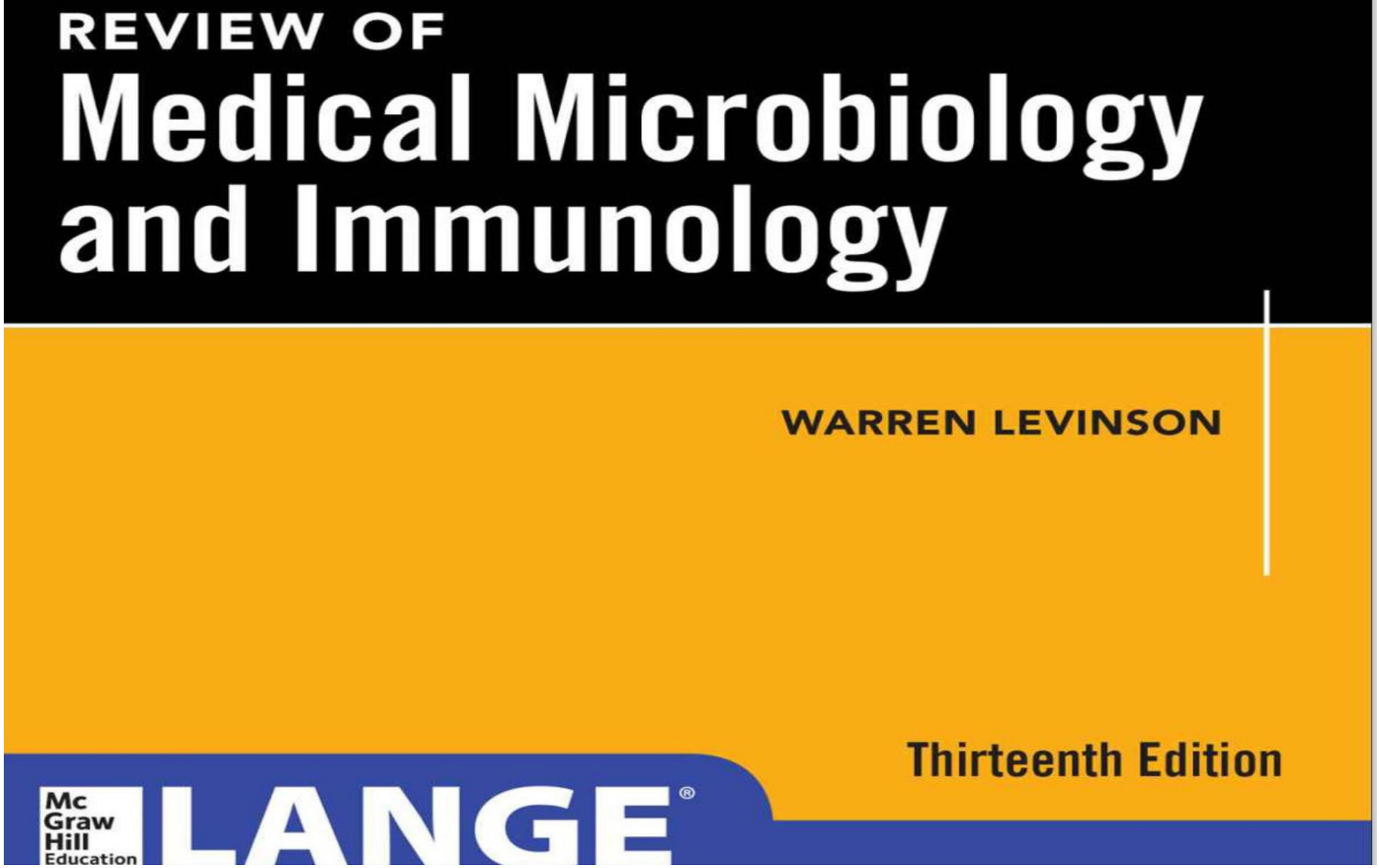


Chapter 57, all tables and figures taken from this chapter

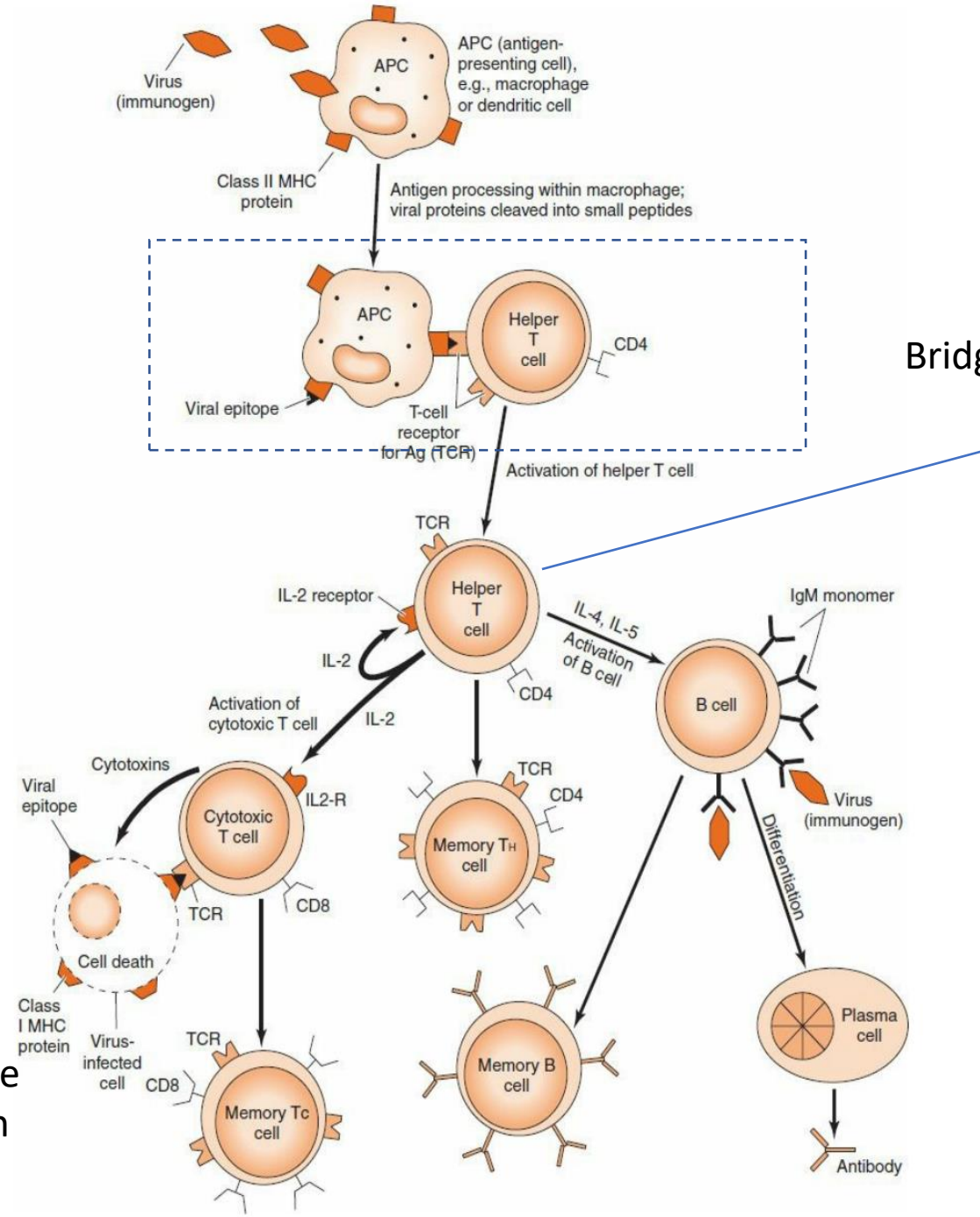
Activation of T Cells

- To activate helper T cells, an antigen presenting cell must posses a MHC-II complex, which carries (as a complex) an antigen, which the T-cell receptor is able to recognize. (antigen presenting cells are usually macrophages and dendritic cells, but there are others).
- The activation of cytotoxic T cells on the other hand requires antigen presentation from cells on MHC-I, that is complexed with an antigen recognizable by the cytotoxic CD8 cell TCR.
- APCs have both class I and class II proteins on their surface.
- The first step in the activation of helper T cells is the uptake of the foreign protein-antigen, microbe- by the APC.
- This microbe or protein is then digested within the APC into smaller parts – processing into small peptides for example-, and these unique small peptides are then complexed with MHC-II proteins and presented on the outside of the cell for a CD4 cell(using its TCR) to recognize it.

- T cells are usually harbored in lymph nodes, while at the same time the antigen is being encountered in mucosal surfaces where APC are present under these epithelial surfaces.
- how do these APCs recruit the T cells from such distance?
- An APC that it is carrying an antigen on its surface will produce a specific receptor on its surface (which indicates it is currently presenting an antigen), this receptor is for(reactive to) the chemokine CCR7.
- The chemokine signal of CCR7 is being produced all the time (like a radio wave, seen as a gradient of CCR7, highest in the lymph node and gets lower and lower away from the lymph node) from T cells in the lymph node at all times, once the correct radio (the receptor on the APC) is produced it will start to migrate to the NEAREST signal -lymph node- going from low concentrations of CCR7 (away) to higher concentrations gradually (towards the NEAREST lymph node).

