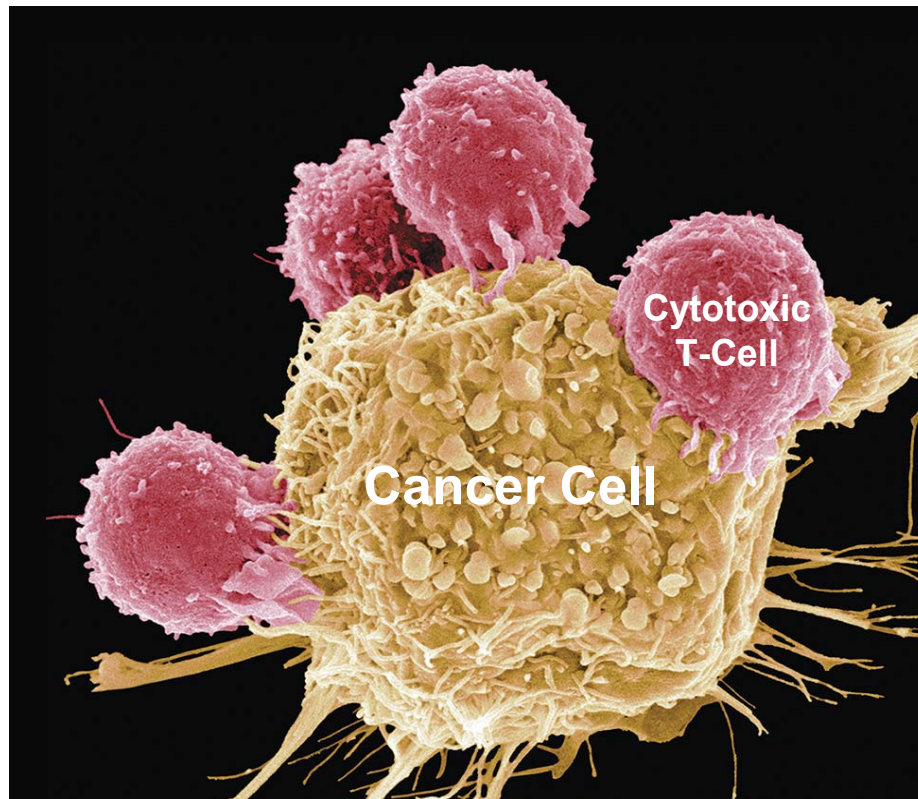


The Third Line of Defense

“Acquired Immunity”

(Also Called “Adaptive Immunity”)





What is immunity?

- Immunity protects us against *internal and external threats*.
- Immunity may be either innate or acquired (also called adaptive)
- *Innate immunity* exists at time of birth // Relies on numerous factors including physical barriers, cellular phagocytes and many different types of molecules
- Innate immunity is characterized as being “*non-specific resistance*” with general characteristics (plasma molecules) shared by many different pathogens
- *Acquired or Adaptive (Non-innate) Immunity* means it does not exist at birth /// develops after birth /// characterized by “*specificity and memory*”
- We fight infections by using *three lines of defenses*:
 - #1 - Physical barriers ————— (both innate)
 - #2 - Non-specific resistance ————— (not innate also called adaptive immunity)
 - #3 - Acquired immunity —————

The dual nature of the adaptive immune system.

humoral

Humoral (antibody-mediated) immune system
Control of freely circulating pathogens

Extracellular antigens

- 1 A B cell binds to the antigen for which it is specific. A T-dependent B cell requires cooperation with a T helper (T_H) cell.

B cell

- 2 The B cell, often with stimulation by cytokines from a T_H cell, differentiates into a plasma cell. Some B cells become memory cells.

Plasma cell

- 3 Plasma cells proliferate and produce antibodies against the antigen.

Memory cell

Some T and B cells differentiate into memory cells that respond rapidly to any secondary encounter with an antigen.

cellular

Cellular (cell-mediated) immune system
Control of intracellular pathogens

Intracellular antigens are expressed on the surface of an APC, a cell infected by a virus, a bacterium, or a parasite.

- 1 A T cell binds to MHC-antigen complexes on the surface of the infected cell, activating the T cell (with its cytokine receptors).

T cell

Cytokines

- 2 Activation of macrophage (enhanced phagocytic activity).

- 3 The CD8⁺T cell becomes a cytotoxic T lymphocyte (CTL) able to induce apoptosis of the target cell.

Cytotoxic T lymphocyte

Lysed target cell

KEY CONCEPTS

- The adaptive immune system is divided into two parts, each responsible for dealing with pathogens in different ways. These two systems function interdependently to keep the body free of pathogens.
- **Humoral immunity**, also called antibody-mediated immunity, is directed at freely circulating pathogens and depends on B cells.
- **Cellular immunity**, also called cell-mediated immunity, depends on T cells to eliminate intracellular pathogens, reject foreign tissue recognized as nonself, and destroy tumor cells.

How is acquired immunity managed?



T-cells and B-cells are the key cells responsible for acquired immunity /// these cells must first be **born, educated, deployed** /// after being deployed these cells will “rest” until a pathogen enters the body // this will cause the T and B cells to enter their second phase: **recognize, react, remember**

Born = place where T and B cells are formed (created) // red bone marrow

Educated = this occurs when T and B cells receive “unique receptors” attached to billions of different possible foreign antigens // B cells educated in bone marrow and T cells educated in thymus

Deployed = after receiving their receptors, they are called naive immunocompetent T and B cells and are released into the blood. These cells are free to wander anywhere throughout the body but many rest in the lymph nodes /// The next step occurs when pathogen enters the tissue > the three “R”s.

