IMMUNOLOGY

DOCTOR 2019 | MEDICINE | JU

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T cell Activation-2 (16 part 2).

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T Cells Recognize Only Peptides

- T cells only recognize antigens that are polypeptides (in the majority of conditions) and only when those are presented on MHC proteins.
- The restriction of CD4 cells and CD8 cells to bind MHC-II or MHC-I is due to the fact that binding sites on the TCR only recognize the appropriate MHC protein (CD4 can only bind MHC-II, and CD4 will stabilize that connection, whereas a CD8 cells can do so but only with MHC-I)
- Further more, the CD8 and CD4 proteins which stabilize the connection, further aid in this restriction.

- MHC-I are usually used to present intracellularly produced antigens (viral proteins for example)because we want cytotoxic T cells to be the dominant factor here (cellular immunity) MHC1 usually only shows what is inside the cell , MHC-II proteins usually present antigens of extracellular origin (bacterial proteins) **MHC2 is with the regulatory part of the adaptive immunity** - two distinct pathways with distinct organelles used for each.
- This is why when I give a vaccine composed of dead viral cells, it will not cause a CD8 (cytotoxic response) and cause an antibody response As these viruses will **not** be presented on MHC-I cells, because they did not replicate and infect cells.
- They will instead be presented on MHC-II and go through the B cell humoral response. **That's why the majority of vaccines will become extracellular antigens which are taken up by APS which presented to cd4 cells and then produce a th2 or humoral response.**
- You will have ready made antibodies that will trap the virus before entry to cells (or when they burst open cells) **that's the majority of your defense that you get from the vaccine which is actually protective**-so next time you meet the virus, you have antibodies to intercept before it enters your cells-.

- This restriction, is due to the distinction in the acquisition and PROCESSING of these proteins(between intracellular parts and extracellular parts) through different organelles and pathways.
- 1) An endogenous protein (viral protein – cancer protein) is processed in different compartments(that will ultimately restrict them and mark them as intracellular proteins within the cytoplasm and then they are different in compartment than those derived from extracellular sources).
- The association of endogenous foreign proteins with MHC-I complex happens due this difference in processing, where these proteins are cleaved by a proteasome into smaller parts and then the peptides are chaperoned by a "TAP transporter" that transports these proteins to the Rough ER where it is linked with MHC-I. this process is completely distinct and separated from the other process if protein is derived from extracellular sources.
- The endogenous protein-MHC-I complex now travels to Golgi(like making any internal protein) and then to the cell surface where it is presented → in short, MHC-I presented proteins go through the typical endogenous protein manufacturing process and end up on MHC-I

- 2)The other route is for extracellular proteins (this will be taken by Phagocytes) is through the cleavage of these proteins in an **endosome (as opposed to rough ER)**, this is where the peptide fragments are linked with the MHC-II protein into a complex.
- From the endosome the peptide-MHC-II complex migrates to the cell surface.
- Major question: why don't the intracellular proteins –some of those get degraded, get presented on MHC-II? →There is a protection mechanism placed here that (mostly) prevents endogenously produced proteins from being linked with an MHC-II protein (and hence the restriction mechanism would be bypassed).
- This occurs due to the presence of an invariant chain attached to MHC-II proteins when they are not inside the endosome (sort of like a lock mechanism), no proteins will be able to attach to MHC-II outside the endosome (**while it is being sent from endosome to the membrane because MHC2 proteins are being produced somewhere else(golgi**) from indigenous proteins), and no endogenously produced proteins enter the endosome, effectively creating the restriction mechanism. (the lock mechanism is only removed for MHC-II proteins within the endosome only).
- **That is the main protection mechanism of how I prevent intracellular proteins from binding my MHC2 complex, because if I presenting MHC2 with indigenous proteins to cd4 cells then they will become activate against my indigenous(self) protein(if they don't meet this protein in thymus during training by mistake) so I will have autoimmune disease.**

Important information

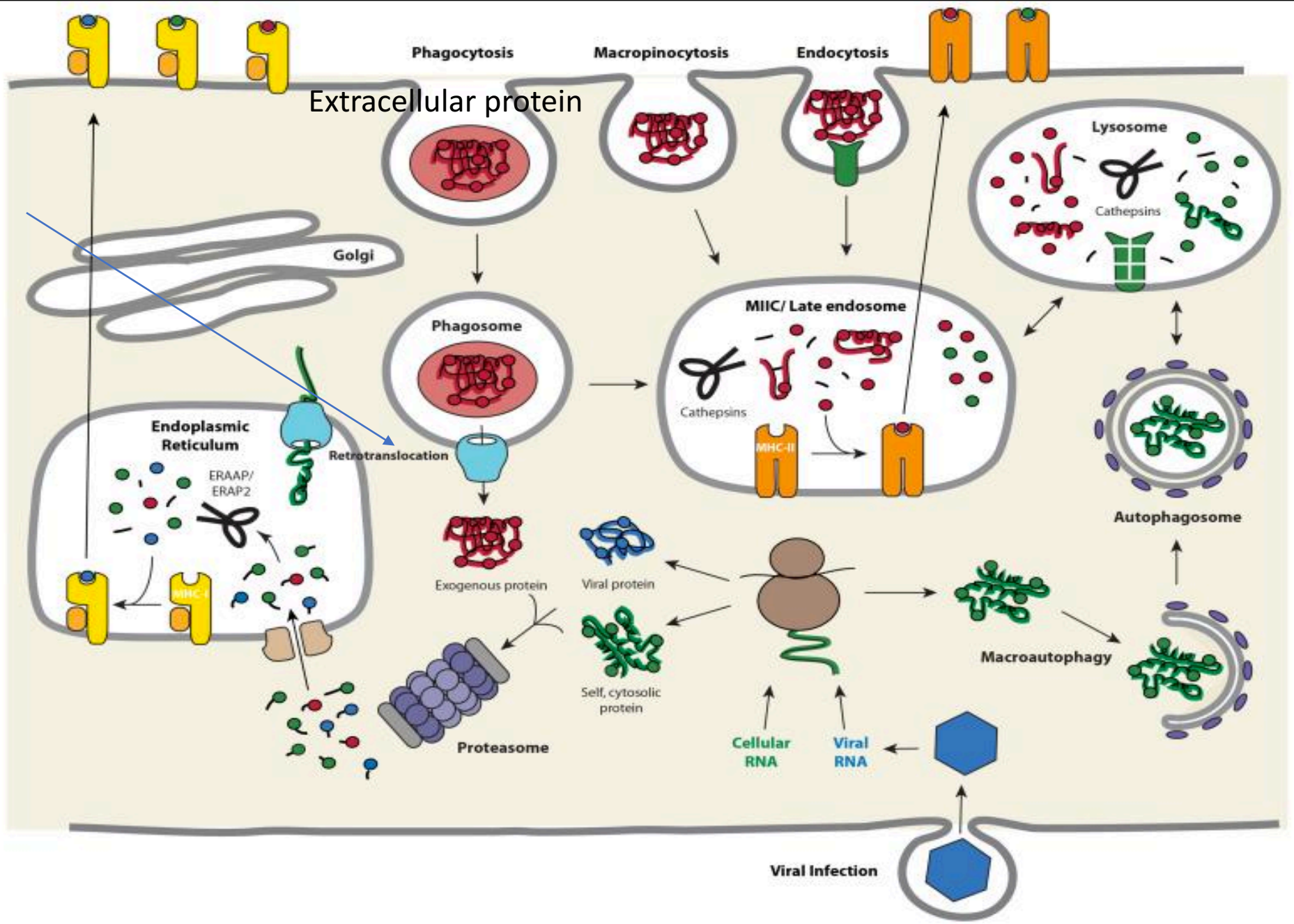
- **What as you are breaking down a protein How is the most unique part of the protein selected?... Actually they don't know.. What happens is that the protein is not just a sequence of amino acids, it is actually folded in the secondary and tertiary structures and every protein is unique otherwise all protein have the same function, so when I break this protein down I will find that my enzymes find it hard to reach the areas of protein that are heavily folded, so when it cuts the protein these remaining parts that my enzymes could not get into will be the most unique part of the protein and that is usually presented to the MHC molecules**

