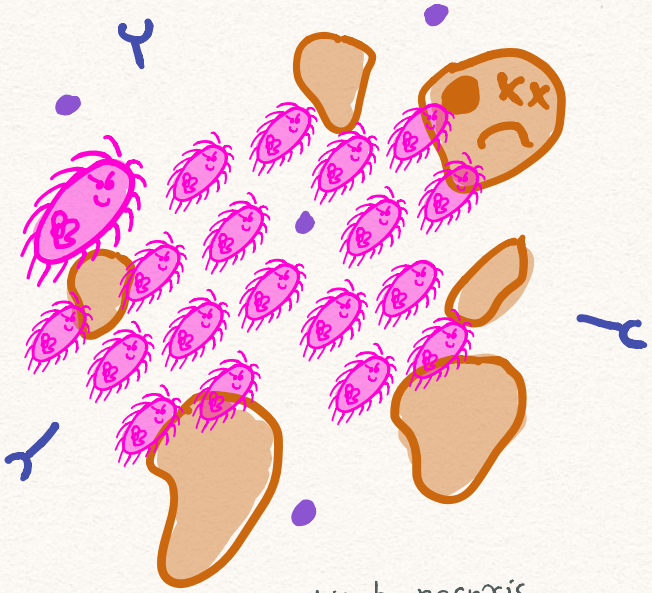
① TB bacterium enters body

② Bacterium is phagocytosed by macrophage

③ phagosome is modified by bacterium and the macrophage cannot fuse it with lysosomes

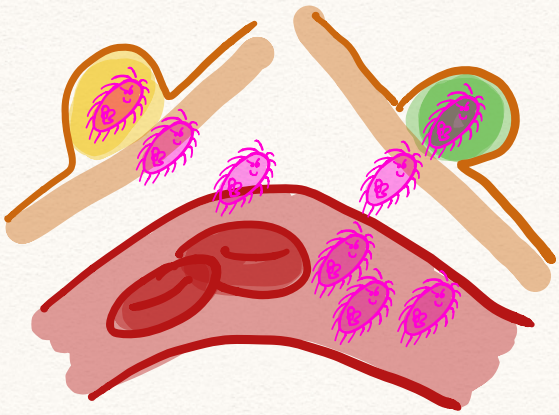


④ The TB bacterium replicates inside the macrophage using its machinery



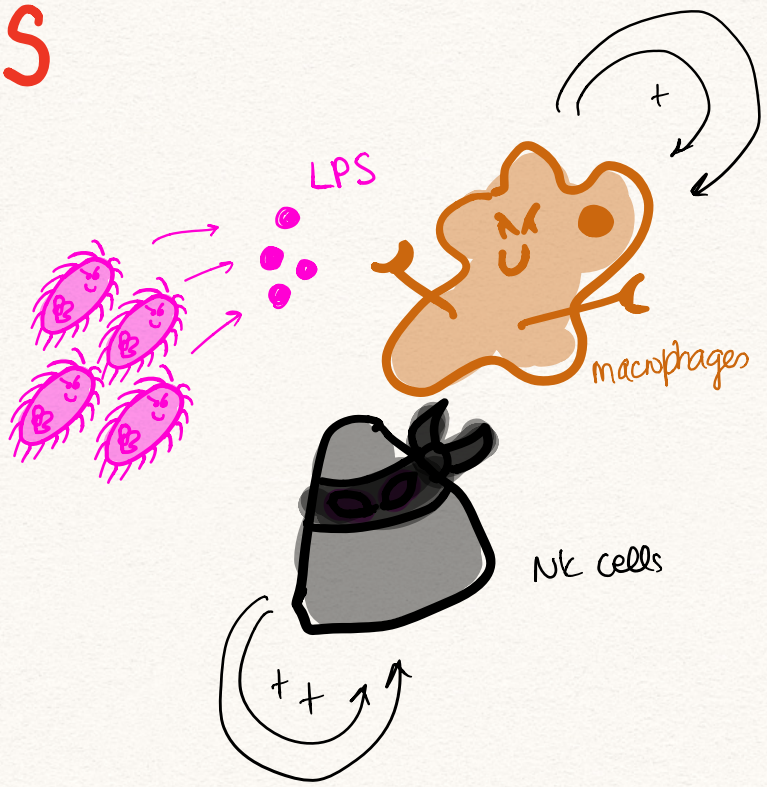
⑤ the macrophage dies by necrosis
- → the bacteria are released
- → the cytokines explode recruiting more macrophages
- → the cytokines cause inflammation which damages the lung tissue