- As for the activation of cytotoxic T cells, this happens when the APC itself is infected with a virus, the virus within the cell is now producing foreign proteins which are presented on the surface with an MHC-I protein which activates the CD8 cells to perform cytotoxic function.
- The same happens when a piece of a dying infected cells is presented to CD8 cells on MHC-I proteins (also viral antigens are being presented on MHC-I protein).
- A Non APC cell will also present viral antigens on its surface on a MHC-I complex (all nucleated cells have MHC-I)
- To easily remember this, know the rule of eight: CD4 cells interact with class II (4 × 2 = 8), and CD8 cells interact with class I (8 × 1 = 8).

- Macrophages and other phagocytic cells (dendritic cells) participate in **both** the innate and adaptive arms of the immune response.
- They act as a bridge between the innate and adaptive immune systems.
- As part of the innate system→ they phagocytose and ingest various microbes (without specificity).
- They also present antigen to helper T cells, which is the essential first step in the activation of the adaptive system(specific to that presented antigen).
- HOWEVER, neutrophils, which are also phagocytes, have excellent microbe killing abilities, but they do not present antigens to helper T cells and therefore are part of the innate system and not the adaptive one

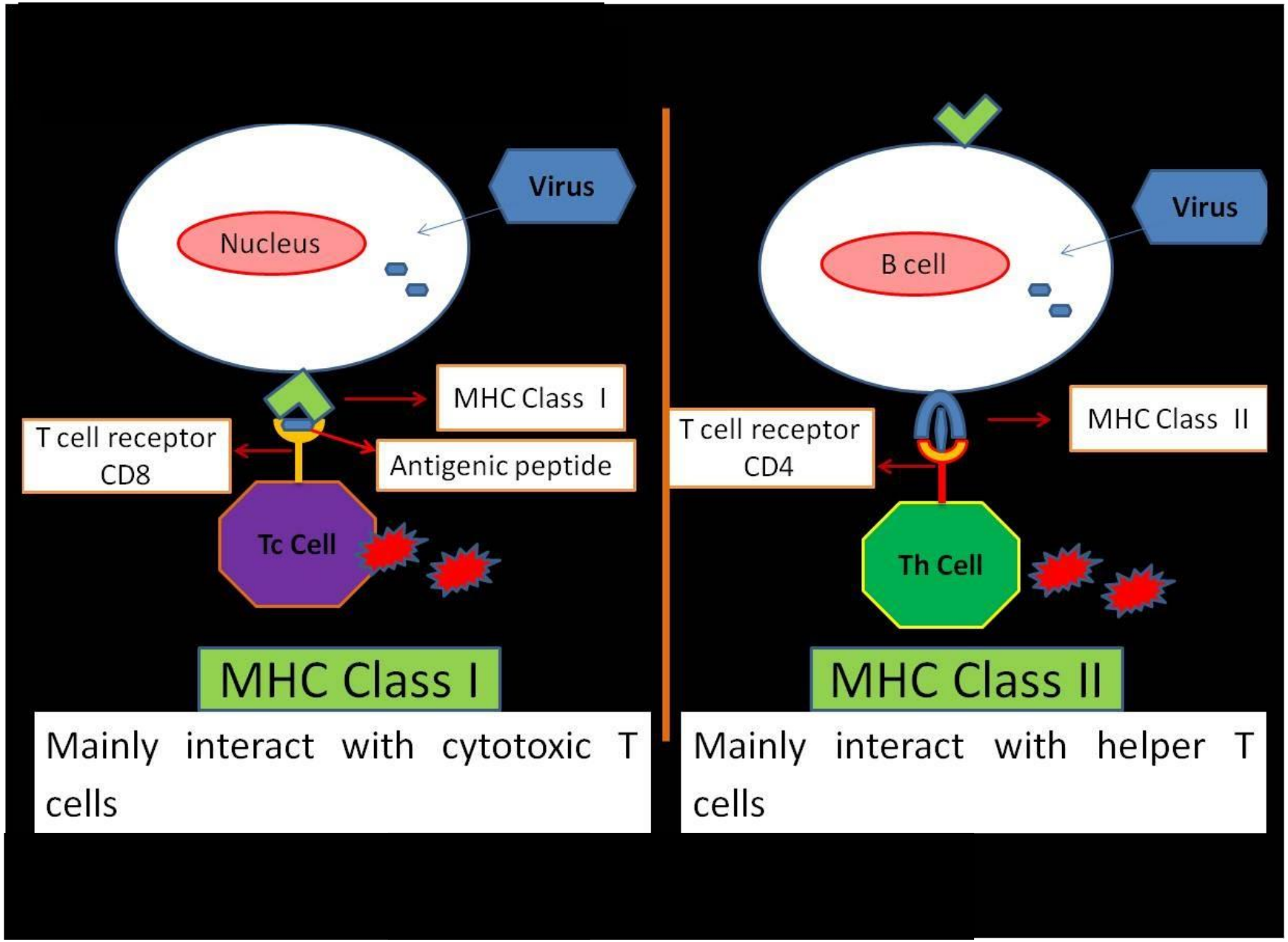


Bridge!

This is now an armed CD4 cell

B cells with the BCR specific to that
Antigen will be activated by the
Armed CD4 cell that is specific to
The same antigen

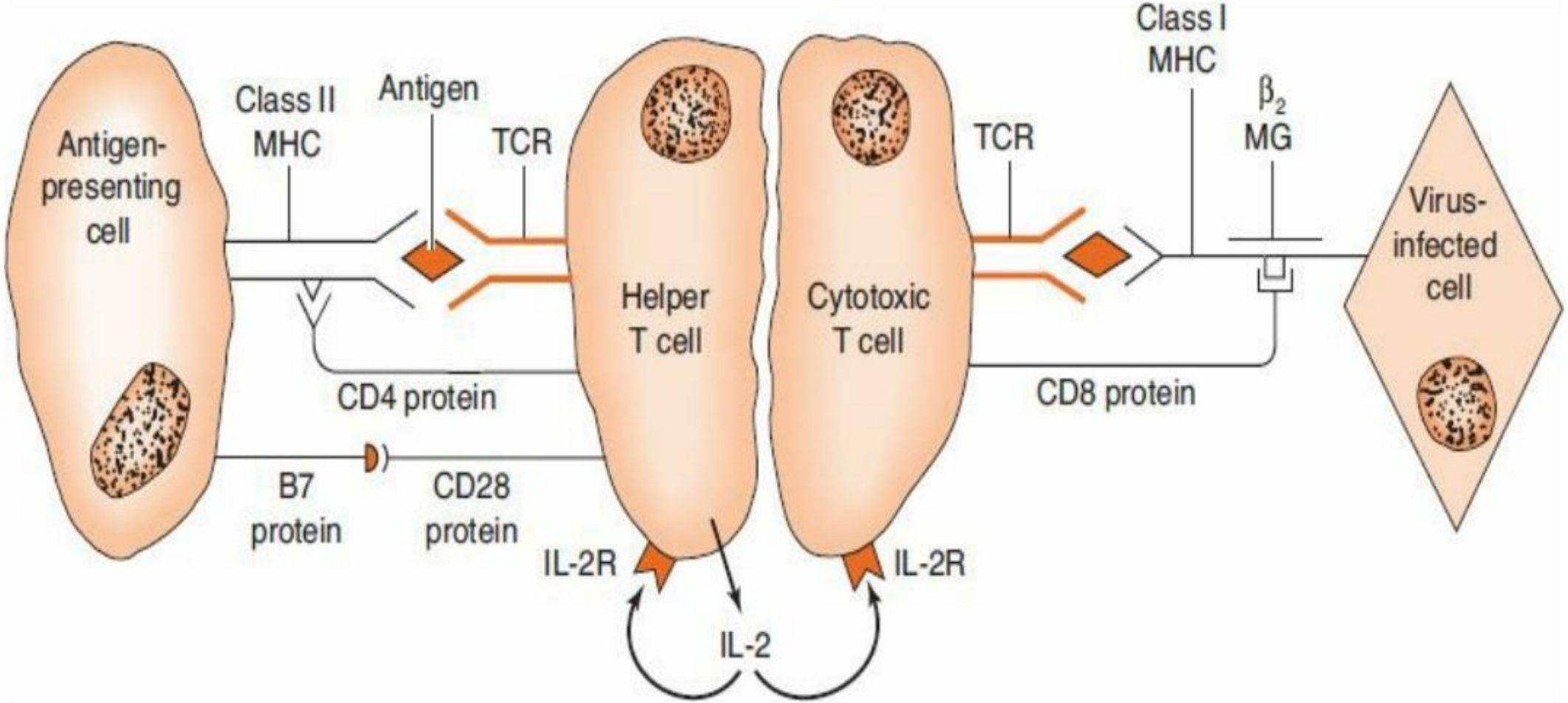
Notice the
CD8 cell is
Specific to the
Same antigen


Virus
Nucleus
MHC Class I
T cell receptor
CD8
Antigenic peptide
Tc Cell
MHC Class I
Mainly interact with cytotoxic T cells
Virus
B cell
T cell receptor
CD4
MHC Class II
Th Cell
MHC Class II
Mainly interact with helper T cells