*some crossing between the two pathways DOES occur:

MHC-I can bind peptides derived from exogenous proteins internalized by endocytosis or phagocytosis then exit it by certain mechanisms , a phenomenon called cross-presentation. which is good actually because i might want to see if this cell is infected by something that is not being picked up..this is a protection mechanism.

this i Specific subsets of dendritic cells (DCs) are particularly adept at mediating this process, which is critically important for the initiation of a primary response by naïve $CD8^+$ T cells

This is actually beneficial which would allow cytotoxic response against certain cells that have taken up certain toxic material (toxins)



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- As for B cells the story is quite different, these cells interact with their surface immunogloblulin (IgM and IgD)(not a TCR).
- Since antigen presentation with MHC-II is not needed to activate B cells (not always).

Remember the *T cell independent antigen loop and the ability of B cells to present antigens (which are not always peptides), which ultimately activate themselves indirectly by presenting the antigen to a CD4 cell*.

- In contrast to MHC-II antigen presentation, where it can only present peptides, the IgM and IgD antigen receptors on the surface of the B cell can recognize **non peptides** as antigens (polysaccharides, nucleic acids, and small molecules -drugs such as penicillin-).
- As mentioned in previous lectures, this is how haptens (non peptides and small) can bypass the peptide requirement(**by conjugating them to carrier protein**)and act as an immunogen (and then satisfy the size requirement using the carrier protein).
- Then to be associated with MHC-II antigen presentation, the carrier protein's peptides are instead used in this case, bypassing a third requirement (peptide presenting to CD4 on MHC-II) to activate CD4 helper T cells **then I will have a T cell dependent B cell activation and then I can class switch my antibodies and make Igg or something else.**
- Now at this point the helper T cell will produce the appropriate cytokines (lymphokines) to activate a the B cell to start producing antibodies against this hapten complex

- **Signal transduction:**
- Antigen-MHC complex on the APC interacts with the TCR on the surface, the effect o this interaction is produced by a signal sent from the TCR to the inside of the cell (nucleus).
- The signal is transmitted by the CD3 protein **which detects if the tcell receptor is occupied and then it transmit the signal down to the nucleus** (remember CD3 is a part of the TCR) complex through certain pathways that eventually lead to an influx of Calcium into the cell (the stimulus to transduce the signal).
- The influx of Calcium causes (activates) a specific protein (Calcineurin) (a serine phosphatase enzyme) to exert its enzymatic function in the nucleus (switch on the genes for IL-2 and IL-2 receptor)
- Now that we know what is calcineurin and how it functions, we can remove MHC-II cell mediated immunity by blocking calcineurin (a drug called cyclosporine does this), this is useful in organ transplantation (cell immunity is responsible for organ rejection*) and autoimmune diseases.
- →but why does block only cell mediated and not AB mediated? Because you have blocked IL-2 which you will need for the maintenance of a th-1 response.

IL-2

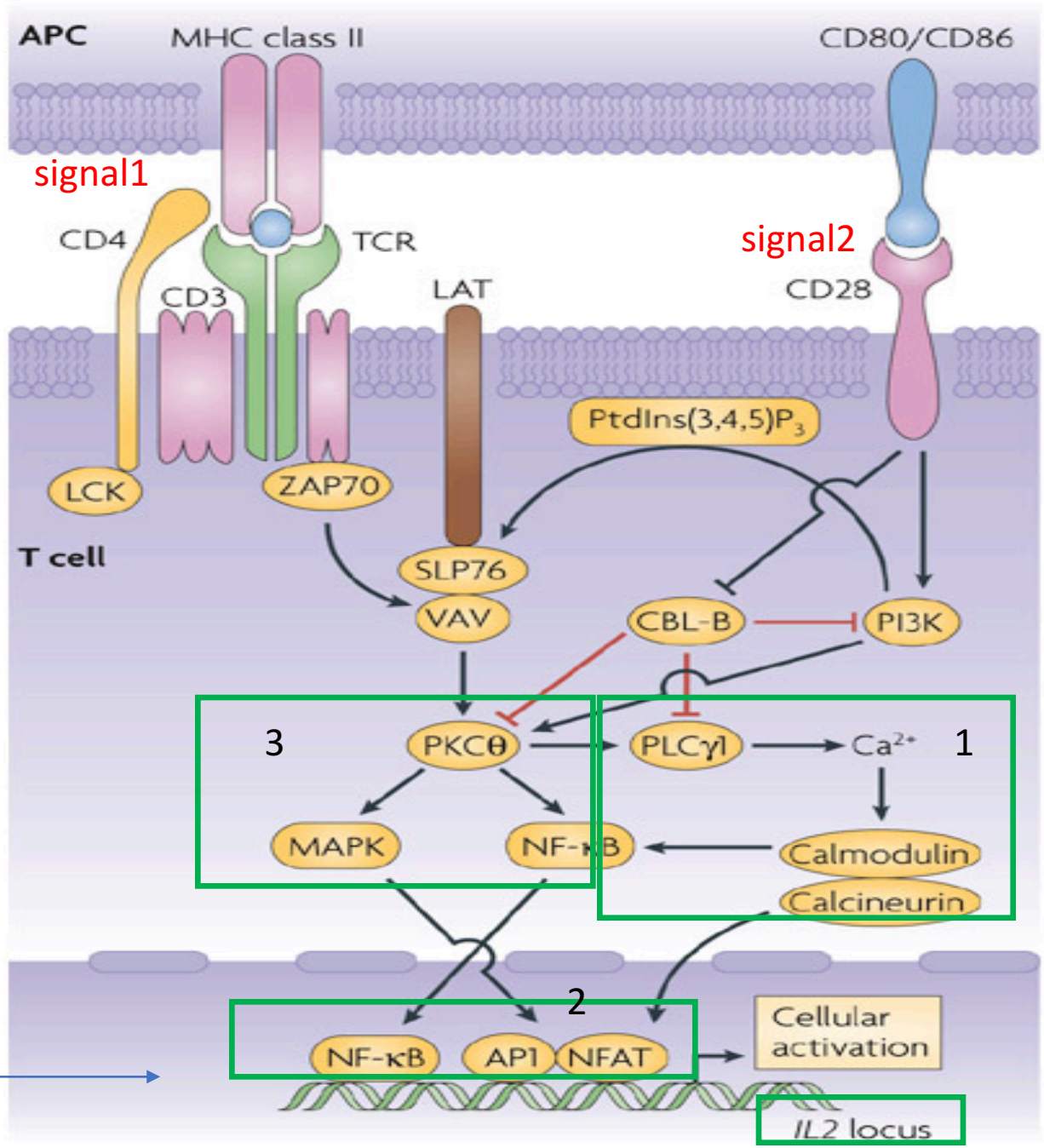
- IL-2 is produced by CD4 cells which is activated by APC presenting on MHC-II

- IL-4 from unknown source is what activates Th2 response!