SEPSIS

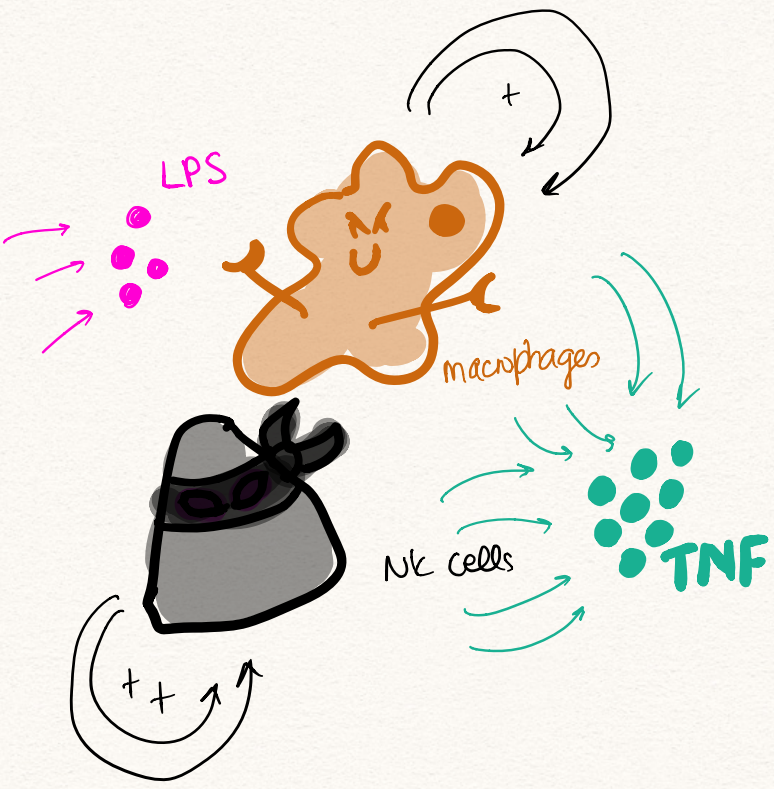


① bacteria from an abcess or local infection escapes and enters bloodstream
→ a lot needed in someone healthy
→ few needed in someone immunosupressed (eg. cancer medication)

* usually gram – E. coli with LPS on their surface



② LPS released from the bacteria activate macrophages and NK cells, which then enter positive feedback loops



③ TNF released by the cells make blood vessels leaky:
→ this happens all around the body
→ fluid leaks out of the vessels
→ in extreme cases, the amount of fluid loss is so high that you can go into