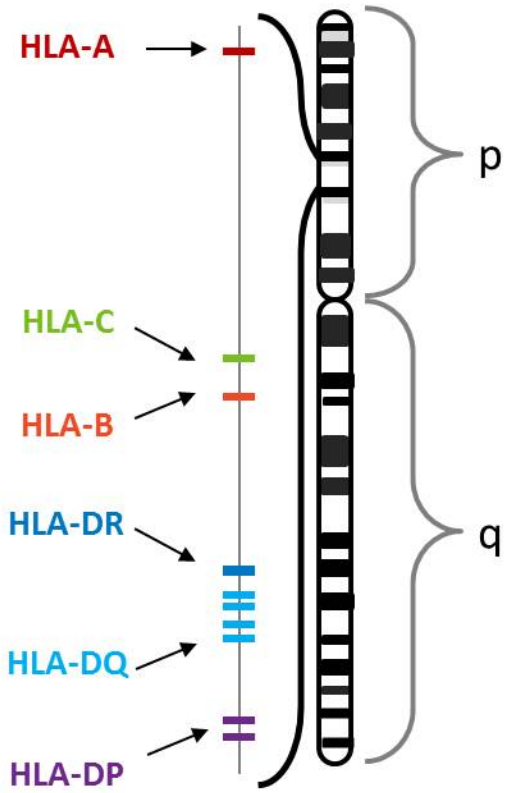
Costimulation Is Required to Activate T Cells we need two signals

- The first signal is the initial activation of the T cell by the interaction between the MHC complex protein with an antigen that is specific and interacts with that TCR. (is the TCR then unique to each antigen?)
- It is an important observation that the CD4 protein on the surface of these T cells functions in stabilizing the connection between TCR and MHC protein on the surface of the APC.
- Other proteins also serve to stabilize the contact between the two cells (APC and T cell)
  - **lymphocyte function-associated antigen 1** [LFA-1] protein 2 on CD4 or CD8 T cells binds with intracellular adhesion molecule 1 [ICAM-1] protein on the surface of APCs this is how the connection is established, which is then further strengthened by CD4

- A second signal, costimulatory signal is also required
- B7 protein on the APC must interact with CD28 protein on the **helper T cell** to proceed with the costimulatory signal.
- If the secondary co stimulation occurs, only then that IL-2 is produced by the helper T cell
- ***The production of IL-2 is the vital step that produces activated helper T cells*** that are able to regulate the immune response in Th-1 or Th-2 manner and produce memory cells.
- If this costimulatory signal does not occur a state of Anergy occurs (unresponsiveness). This unresponsiveness will only be specific to that epitope (they will still respond to other epitopes).
- Production of the costimulatory protein depends on activation of the Toll-like receptor on the APC surface.
- This is yet another defense mechanism against an immune response towards self proteins, there is no B7 production for self proteins however, foreign antigens are able to induce the production of B7.


Antigen-presenting cell
Class II MHC
Antigen
TCR
Helper T cell
Cytotoxic T cell
TCR
Class I MHC
β_2 MG
Virus-infected cell
CD4 protein
CD8 protein
B7 protein
CD28 protein
IL-2R
IL-2R
IL-2

MHC



MHC Class I

HLA-A

HLA-B

HLA-C

MHC Class II

HLA-DRB1

HLA-DRB3

HLA-DRB4

HLA-DRB5

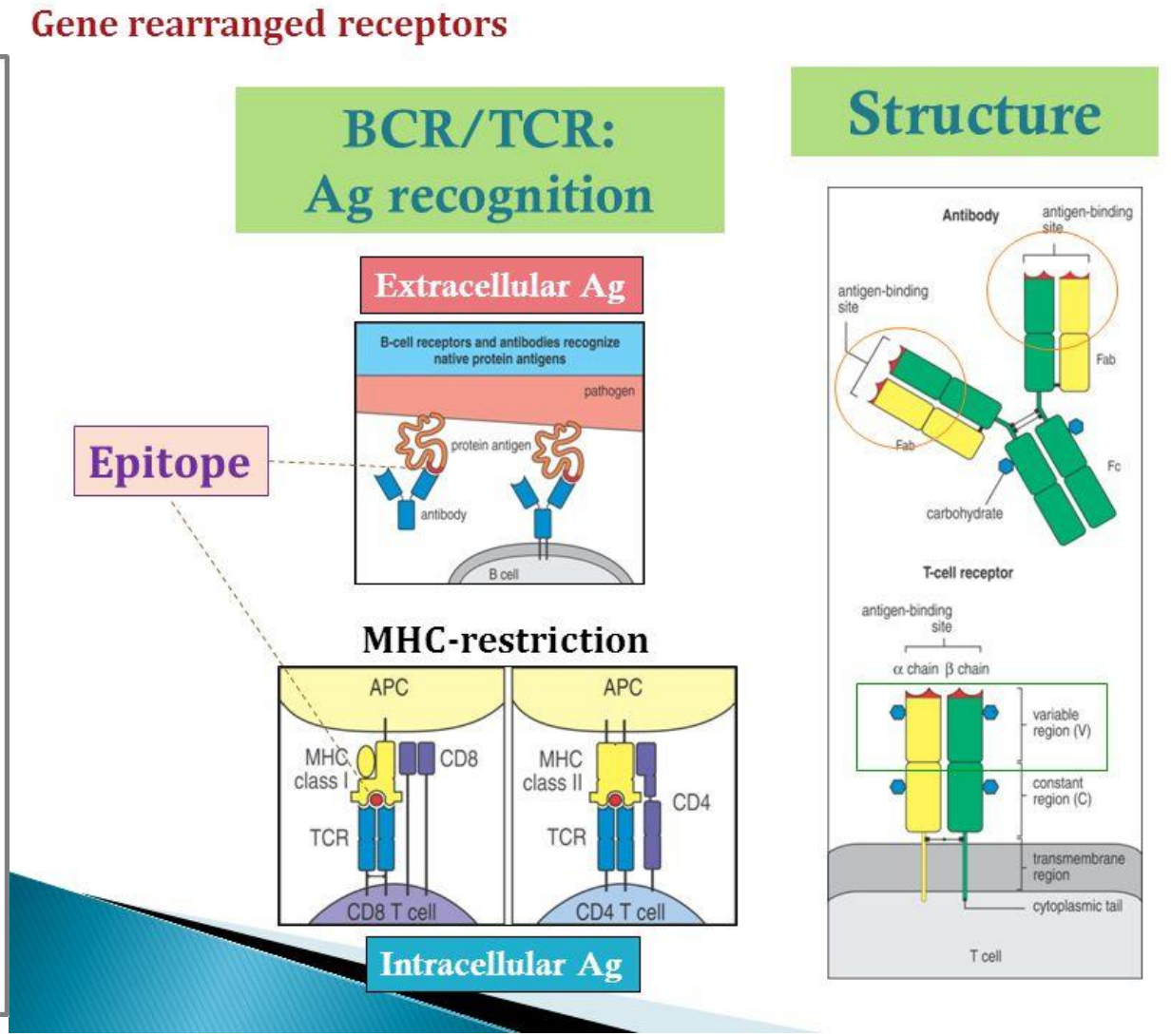
HLA-DQA1

HLA-DQB1

HLA-DPA1

HLA-DPB1

TCR/BCR



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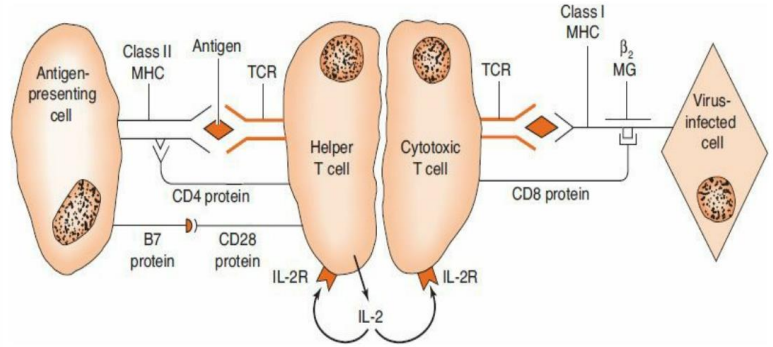
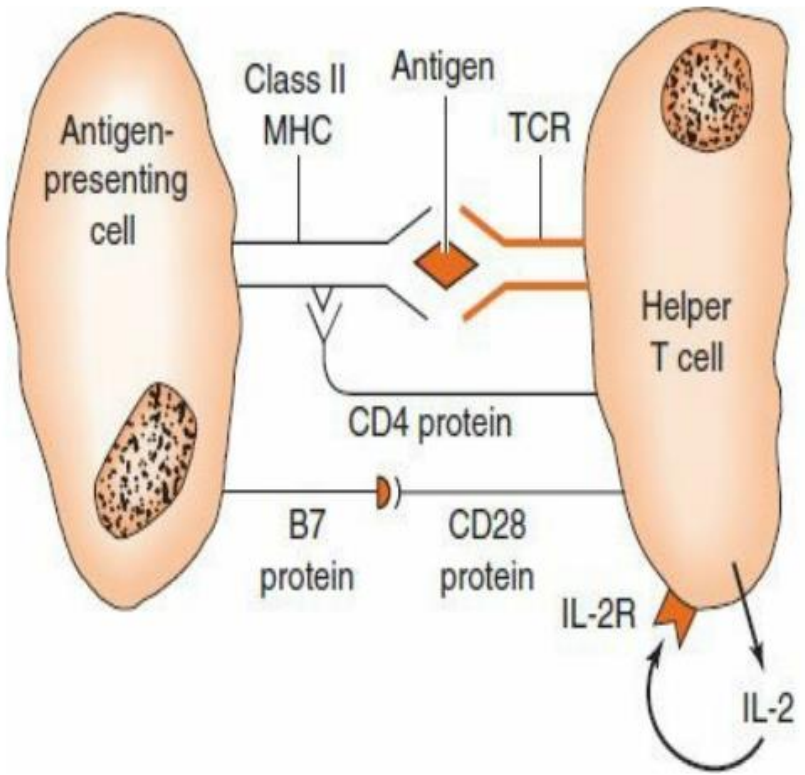
Activation of T cells.