- Signal transduction pathways involved in T-cell anergy.
- Stimulatory signals delivered by the engagement of the T-cell receptor (TCR; signal 1) and co-stimulatory molecules (CD28; signal 2), both work to induce different signaling pathways that result in the activation of multiple transcription factors at the gene level
- The positive signals include:
- 1- phospholipase C1 (PLC1), which induces the Ca2+ influx, which then acts with calmodulin and calcineurin.
- 2- nuclear factor of activated T cells (NFAT)- nuclear factor-B (NF-B) pathway by PKC
- 3- protein kinase C (PKC), which regulate the nuclear 4- activator protein 1 (AP1) pathways. (controlled by signal 2 -costimulation)
- In the nucleus, NFAT + AP1 + other transcription factors = induce a program of gene expression that leads to interleukin-2 (IL-2) production and **activation**.

- TCR engagement in the absence of co-stimulation (signal 1 without signal 2) results in the induction of NFAT proteins without concomitant AP1 activation(you will not activate PKC). In the absence of cooperative binding to AP1 ,NFAT alone will regulate the transcription of a distinct set of genes that will produce anergy response NO IL-2, such as Casitas B-lineage lymphoma B (CBL-B). Anergy-associated factors inhibit T-cell function at different levels leading to T-cell unresponsiveness (NO IL-2 PRODUCTION).

Ultimate things I want to activate the genes on the IL-2 locus



- It is in this step (IL-2 production) that clonal proliferation of helper T cells happens for that specific antigen (you will always have memory against this antigen)- meaning if the CD4 cell reaches the IL-2 production level, it will also proliferate to make clones for itself:
- IL-2 (also known as T-cell growth factor), stimulates the helper T cell to multiply into a clone of antigen-specific helper T cells (it also stimulates CD8 cells).
- The majority of these helper T cells will carry out their effector and regulatory functions.
- From these clones of cells a few are kept away as memory Cells for rapid function in subsequent exposures to this antigen.
- Cytotoxic T cells and B cells clones made for a specific antigen also form memory cells.
- Activated CD4-positive T cells also produce another lymphokine called gamma interferon, which enhances the ability of APCs by making them produce more MHC-II proteins (and thus present more antigen).
- Gamma interferon also enhances the microbiocidal activity of macrophages.

- It is important to know that activation of T cells is not all or none. There is a grey area of partial activation that may occur.
- Full activation has the full complement of lymphokines released, partial activation leads to a release of a few of those lymphokines which would lead to a weaker response.
- This is dependent on the epitope that was used in the activation of the T cell, which would result in a different transduction pathways being used for transduction of the signal (and activation of the proper lymphokine producing genes)
- The explanation for this is as follow (which explains why some people can clear certain infections more efficiently than others…genetics! Perhaps even random events)
- As our cells have three genes for the class I locus (A, B, and C) and three genes at the class II locus (DP, DQ, and DR) from each parent (for a total of six possible copies of each gene in Class I or 6 copies making Class II proteins).
- as each gene copy has multiple alleles for each locus, each MHC protein is now able to present peptides with different amino acid sequence

Memory T Cells

- With these cells we are able to mount a quicker, effective response to antigens –YEARS– after the initial exposure to an antigen.
- This memory response to a specific antigen is due to several features:
- (1) in the first exposure to an antigen, there are very few cells responding to this stimulus (they have to start from zero cells), for activation of CD4 cells and so on, second exposure will find many cells already produced and ready (don't need to start from zero at this point) **(so each time you meet the same antigen, your memory gets stronger and stronger because you need to have a larger response for it rather than an antigen you'd only get exposed to it once -> Low memory for this antigen).**
- So a T cell has to reach activation (production of IL-2) by finding proper MHC-II and TCR interaction, then reach activation, at this point some of the cells are kept as memory cells.
- (2) cells (as opposed to antibodies) can live for many years and replicate themselves (maintenance) whereas antibodies cannot **(they'd survive for months at best).**
- (3) a memory cell has a special ability which allows it to have a much stronger (almost exaggerated) response to a smaller amount of antigen, and would require less co stimulation, this heightened response is because these cells produce higher amount of interleukins than regular naïve cells , this is the basis how your memory cells will produce a fast response against a certain antigen.