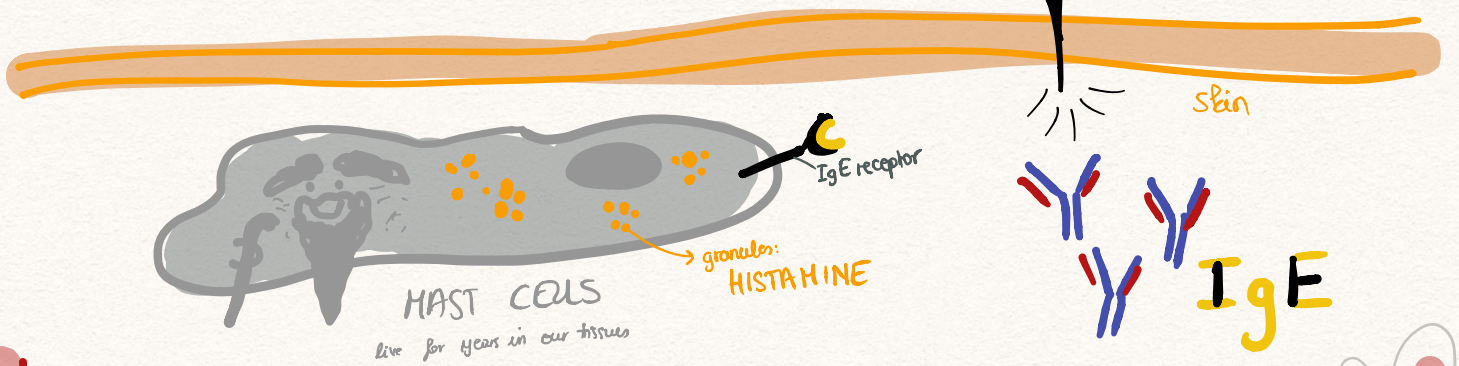
SEPTIC SHOCK

because the blood pressure falls low

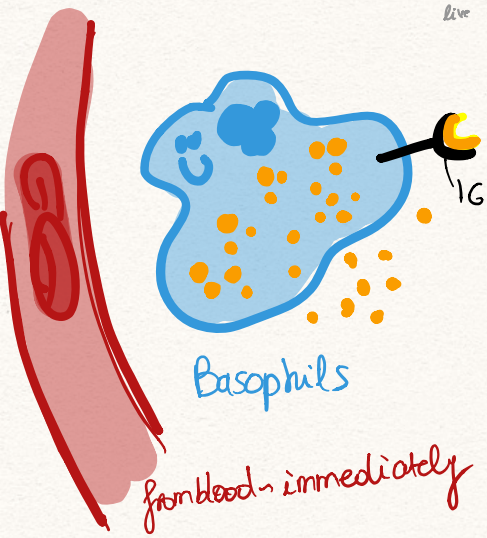
Positive feedback loops, which normally allow quick and strong reactions locally, go into overdrive and cause a system-wide reaction

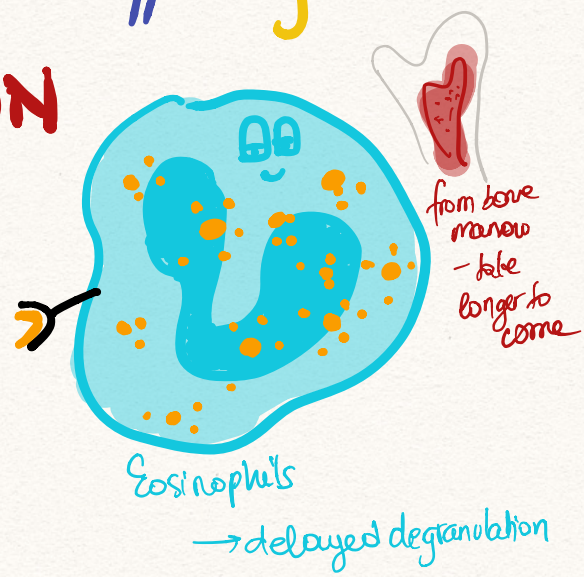
WHEN THE IMMUNE SYSTEM GOES WRONG

ALLERGIES



DEGRANULATION





How is this normally useful? Degranulation?

Large parasites cannot be phagocytosed, they get surrounded by IgE antibodies, to which mast cells, basophils and eosinophils can bind and release their granules to destroy

So why are extra IgE made (when not needed), instead of IgG?

→ The type of T-cell in the secondary lymphoid organ determines the type of antibody stimulated to be made
→ People who have allergies have more of the Th2 type of T-cells