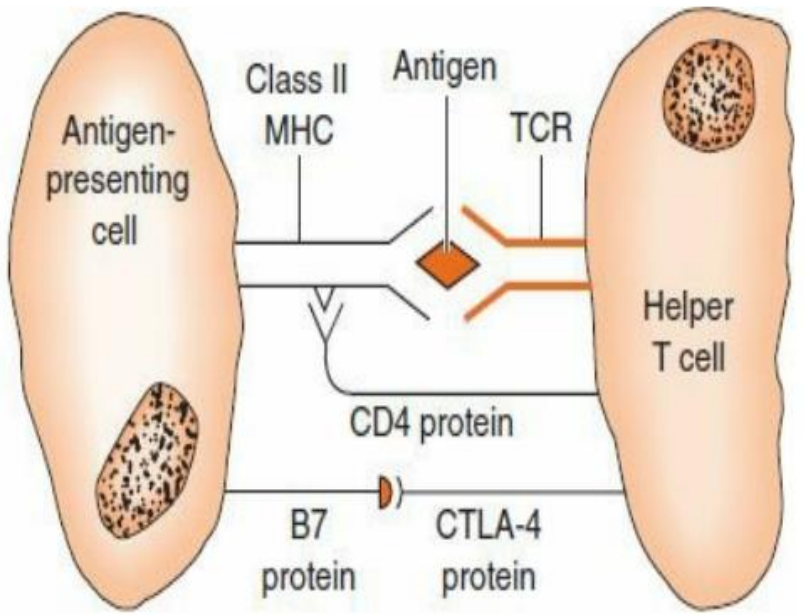


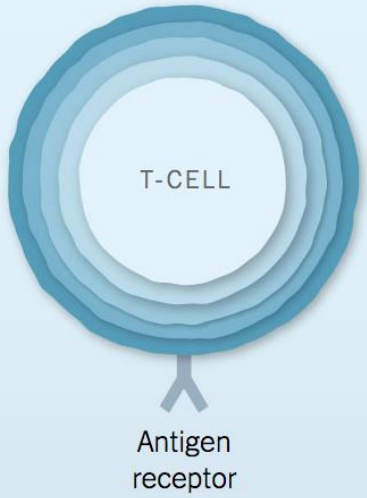
- On the left: APC presenting antigen with MHC-II → TCR specifically recognizes antigen→CD4 helper cell is activated and produces IL-2 which will only occur if the B7 protein binds the CD28 protein on the T cell. CD4 protein helps stabilize the connection between the cells.
- On the Right: A virus-infected cell uses its MHC-I to present viral antigen--> viral antigen recognized by TCR (it is specific to that antigen)→IL-2 produced by the helper T-cell activates this CD8 cell to kill the viral infected cell.→ CD8 protein helps stabilize the interaction between the two cells.
- Class II MHC protein consists of two polypeptides, both of which are encoded by genes in the human leukocyte antigen (HLA) locus, whereas Class I MHC protein has only one of its polypeptide encoded by the HLA locus and β2 - microglobulin (β2 MG), which is encoded somewhere else.

- To turn off these helper T- Cells, a different protein called cytotoxic T lymphocyte antigen-4 (CTLA-4) appears on the T-cell surface and binds to B7 and displaces the bound CD28.
- Now the co stimulatory signal is no longer working and thus CTLA-4 inhibits T-cell activation (IL-2 is now not produced due to the lack of the costimulatory signal).
- This is a regulatory mechanism to control the T cells and create a balance between on and off status.
- If this OFF switch is not present (mutant T cells that do not have CTLA-4) cannot be deactivated and cause autoimmune reactions.
- The use of CTLA-4 protein is shown to reduce the rejection of organ transplants in experimental animals (remember it is a cellular response).

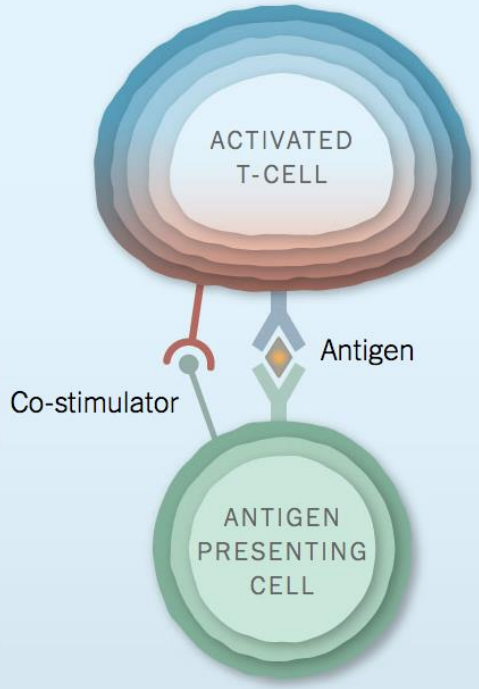
Inhibition of activated helper T cells.



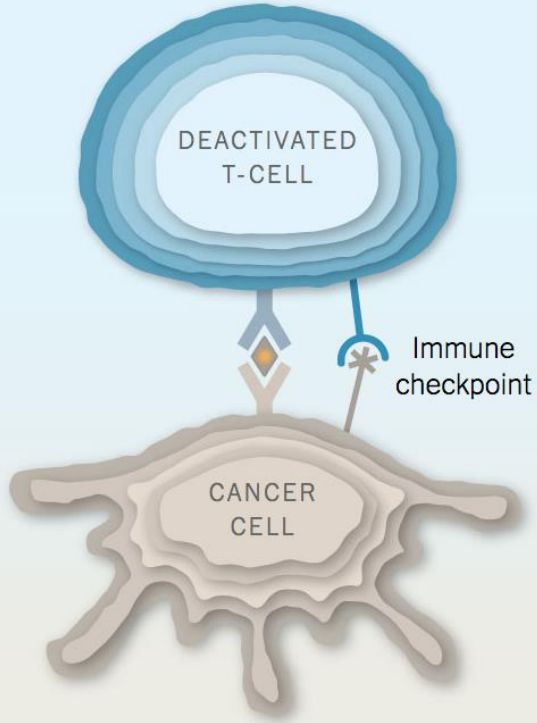




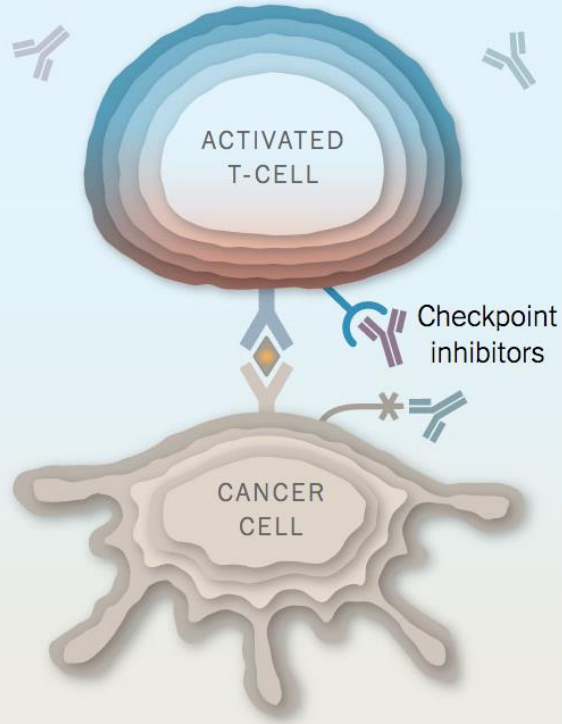
T-CELLS
T-cells are a type of white blood cell that can identify and kill infected, damaged or cancerous cells. Each T-cell has clawlike receptors on its surface that can recognize and lock onto antigens, foreign or abnormal protein fragments on the surface of infected or cancerous cells.



ACTIVATING A T-CELL
The T-cell must be activated before it can find and attack cancer cells. A specialized cell presents the T-cell with an antigen from a cancer cell, along with a co-stimulator protein. The T-cell begins to hunt down and kill any cells that are covered with the same antigen.



CANCER AND CHECKPOINTS
Cancer cells can avoid destruction by taking advantage of a switch on the T-cell called an immune checkpoint. The checkpoint can shut down the T-cell and suppress the immune response, allowing the cancer to grow undisturbed.



CHECKPOINT INHIBITORS
Drugs known as checkpoint inhibitors can physically block the checkpoint, which frees the immune system to attack the cancer. A single T-cell can kill thousands of cancer cells.