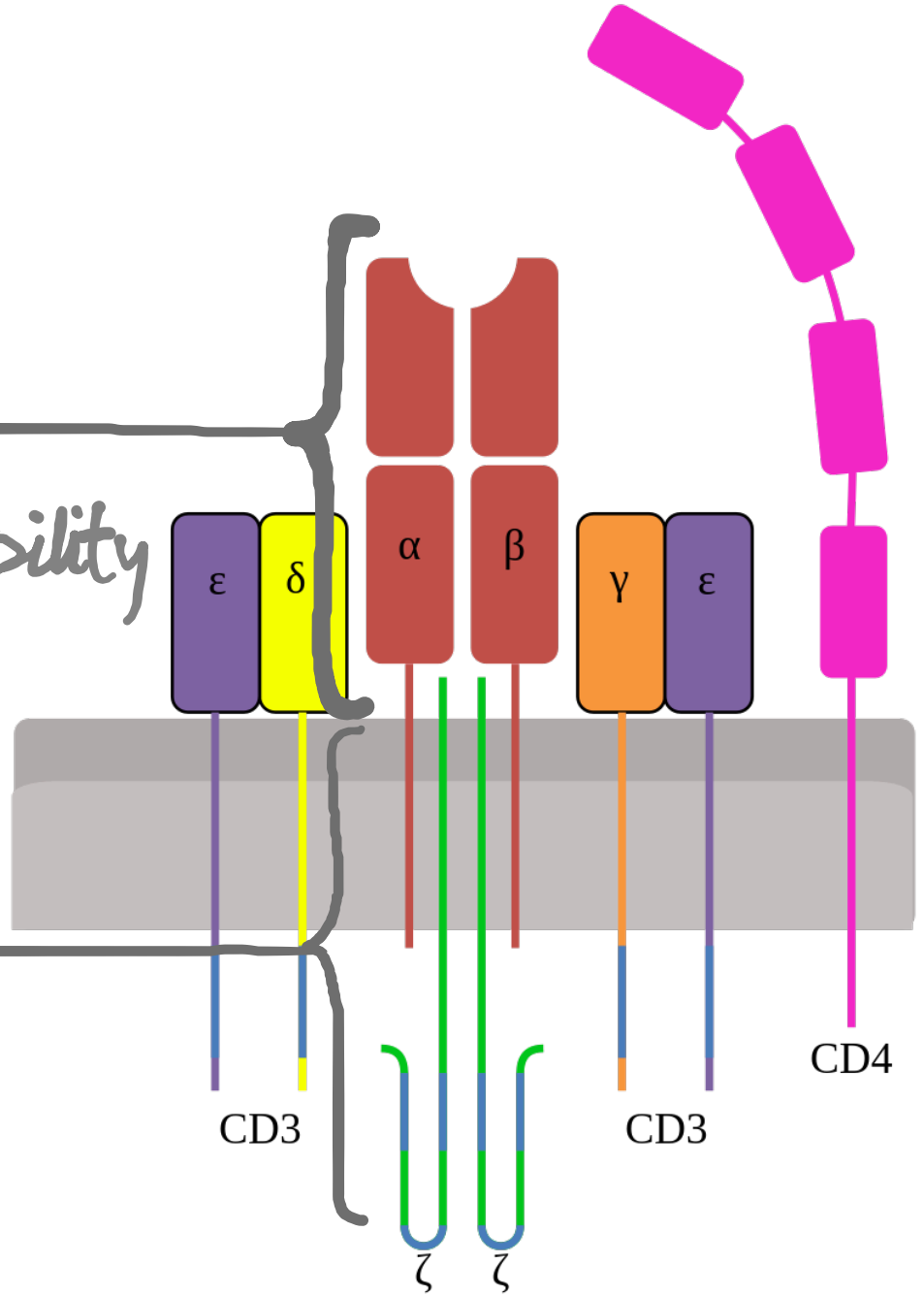
The T-Cell Receptor

- From the previous/next figure we find that the the TCR is composed of composed of 2 polypeptide chains (alpha and beta), which are associated with CD3 proteins (the T cell receptor and CD3 protein work together in receiving the antigen- mostly TCR and transduction of the signal , which is done mainly by CD3 alongside TCR transmembrane apparatus).
- In order for the TCR to detect many different antigens, it thus has a structure that resembles immunoglobulin heavy chains in a few ways which would allow it to bind to different antigens:
- (1) the genes that code for TCR chains are made by the rearrangement of multiple regions of DNA (which creates variability)
- (2) the gene loci have many segments -V (variable), D (diversity), J (joining V and D with C), and C (constant) , all of which work together to provide high variability and diversity (at this level of diversity more than a 100 million different receptor proteins can be made)
- (3) the variable regions have hypervariable domains (even more diversity at the end of the protein)
- (4) the two genes (RAG-1 and RAG-2) that encode the recombinase enzymes that catalyze these gene rearrangements are similar in T cells and B cells.

Why do we have to have a constant region? Because we want to have a constant reaction with the TCR. Antibodies have the same thing, every antibody should have FC region recognized as a constant region by phagocytes for example.

here we have diversity & variability genes (encoded).

constant part here.



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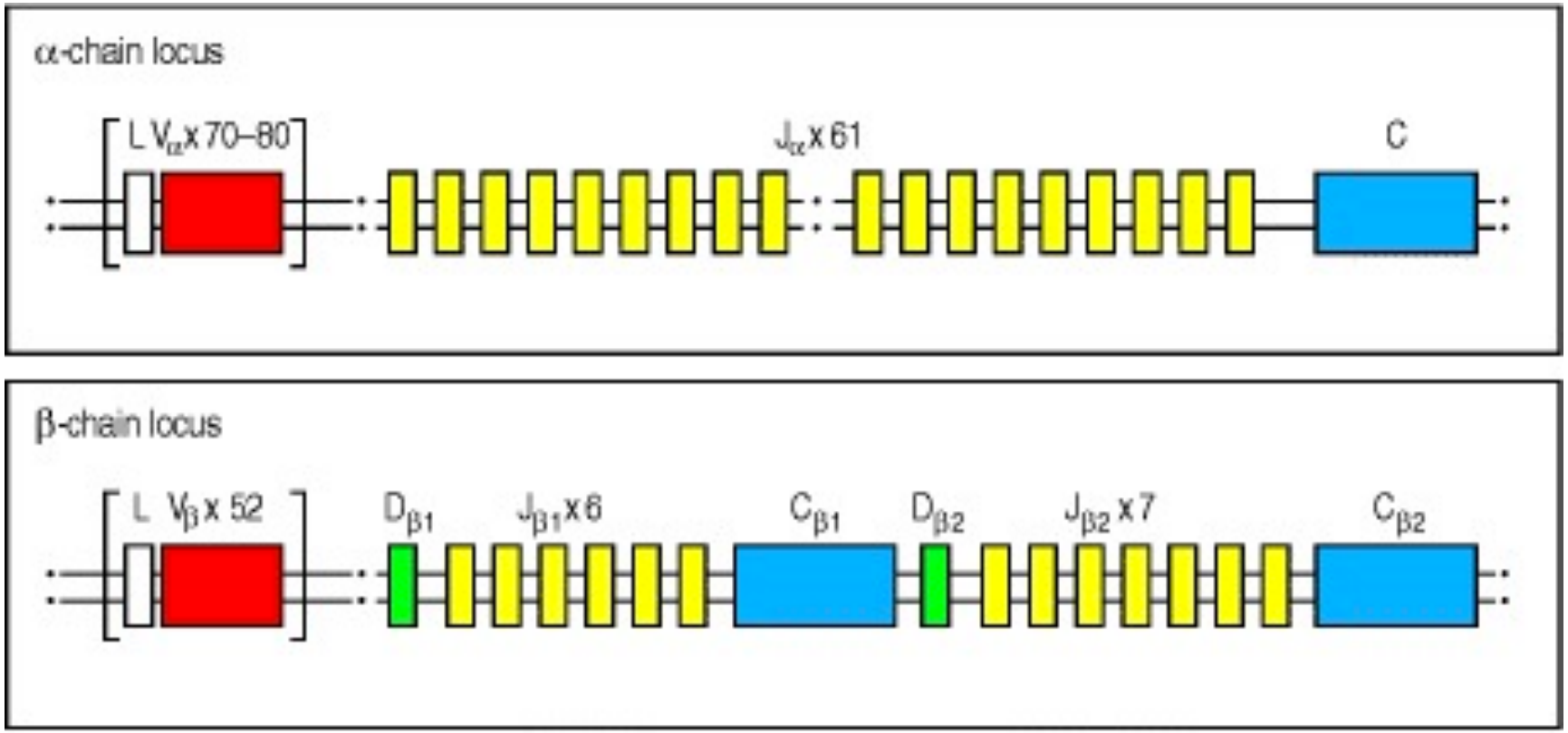
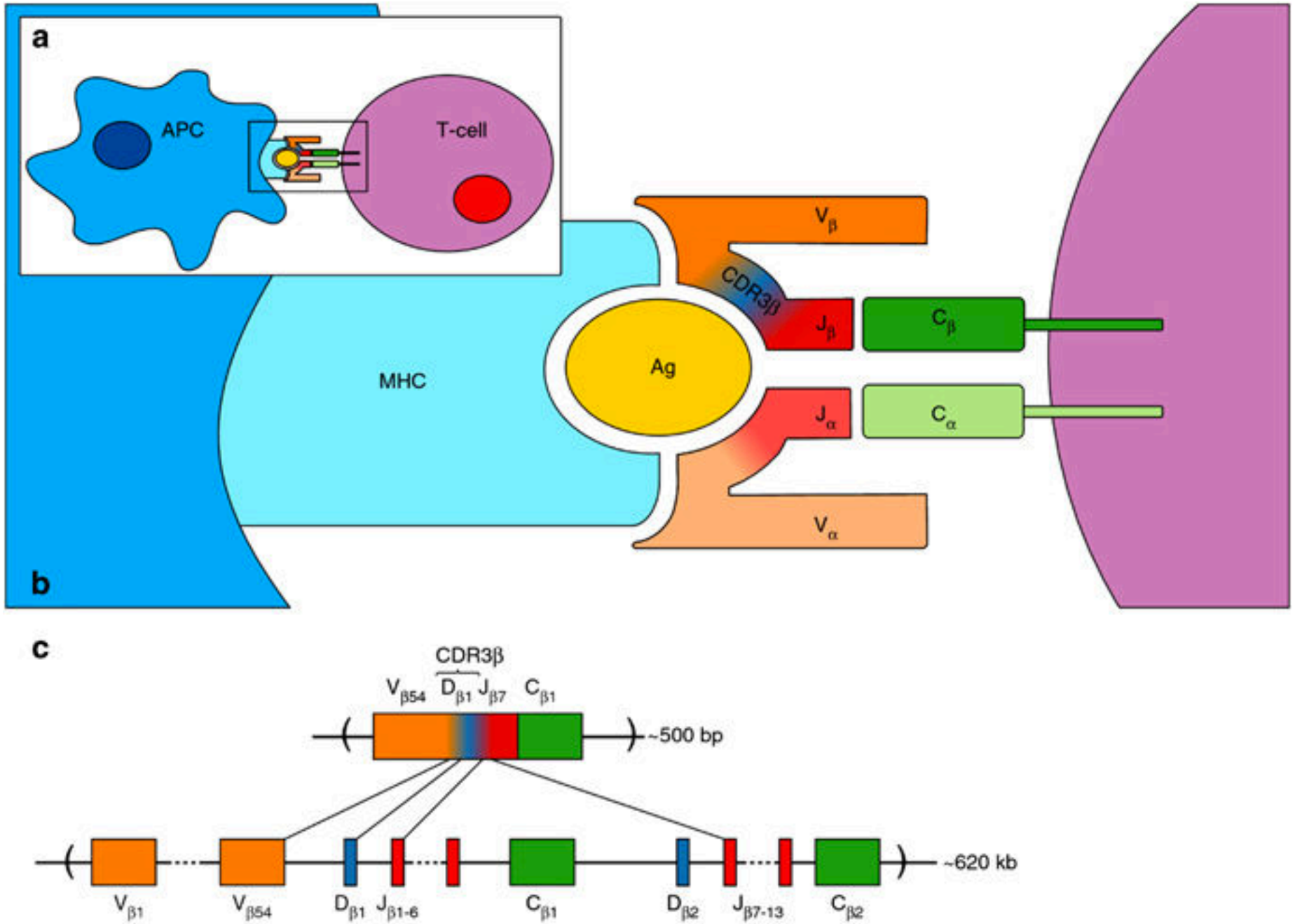