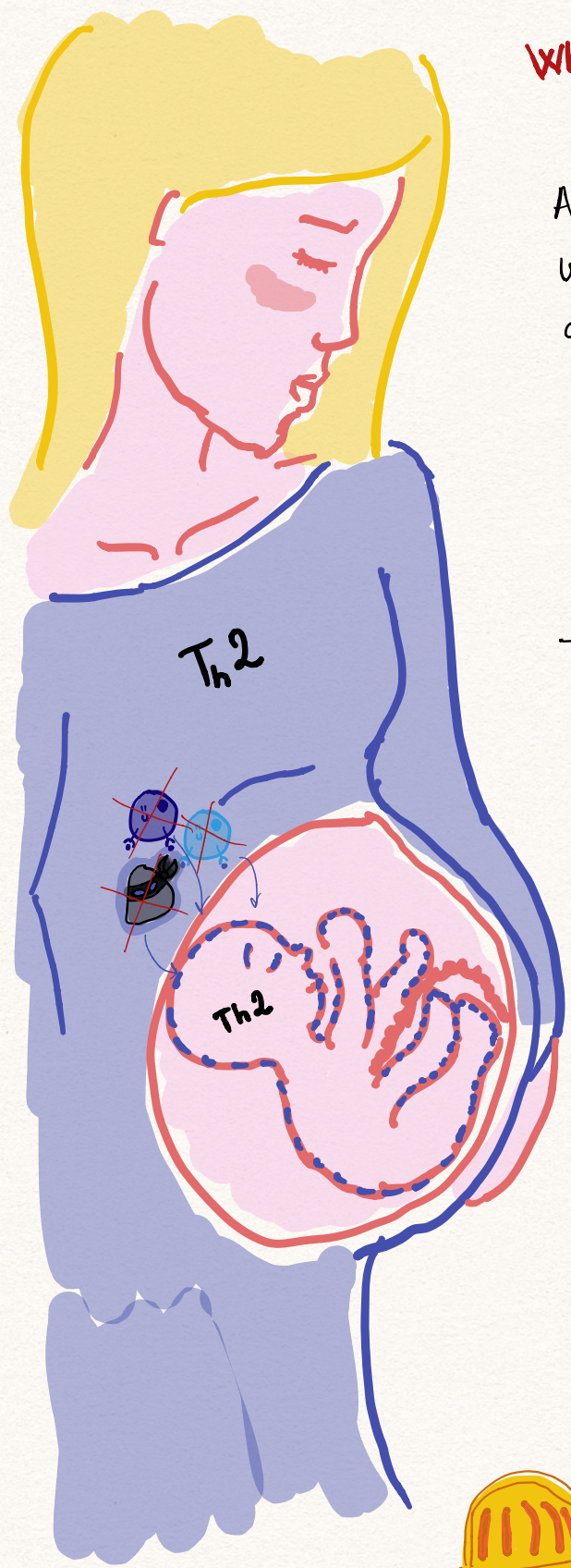
WHY DO ♂ WE HAVE ALLERGIES?

A foetus has both maternal ✓ and paternal ⚠ antigens, which when expressed, may prompt the mothers' immune system to attack it, as though it were a transplant.

⚠ Th1 → TNF, IL2 → activate immune system

Th2 → IL4, IL5 → activate IgE

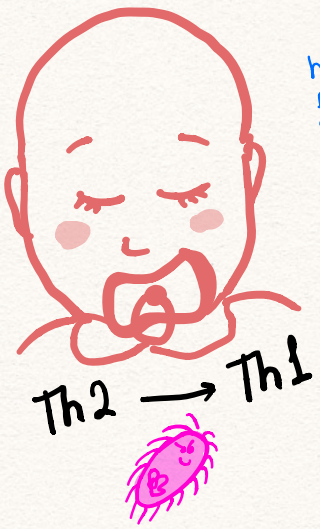
→ also the foetus will have mainly Th2 T-cells (because it shares the maternal cytokines which promote Th2 expression)



HYGIENE HYPOTHESIS

Once born, the presence of antigens & microbes will prompt the Th1 system, the formation of memory T-cells and B-cells and rewire the immune system (which is very hard to be changed).

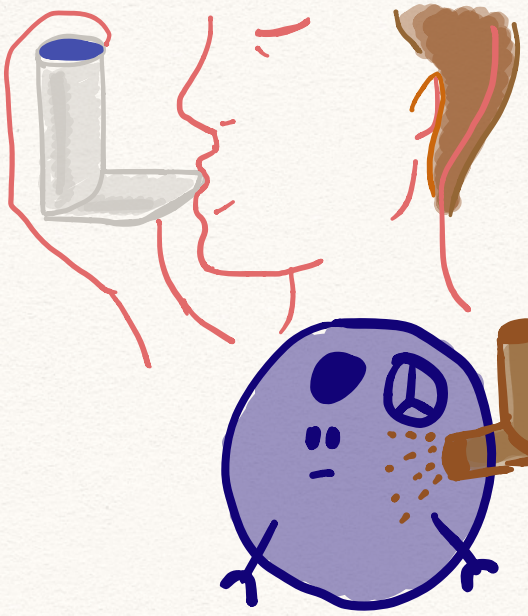
If the baby is not exposed to these pathogens, the immune system will not be rewired, and will remain Th2 favouring