- Agonists of CTLA4 are used coupled with Ig to reduce immunity and are in trials to treat immune disorders such as Rheumatoid arthritis and renal transplants in specific patients (with EBV virus).
- Ig Fc fragment provides resistance against degradation, resulting in increased plasma levels of CTLA-4 for a longer duration than CTLA-4 alone

- Antagonists of CTLA4 (enhancers of cellular immunity) are used to increase immunity, this is in trials to be used as a potential therapy to reduce the tolerance of immune system to tumor cells and thus help mount a response against them

- Antagonists to CTLA-4 can be in the form of antibodies, that would inactivate CTLA4 and thus improve the immune response against some human cancer cells and cause the cancer to regress.
- So the antibody is an inhibitor of an inhibitor of the immune response.
- Another inhibitory protein on the surface of T cells has also been described (PD-1 (programmed cell death-1)).
- When PD-1 interacts with its ligand (PDL-1) on the surface of APCs, such as dendritic cells and macrophages, the immune response is inhibited-similar to CTLA-4. Similarly, antibodies against PD-1 enhance the immune response and are effective against some cancers, as shown in recent trials.

T CELLS

- T cells have two major roles in the immune reaction. They are either regulatory cells (helper cells) or as effector cells (Cytotoxic).
- Regulator (tell cells what to do by signals), effector (perform the function itself).
- The regulatory role of CD4 helper cells is mediated by signal proteins (interleukins). For example, helper T cells make
  - (1) interleukin (IL)-2, which activates CD4 and CD8 cells
  - (2) IL-4, which help B cells make antibodies, especially IgE
  - (3) gamma interferon, which enhances killing by macrophages.
- The effector functions of T cells are carried out mainly by cytotoxic (CD8) T cells, which DIRECTLY kill cells (virus infected cells, tumor cells , allografts).

TABLE 58–3 Main Functions of Helper T cells

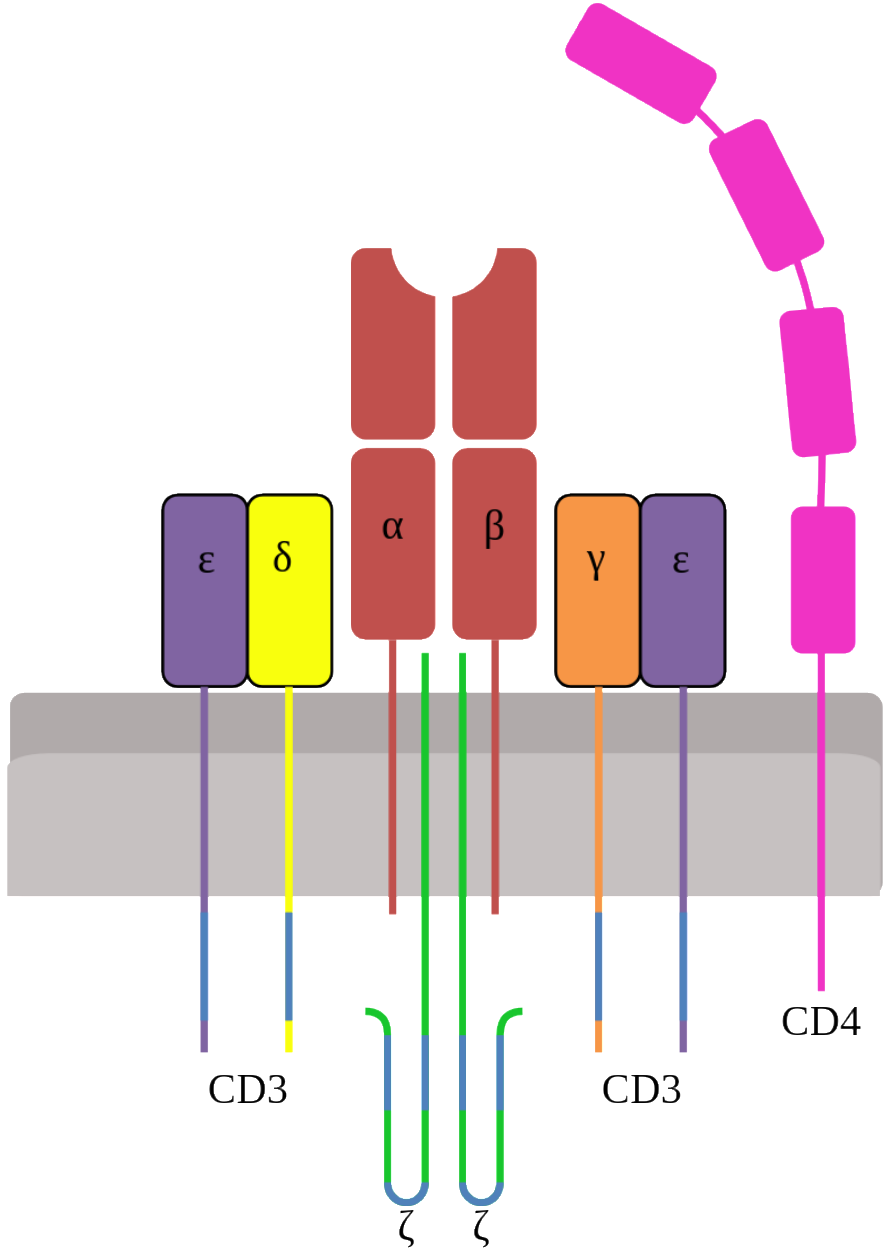
Main Functions	Cytokine That Mediates That Function
Activates the antigen-specific helper T cell to produce a clone of these cells	IL-2
Activates cytotoxic T cells	IL-2
Activates B cells	IL-4 and IL-5
Activates macrophages	Gamma interferon

IL = interleukin.

CD4 & CD8 Types of T Cells

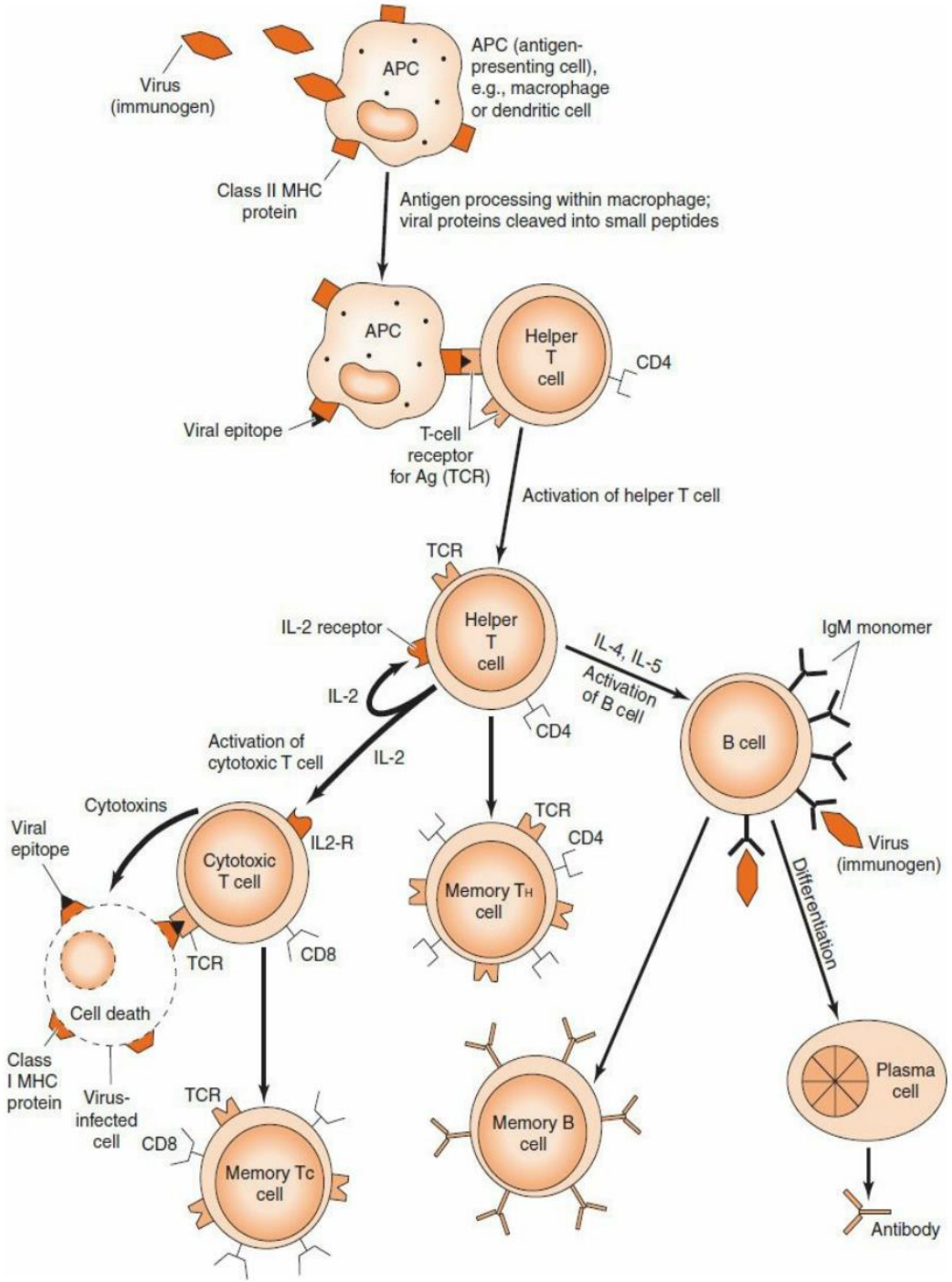
- T cell progenitor cells differentiate from the outer layer of cortical epithelial thymus cells (nurse cells), T cell progenitors differentiate under the influence of Thymic hormones (Thymosins and thymopoietins) into T-cell subpopulations that are characterized by their surface proteins (CD3, CD4, and CD8).
- CD3 is present on the surface of ALL T cells, and is associated with antigen receptors (TCR).
- The CD3 is a complex of five transmembrane proteins, its main function is the transmission of signals from outside the membrane to within the cell (hence the transmembrane part!)