- variable (V), diversity (D), joining (J) gene segments, and constant (C) genes.
- The TCRα locus (chromosome 14) consists of 70–80 V_α gene segments, each preceded by an exon encoding the leader sequence (L) in white. A cluster of 61 J_α gene segments is located a considerable distance from the V_α gene segments. The J_α gene segments are followed by a single C gene, which contains separate exons for the constant and hinge domains and a single exon encoding the transmembrane and cytoplasmic regions. The TCRβ locus (chromosome 7) has a different organization, with a cluster of 52 functional V_β gene segments located distantly from two separate clusters each containing a single D gene segment, together with six or seven J gene segments and a single C gene. Each TCRβ C gene has separate exons encoding the constant domain, the hinge, the transmembrane region, and the cytoplasmic region (not shown). The TCRα locus is interrupted between the J and V gene segments by another T-cell receptor locus—the TCRδ locus



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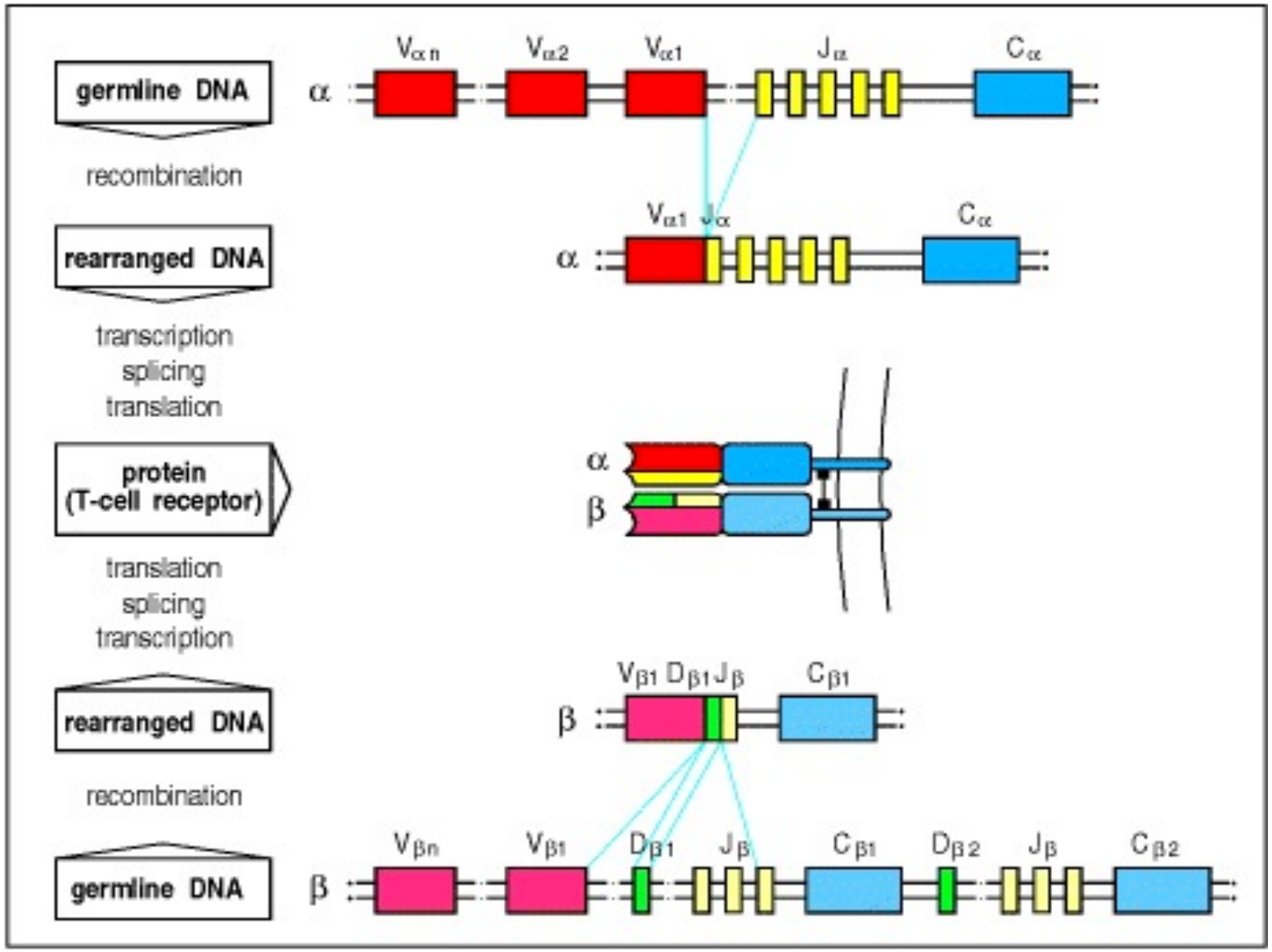