EXPOSURE HYPOTHESIS

This is the idea that the more exposure one has to an antigen the more T-cells will be created for it, and the higher the chance iTreg cells will be created for it, which will dampen the immune response to that pathogen

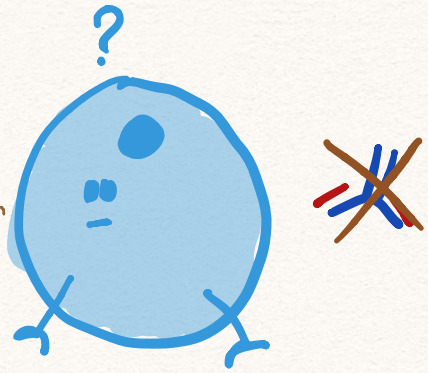
Treg cell



TREATMENT FOR ALLERGIES

CORTICOSTEROIDS

prevent cytokine formation and release by T_h cells



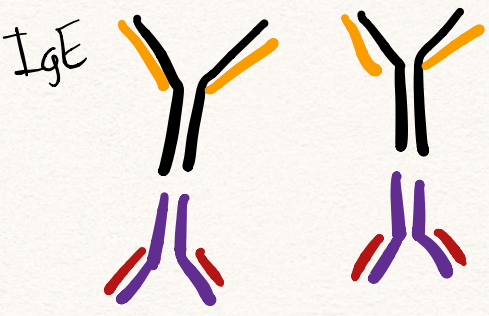
B-cells do not get the signal needed for activation

→ no antibodies formed

⚠ This is non-specific blocking of B-cells

→ So if corticosteroids are taken for extended periods of time, this leads to immunosuppression

-ZUMAB



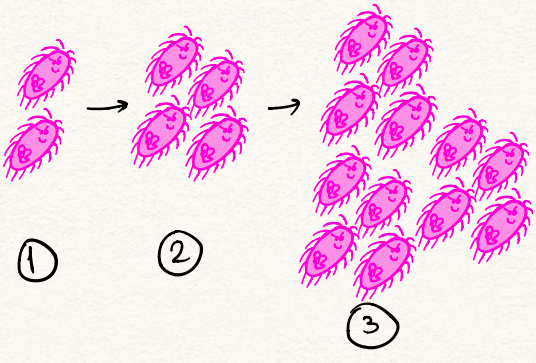
These are antibodies produced in the lab which bind to the F_c region of IgE antibodies, thus deactivating them

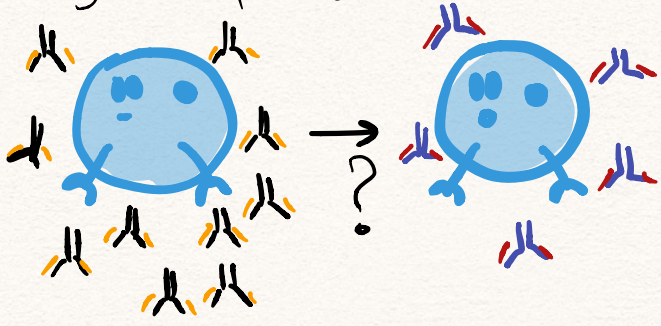
→ good for extreme allergies

⚠ also immunosupressants

SPECIFIC IMMUNOTHERAPY

increasing doses of antigen administered to patient





This somehow results in IgE → IgG producing cell??
B-cel

Molecular Mimickery

When the antigen is similar to a part of a bodies own cells, the B-cells and T-cells for it will become activated and proliferate during an infection.

→ at the same time, it can now attack the body where it is similar to it:

eg. streptococcal throat infection
and mitral heart valve cells

⇒ Rheumatoid heart disease

Because the self-tissue is unable to activate the immune system even if recognized by it, because it lacks the co-stimulatory signals, the attack can only occur while the other pathogen is still present and CONTINOUSLY ACTIVATING the immune system to attack it, and those activated cells can also then attack the body