- As it is associated with the antigen receptor (TCR) the signal transmitted its that the TCR is occupied (ON). (One of the **CD3 transmembrane proteins**, the zeta chain, is linked to a tyrosine kinase called fyn, which is involved with signal transduction).
- Second messengers further transmit the signal (see later).
- CD4 is a single transmembrane protein, whereas CD8 is made up of two transmembrane proteins. (Lck kinase is a possible way for their signal transmission)
- T cells are subdivided into two major categories on the basis of whether they have CD4 or CD8 proteins on their surface, when they mature they have either one, but not both.

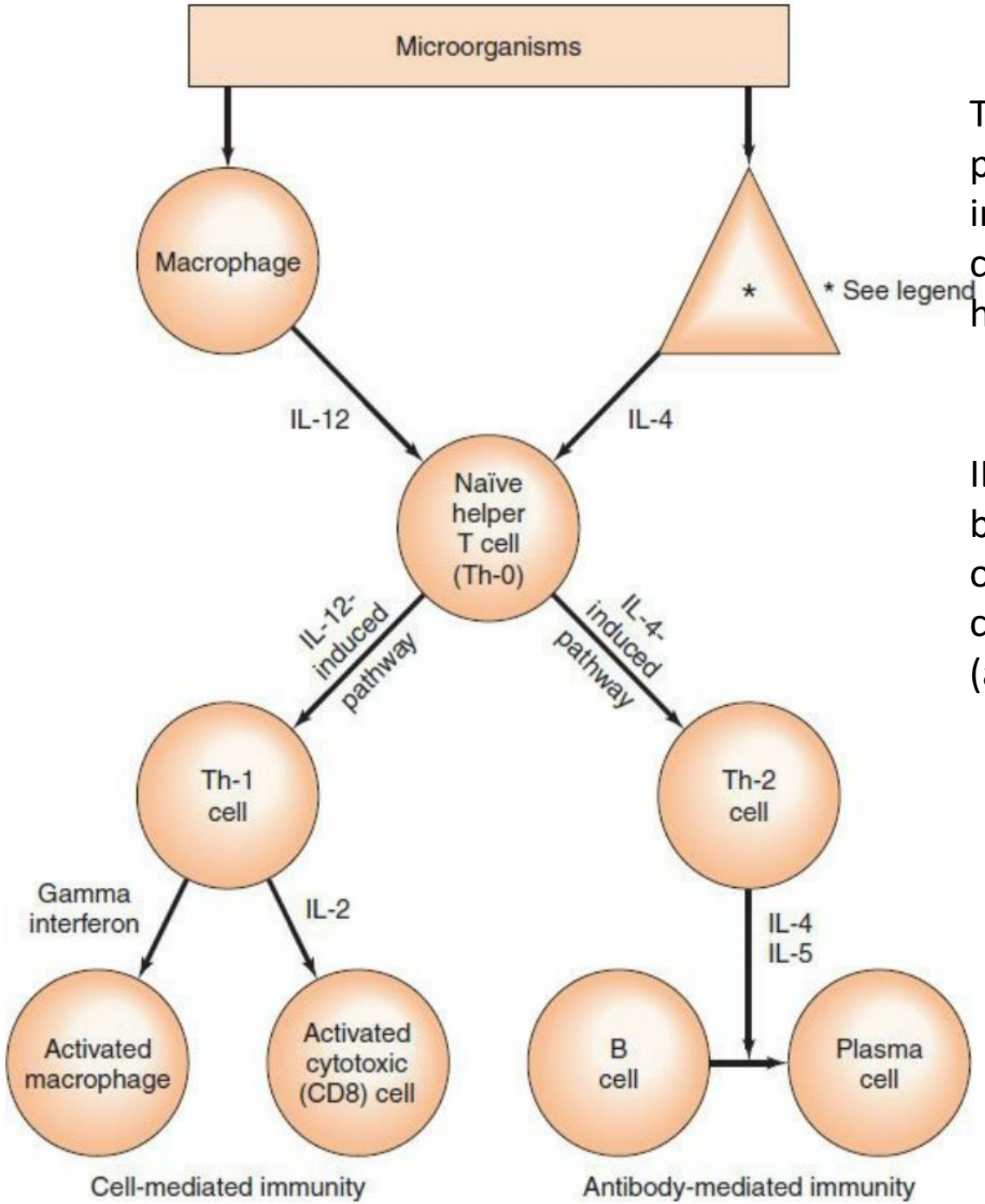


https://commons.wikimedia.org/wiki/File:TCR_complex.svg

- CD4 lymphocytes perform their regulatory functions in the following manner:
- (1) they help activate CD8 T-cells to become activated cytotoxic T cells
- (2) They help activate B cells to develop into antibody-producing plasma cells
- (3) they help macrophages effect delayed hypersensitivity (e.g., limit infection by Mycobacterium tuberculosis).
- The first two functions are carried out by two different subpopulations of CD4 cells.
- The first function is carried out by Th-1 CD4 cells help activate cytotoxic T cells by producing IL-2 and help initiate the delayed hypersensitivity response (the third function) by producing **primarily IL-2 and gamma interferon**
- The second function is carried out by Th-2 cells, which help activate B-cells by producing primarily IL-4 and IL-5 .
- HOWEVER, the role of Th1 cells (e.g., gamma interferon) , also affects B cells to class switch from IgM to IgG by producing cytokines which produce two subclasses of IgG (namely IgG 1 and IgG 3) that are very effective in opsonisation of bacteria. (we will get to this during antibody lectures)


Virus
(immunogen)
APC
APC (antigen-presenting cell), e.g., macrophage or dendritic cell
Class II MHC protein
Antigen processing within macrophage; viral proteins cleaved into small peptides
APC
Helper T cell
CD4
Viral epitope
T-cell receptor for Ag (TCR)
Activation of helper T cell
TCR
IL-2 receptor
Helper T cell
IL-4, IL-5
Activation of B cell
IgM monomer
IL-2
CD4
B cell
Activation of cytotoxic T cell
IL-2
Cytotoxins
Viral epitope
Cytotoxic T cell
IL2-R
TCR
CD8
Cell death
Class I MHC protein
Virus-infected cell
TCR
CD8
Memory Tc cell
TCR
CD4
Memory TH cell
Memory B cell
Virus (immunogen)
Differentiation
Plasma cell
Antibody

Ingested bugs→IL-12 produced→IL-12 induces naïve Th-0 cells to become Th-1 cells → gamma interferon and IL-2 (cell mediated immunity)



The human cell that produces the IL-4, which induces naïve helper T cells to become Th-2 cells, has not been identified.

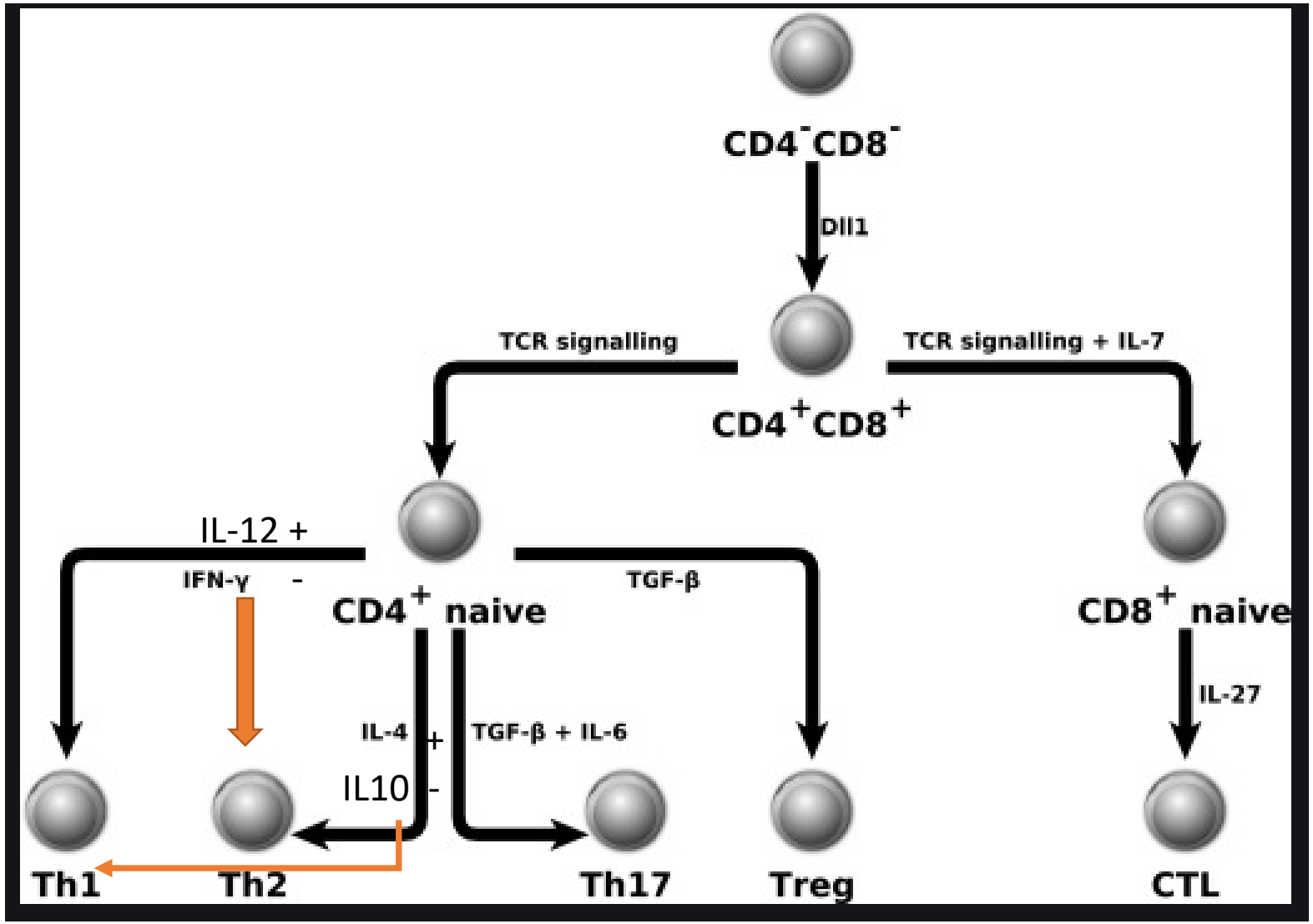
IL-4 induces naïve Th-0 cells to become Th-2 cells→ production of IL-4 and IL-5→ activation of B cells to become plasma cells (antibody immunity)