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- From the previous figures, we can deduce that each T cell has a unique TCR on its surface, with hundreds of million of different T cells (with different specific receptors) in each human being.
- Each unique T cell, **once activated,** will proliferate (clonal expansion), to yield a large number of cells that are able to deal with the specific antigen they are unique to.
- Antibodies have a similar genetic rearrangement that yields a high number of hypervariable antibodies.
- However, the TCR (even though it is uniquely specific to an antigen like an antibody is), it differs from the antibody in two ways:
- (1) it has two chains rather than four (2) it recognizes antigen only in conjunction with MHC proteins, whereas immunoglobulins recognize free antigens.
- This is where the B cell (T cell independent activation) is appreciated, B cells don't use TCR but use an immunoglobulin (IgM or IgD) so they bypass the need of MHC.
- Also TCR proteins are always anchored into the outer membrane of T cells, There is no circulating form as there is with certain antibodies (monomeric IgM is in the B cell membrane, but pentameric IgM circulates in the plasma)

Note:

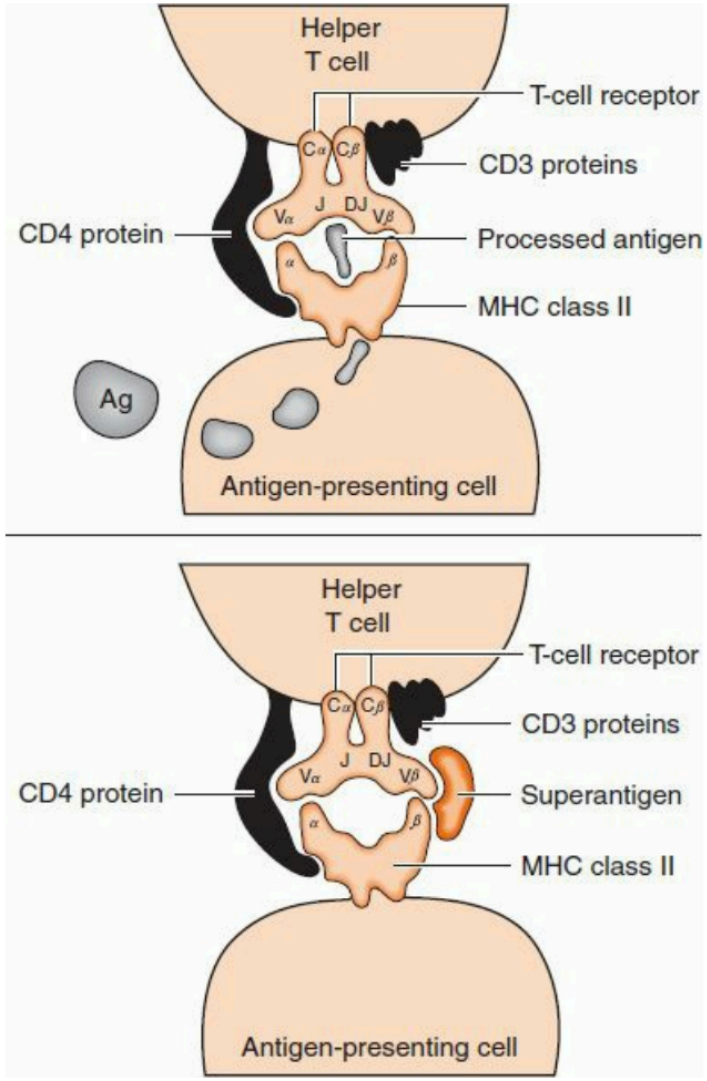
- Antibodies are composed of 4 chains (heavy and light) while TCRs are composed of 2 chains (alpha and beta).
- IgM Ab are huge, that's why they cant cross the placenta while IgG are smaller and **can** cross the placenta.

Effect of Super antigens on T Cells

- Certain proteins, particularly staphylococcal enterotoxins and toxic shock syndrome toxin (TSST), act as "superantigens" (next figure).
- In contrast to the typical antigen, which activates one (or a few) helper T cell, superantigens are "super" because they activate a large number of helper T cells.
- For example, toxic shock syndrome toxin binds **directly** to class II MHC proteins without internal processing of the toxin. **This complex interacts with the variable portion of the beta chain (Vβ) of the TCR of many different T cells.**

MEANING THESE ANTIGENS HAVE REGIONS THAT ARE DETECTABLE BY MANY DIFFERENT TCRs (overcomes their specificity)- which will produce a heightened exaggerated response.

- **This activates the T cells, causing the release of IL-2** from the T cells and IL-1 and tumor necrosis factor (TNF) from macrophages. These interleukins account for many of the findings seen in toxin-mediated staphylococcal diseases.
- Certain viral proteins (e.g., those of mouse mammary tumor virus [a retrovirus]) also possess superantigen activity



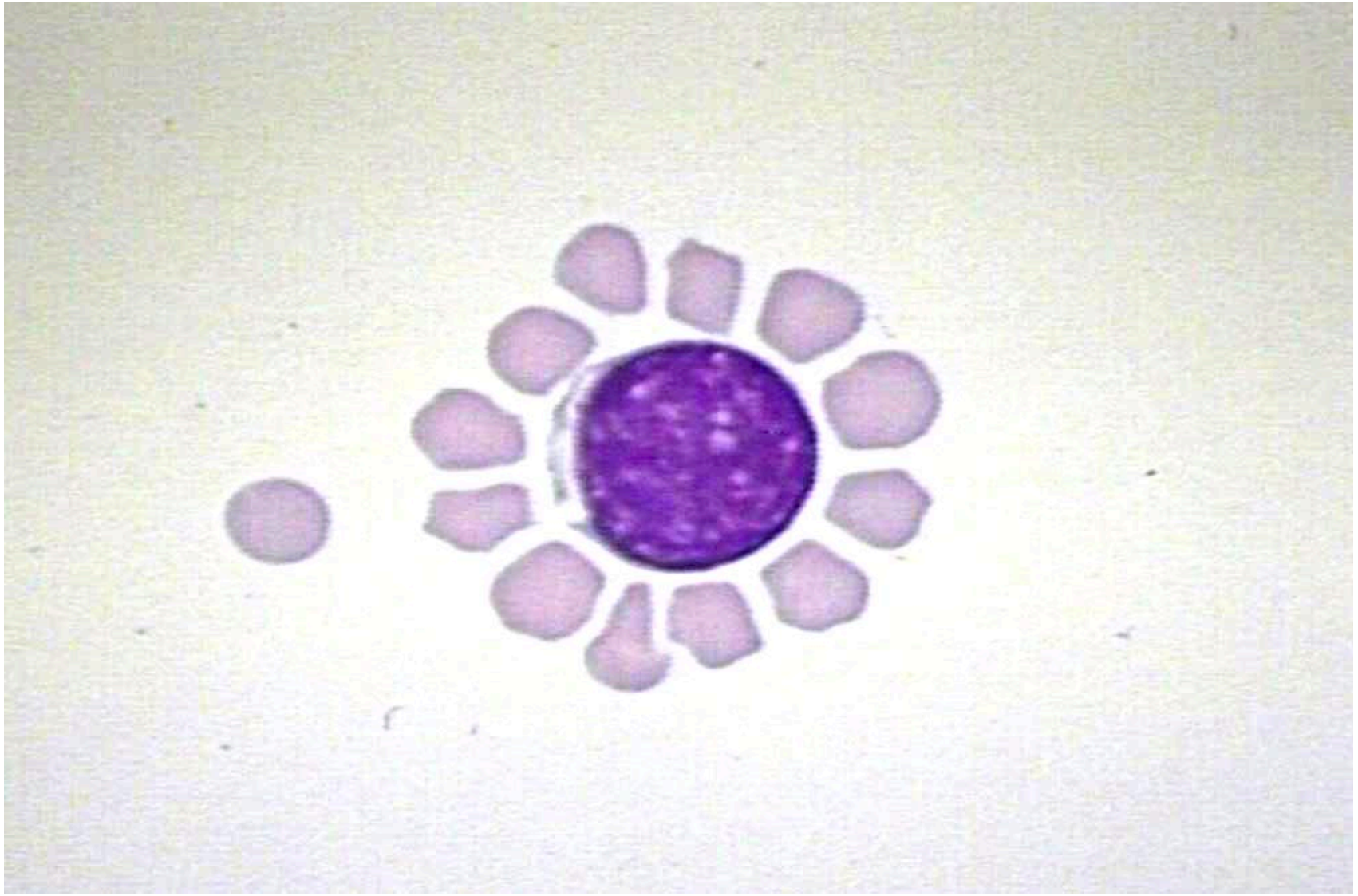
Top: the “regular” antigen processing by an APC is shown, the epitope is then presented on the MHC-II complex and signal transduction and activation of few helper T cell ensues.

Bottom: the super-antigen, is DIRECTLY WITHOUT PROCESSING (so it is FAST acting) is bound to MHC-II protein complex (using the Vβ portion of the T cell receptor).

Because it bypasses the antigen-specific site, super-antigen can activate many helper T cells.

Features of T Cells

- T cells make up about 65% to 80% of the recirculating pool of small lymphocytes, the rest are B cells.
- Within lymph nodes, T cells are found in the inner and subcortical regions, whereas B cells are located primarily in the germinal centers of the lymph node.
- T cells have a very long half life, they can survive for months or even years.
- These cells can be stimulated to proliferate by using mitogens (mitosis generating molecules).
- mitogens for T cells include: phytohemagglutinin or concanavalin A [endotoxin, a lipopolysaccharide found on the surface of gram-negative bacteria, is a mitogen for B cells but not T cells]).
- *T cells are detected in blood by using sheep blood, this is because all T cells have receptors on their surface that reacts with sheep RBCs, and form a unique structure seen by the eye "rosettes*".



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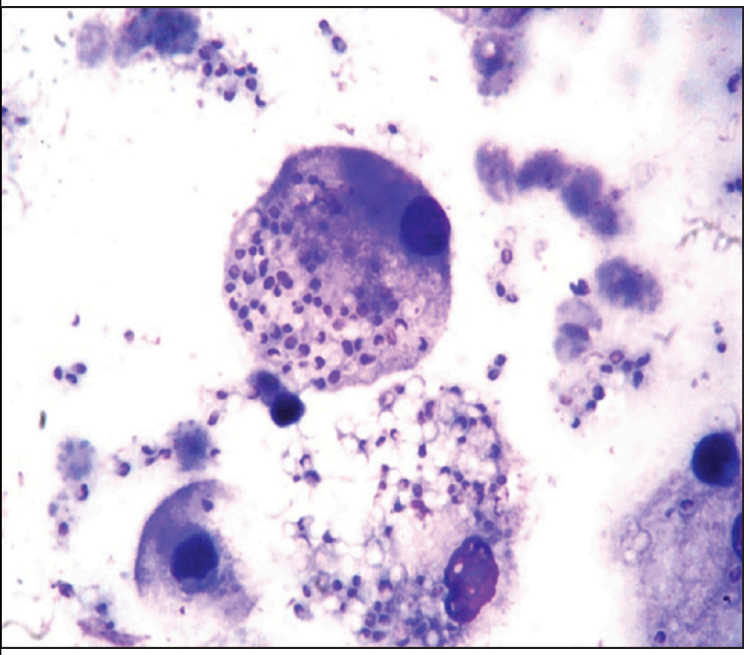
Effector Functions of T Cells- recap

- The four types of T cells (Th-1, Th-2, and Th-17 types of CD4 cells, and CD8 cells) mediate different aspects of our host defenses.
- Th-1 cells mediate delayed hypersensitivity reactions against intracellular organisms.
- Th-2 cells mediate protection against helminths (worms) –antibody response- .
- Th-17 cells protect against the spread of bacterial infections by recruiting neutrophils to the site of infection.
- CD8 cells protect against viral infection by killing virus-infected cells.

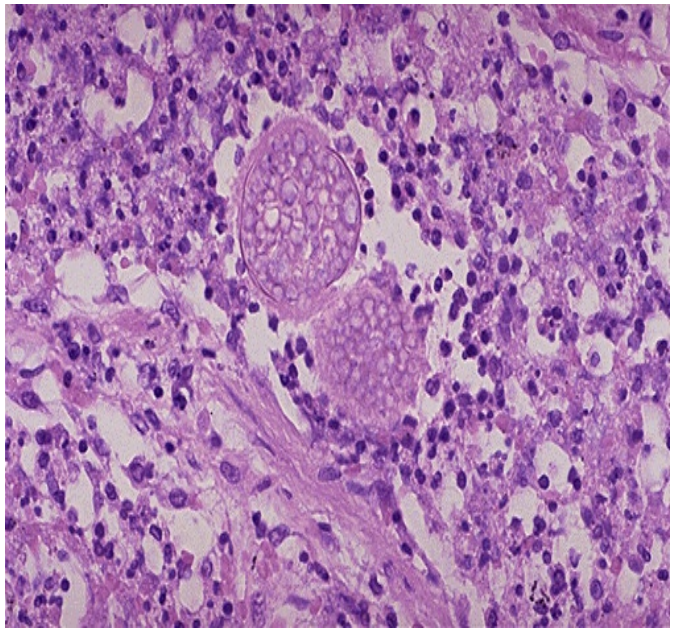
Th-1 Cells

- Th-1 cells and macrophages are the main effectors of cell mediated (also called delayed hypersensitivity reactions, type IV hypersensitivity reaction).
- This type of reaction is aimed to protect against intracellular pathogens (fungi Histoplasma and Coccidioides) and (bacteria such as *M. Tuberculosis*), the main signaling molecule in this type of reaction is GAMMA INTERFERON, with other signals that help recruit or exclude macrophages (macrophage activation factor and macrophage migration inhibition factor (MIF)) also play a role.
- The actual function of destroying these intracellular pathogens is performed by macrophages, however Th-1 cells direct macrophages (recruit them to the site and tell them what to look for) by the production of interleukins.
- If one has a diminished delayed hyprsensitivity reaction, they will of course be unable to clear these pathogens.