- There is a balance between Th1 cells and Th2 cells.
- This balance is is provided by the production of IL-12 from macrophages. IL-12 increases the number of Th-1 cells (cell mediated), enhancing host defenses against organisms that are controlled by a delayed hypersensitivity response.
- Moreover, Interferon from Th1 cells also inhibits the production of Th2 cells, tipping the scale further towards Th1 response). Th1 = IL-12 (stimulatory to Th1) + Interferon (inhibitory to Th2)
- IL-10 produced by Th-2 cells inhibits IL-12 production by macrophages and drives the system toward an antibody response and away from a cell-mediated response (towards Th2).
- CD4 cells make up about 65% of peripheral T cells and predominate in the thymic medulla, tonsils, and blood. Th2 = IL-4 (stimulatory to Th2) + IL10 (inhibitory to Th1)

TABLE 58–4 Comparison of Th-1 Cells and Th-2 Cells

Property	Th-1 Cells	Th-2 Cells
Produces IL-2 and gamma interferon	Yes	No
Produces IL-4, IL-5, IL-6, and IL-10	No	Yes
Enhances cell-mediated immunity and delayed hypersensitivity primarily	Yes	No
Enhances antibody production primarily	No	Yes
Stimulated by IL-12	Yes	No
Stimulated by IL-4	No	Yes

IL = interleukin.

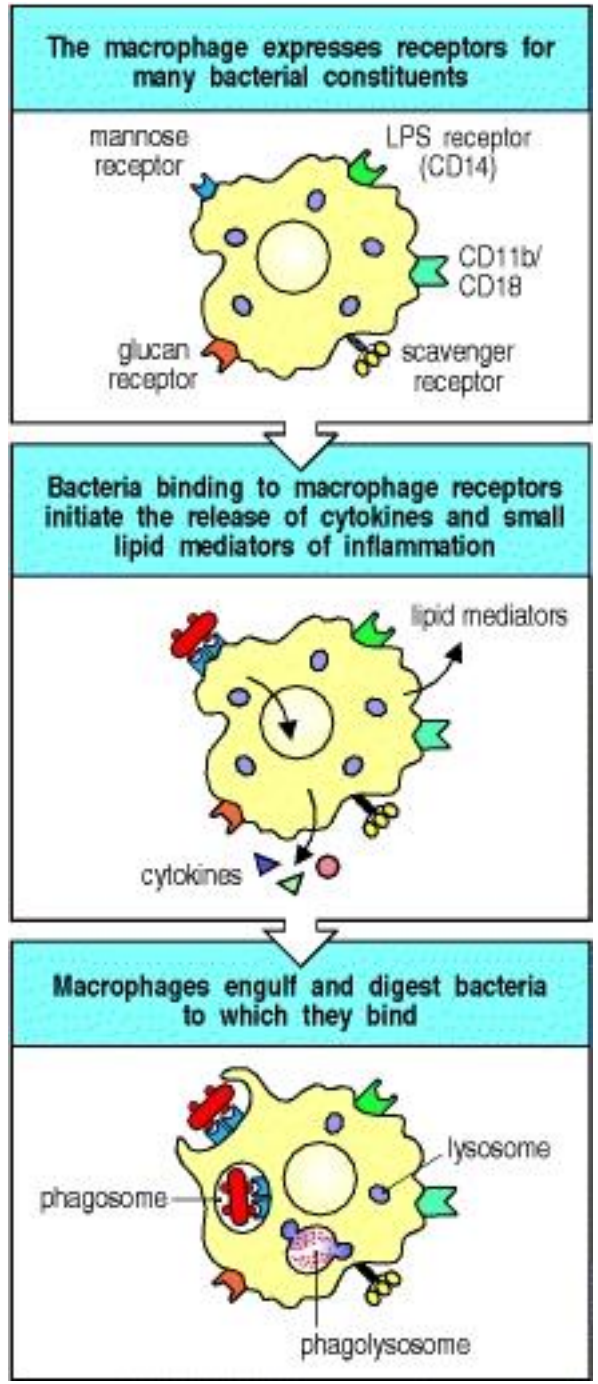

CD4-CD8-
Dll1
TCR signalling
TCR signalling + IL-7
CD4+CD8+
IL-12 +
IFN-γ
-
CD4+ naive
TGF-β
CD8+ naive
IL-27
IL-4
+
TGF-β + IL-6
IL10
-
Th1
Th2
Th17
Treg
CTL

- To mount a protective immune response against a specific microbe requires that the appropriate subpopulation (i.e., either Th-1 or Th-2 cells) to play a dominant role in the response.
- For example, if an individual is infected with *M. tuberculosis* and Th-2 cells are the major responders, then humoral immunity will be stimulated rather than cell-mediated immunity.
- Humoral immunity is not protective against *M. tuberculosis*, and the patient will suffer severe tuberculosis (why?).
- Similarly, if an individual is infected with *Streptococcus pneumoniae* and Th-1 cells are the major responders, then humoral immunity will not be stimulated and the patient will have severe pneumococcal disease (remember this is a capsulated bacteria, you need antibodies to counter it).
- Precisely what component of a microbe activates either Th-1 or Th-2 cells is unknown.

- *M. tuberculosis* is a well studied and well known example of how the response is stimulated.

- It was found that a specific lipoprotein on the surface of that bacterium interacts with a specific Toll-like receptor (TLR) present on the surface of the macrophage, the interaction of the lipoprotein and the macrophage's TLR induces the production of IL-12. (so this is before the bacteria enters cells, it is now detected before entry by macrophages)
- (remember Toll like receptors, part of innate immunity, how cells such as macrophages and dendritic cell use pathogen associated patterns to detect microbes and engulf them)
- IL-12 is the stimulatory signal that drives the differentiation of undifferentiated (naïve) helper T cells to go down the Th-1 type of differentiation which drives a cell-mediated (delayed hypersensitivity) response against the organism/which is here the correct response.

- Another subpopulation of CD4 cells that differentiate into yet another subpopulation of immune responders (called Th-17), they have been shown to have a significant role in the mucosal immunity of the gastrointestinal (GI) tract (this will include the mucosa of the mouth!).
- The reason these cells are different , is that they are producing IL-17 instead of gamma interferon (that is usually produced by Th1 cells, or IL-4 from Th-2 cells)
- The function of IL-17 is as a signal that recruits neutrophils to the site of **bacterial** infections.
- What do neutrophils do? How?


The macrophage expresses receptors for many bacterial constituents
mannose receptor
LPS receptor (CD14)
CD11b/ CD18
glucan receptor
scavenger receptor
Bacteria binding to macrophage receptors initiate the release of cytokines and small lipid mediators of inflammation
lipid mediators
cytokines
Macrophages engulf and digest bacteria to which they bind
lysosome
phagosome
phagolysosome

- how we found the significance of these cells was that HIV SELECTIVLEY targets these cells, which creates an almost total loss of function of Th-17 cells.
- It was shown that those patients have a high rate of blood infection caused by colonic (gut) bacteria such as *Escherichia coli* and *Klebsiella* (the gut is not protecting them from the penetration of these bacteria into the blood). This is how we discovered this subpopulation of CD4 cells.
- In a similar fashion, IL-17 was found to also contribute to our immunity against some fungal infections (chronic mucocutaneous candidiasis).

TABLE 58–5 Signature Cytokine Produced by Subsets of CD4-Positive Helper T Cells

Subset of CD4-Positive Helper T Cells	Signature Cytokine	Function of Cytokine
Th-1 cells	Gamma interferon	Activates macrophages to kill intracellular microbes
Th-2 cells	Interleukin-4 (IL-4)	Stimulates development of Th-2 cells; enhances class switching to IgE
Th-17 cells	Interleukin-17 (IL-17)	Recruits neutrophils to site of infection

T Cells Recognize Only Peptides

- T cells only recognize antigens that are polypeptides 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 intracellulary produced antigens (viral proteins for example), MHC-II proteins usually present antigens of extracellular origin (bacterial proteins) - 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.
- You will have ready made antibodies that will trap the virus before entry to cells (or when they burst open cells) -so next time you meet the virus, you have antibodies to intercept before it enters your cells-.
- .

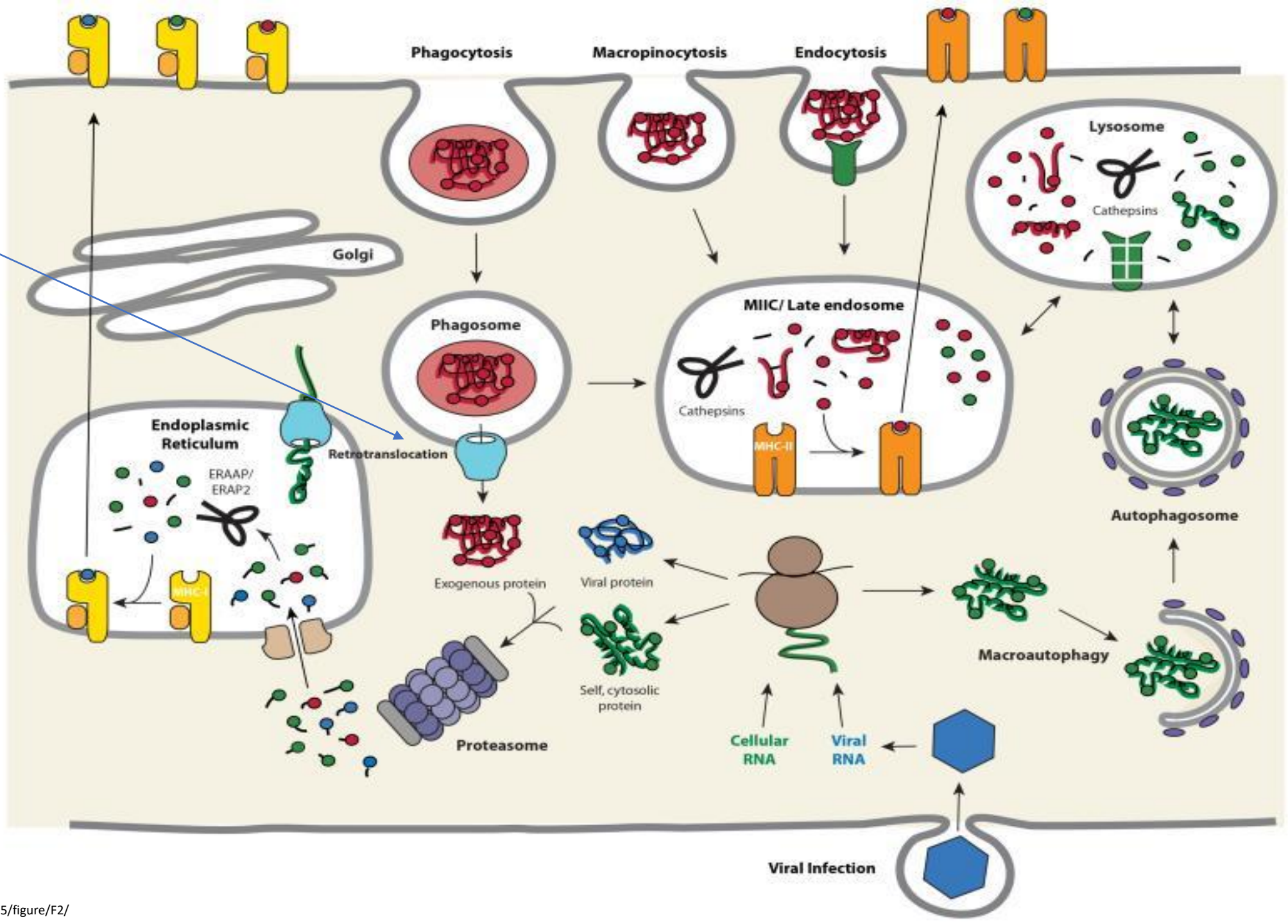
- This restriction, is due to the distinction in the acquisition and PROCESSING of these proteins through different organelles and pathways.
- 1) An endogenous protein (viral protein – cancer protein) is processed in different compartments within the cytoplasm than those derived from extracellular sources.
- The association of endogenous foreign proteins with MHC-I complex happens due this difference in processing, where these proteins are cleaved by a **proteasome** 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.
- The endogenous protein-MHC-I complex now travels to Golgi 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 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), 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).

*some crossing between the two pathways DOES occur:

MHC-I can bind peptides derived from exogenous proteins internalized by endocytosis or phagocytosis, a phenomenon called cross-presentation. 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)



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4026165/figure/F2/

- 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) can bypass the peptide requirement 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.
- 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 (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*)
- →but why does block only cell mediated and not AB mediated?.

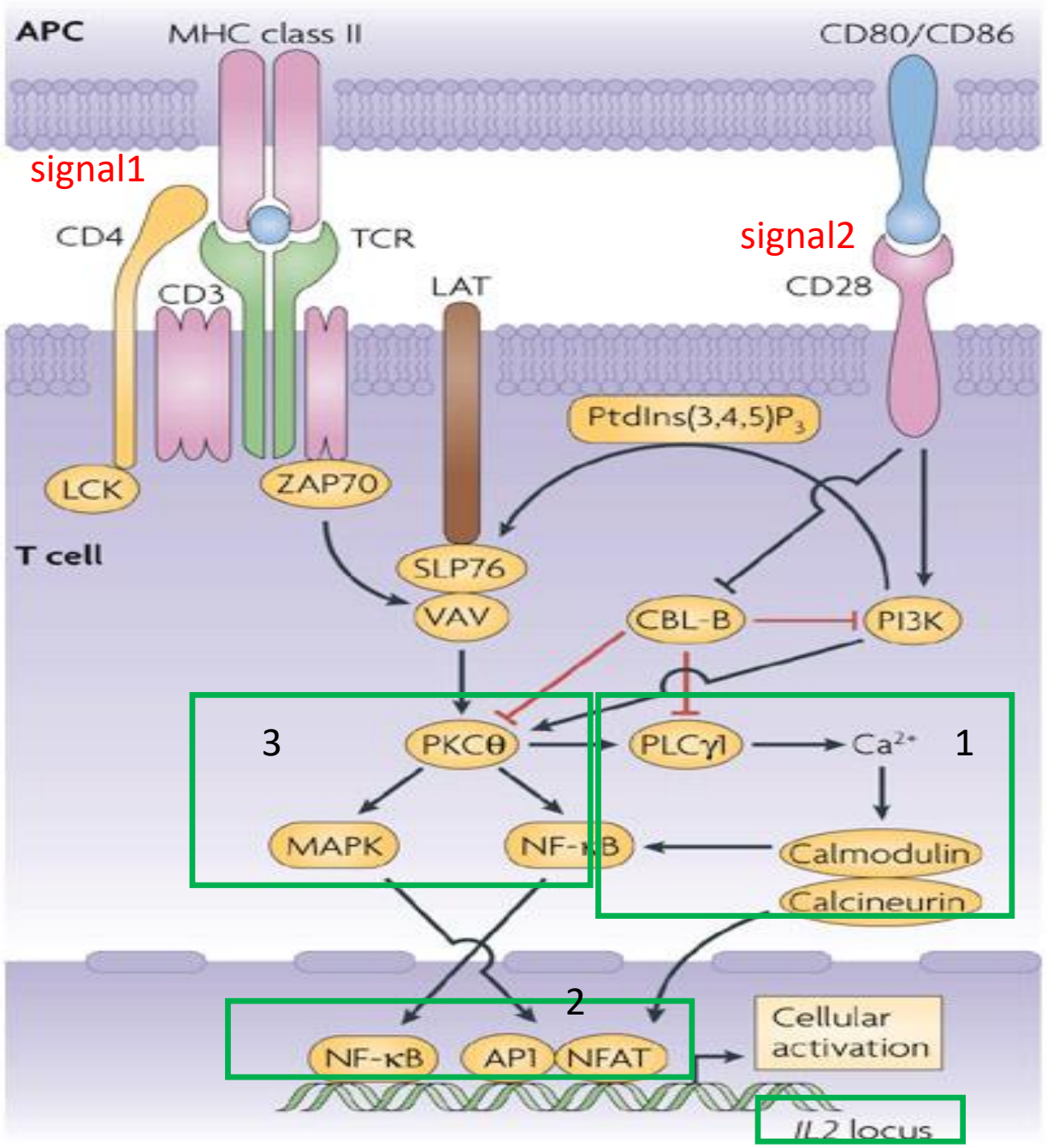
IL-2

- 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,
- 2- nuclear factor of activated T cells (NFAT)- nuclear factor-B (NF-B) pathway
- 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. 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).



- It is in this step (IL-2 production) that clonal proliferation of helper T cells happens for that specific 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