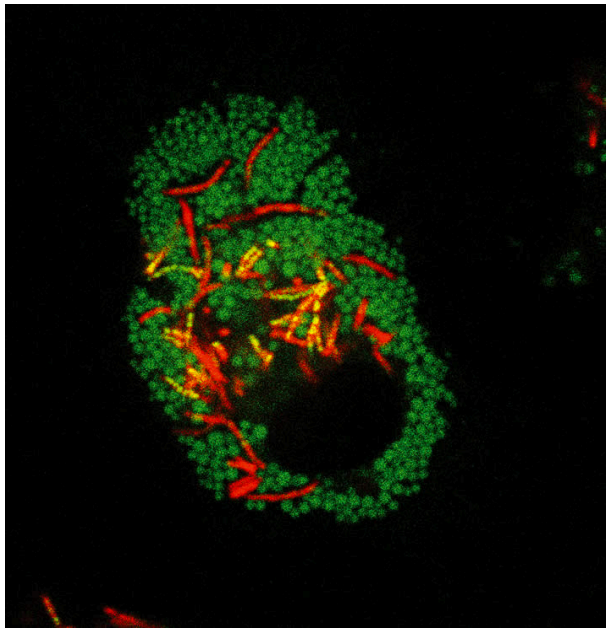
- The well studied case of *M. tuberculosis*, a specific lipoprotein of the bacterium is picked up and then stimulates a specific Toll-like receptor on the macrophage, which signals the cell to synthesize IL-12 (indicating that a foreign object was encountered).
- IL-12 is an inducer of the correct type of response to this lipoprotein (cellular Th1 response), thus IL-12 induces naïve helper T cells to differentiate into the Th-1 type of helper CD4 T cells to start the delayed hypersensitivity response, at this point Th-1 cells produce gamma interferon, which activates macrophages, thereby enhancing their ability to kill *M. tuberculosis*.
- This IL-12–gamma interferon axis is very important in the ability of our host defenses to control infections by intracellular pathogens, such as *M. tuberculosis* and *Listeria monocytogenes*.
- recap: Macrophage found a foreign protein→ IL-12→ activate Th1 CD4 cells →G-INF →activate macrophages



Histoplasmosis



coccidosis



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Th-2 Cells

- *Th-2 CD4 cells along with **eosinophils*** constitute the main effectors of reactions that are protective against helminths (worms) such as Schistosoma and Strongyloides (**remember IgE and eosinophils**).
- The most important interleukins for these reactions are IL-4 (why? Because we need Th2 response to produce IL-4),
- IL-4 increases the production of IgE, and IL-5, which activates eosinophils.
- IgE binds to the surface of the worm. Eosinophils then bind to the heavy chain of IgE and secrete their enzymes that destroy the worm.
- **Th-17 Cells**
- Th-17 cells protect against the spread of bacterial infections at mucosal surfaces by producing IL-17. →IL-17 attracts neutrophils to the site of infection whereupon the bacteria are ingested and destroyed.

CD8 Cells

- CD8 cells mediate the cytotoxic response that is concerned primarily with destroying **virus-infected cells and tumor cells** but also play an important role in graft rejection(MHC-I).
- In response to virus-infected cells, the CD8 lymphocytes must recognize both viral antigens and class I molecules on the surface of infected cells.
- To kill the virus-infected cell, **the cytotoxic T cell must be activated by IL-2 produced by a helper (CD4-positive) T cell, whereas a NK cell doesn't**.
- To become activated to produce IL-2, helper T cells recognize viral antigens bound to class II molecules on an APC (e.g., a dendritic cell or macrophage).
- The activated helper T cell, once it has recognized the MHC-II with viral epitope, will secrete IL-2 that will stimulate the CD8 cell that is specific to that virus- which then will form a clone of that now **activated cytotoxic T cells.**

- Activated cytotoxic T cells kill virus-infected cells primarily by inserting perforins and degradative enzymes called granzymes into the infected cell.
- 1- Perforins form a channel through the membrane, the cell contents are lost, and the cell dies.
- 2- Granzymes are proteases (enzymes that degrade proteins) and work against the proteins in the cell membrane, which also leads to the loss of cell contents.
- 3- Granzymes also activate caspases (a type of protease) that initiate apoptosis, resulting in cell death.
- After killing the virus-infected cell, the cytotoxic T cell itself is not damaged and can continue to kill other cells infected with the same virus.
- **Cytotoxic T cells have no effect on free virus, only on virus-infected cells.**

- The main Apoptotic mechanism, by which cytotoxic T cells kill target cells is activation of apoptosis through the the Fas-Fas ligand (FasL) interaction.
- This apoptosis mechanism happens when Fas (which is a protein displayed on the surface of many cells) and cytotoxic TCR recognizes an epitope on the surface of a target cell (MHC-I), FasL (Fas Ligand) is induced in the cytotoxic T cell.
- Once FasL and Fas interact, apoptosis (death) of the target cell occurs.
- **NK cells can also kill target cells by Fas-FasL–induced apoptosis**.

Here we have a bridge between humoral and cellular immunity. (enhanced phagocytosis).

- To eliminate virus infected cell, an antibody mediated mechanism is employed as well (In addition to direct killing by cytotoxic T cells) this is done by a combination of **IgG** and phagocytic cells.
- In this **antibody-dependent cellular cytotoxicity (ADCC),** the antibody directed at the virus, is bound to the surface of the infected cell. The bound Antibody is then recognized by phagocytic cells (macrophages or NK cells) by an IgG receptor on their surface → the infected cell is killed.
- The ADCC process is the mechanism of killing helminths (worms).
- However, in this case, ADCC is mediated by IgE, and eosinophils (not phagocytes) are the effector (does the function, in this case killing) cells.
- The mechanism is quite similar, IgE binds to surface proteins on the worm, and eosinophils have a receptor on their surface for the epsilon heavy chain (IgE).
- The actual killing is mediated by granules inside the eosinophils that are released after they are activated by IgE, the major basic protein in these granules damages the surface of the worm.

So, cellular cytotoxicity can be directed against non-polypeptides (here I'm using antibodies which can target antigens and pathogens that are not peptides).

- In tumors, new antigens (not self) will be displayed on their MHC-I surface protein → CD8 cells will recognize this (and will stimulated to proliferate by IL-2) and target these tumor cells for destruction (either direct or by inducing apoptosis)
- IL-2 produced means that this clone of CD8 cell will proliferate, which will mean that this **CD8 clonal expansion is now able to kill this type of tumor cells** (this phenomenon is called **immune surveillance**).

Does this make you immune to this type of cancer? Yes and no. Because you're immune to this stage of cancer. However, if the cancer progresses further in other cells then a new reaction needs to be produced and cancer cells may progress further in a way they don't display anything OR they can cause anergy.

- In allografts, cytotoxic (CD8) cells recognize the class I MHC molecules on the surface of the foreign cells (and depending on how similar it is to the self, they will either reject or accept).
- But what activates these CD8 cells in the allograft rejection? They need IL-2, produced by helper (CD4), they will recognize the foreign class II molecules on certain cells in the graft (APCs from the allograft, macrophages and lymphocytes).
- The activated helper cells secrete IL-2, which stimulates the cytotoxic cell to form a clone of cells that will function to kill the allograft cells (this means now the body has memory against this allograft and there is very little that we can do to help, this also means that if we aim to reduce allograft rejection we must work on having the CD4 cells not activating clones of CD8 cells that target the graft.

Good Luck!💚💚