How is acquired immunity managed?

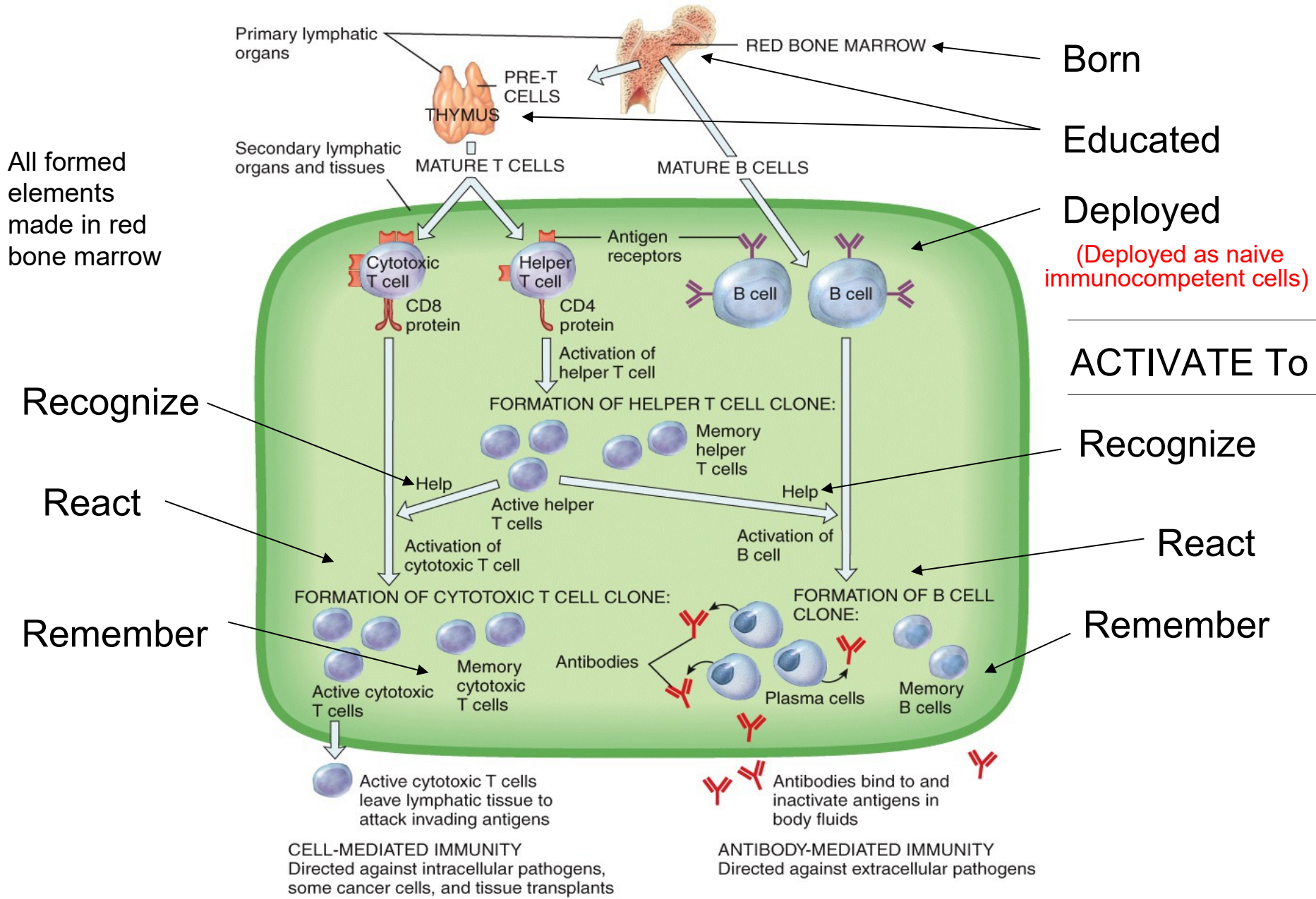


Recognize = naive immunocompetent T and B cells are not able to “see the pathogen” until after an antigen presenting cells “shows” the T and B cells the pathogen now invading the Body // these cells are no longer naive but are now “turned on”

React = where “turned on” cytotoxic T cells (C-Tc) and helper T cells (H-c) eliminate threat From pathogen

Remember = making memory T and B cells to be used in next exposure to same pathogen

Outline for the function of acquired immunity.



What makes acquired immunity so special?



Three important characteristics = “systemic, specificity and memory”

Acquired immunity recognizes the pathogen because it has “non-self antigen”

Acquired immunity use WBC to coordinate the activities of T and B cells

All the WBC must work together (i.e. talk to each other)

WBC use cytokines and leukotrienes to communicate with each other

Innate immunity is local

Adaptive immunity is non-innate and is systemic.

Our immune system defeat pathogens by using both innate and non-innate immunity.

What Are the Two Forms of Acquired Immunity?



- *Humoral and cellular acquired immunity*
- *WBCs called T cells provide **cellular adaptive immunity** // Cytotoxic T cells - kill host's cells infected with bacteria.*
- *WBCs called B cells (when activated they change into plasma cells) provide **humoral adaptive immunity** /// After B cells morph into **plasma cells** they produce **antibodies** /// antibodies do not kill pathogens /// **antibodies** render pathogens harmless and tag them for destruction.*
- ***Clonal selection** occurs after T and B cells are activated by Antigen Presenting Cells /// results in rapid mitosis of T and B cell // all cells have similar receptors matched to a specific foreign antigen to a specific pathogen*
- *Cytotoxic -Tcell, helper-Tcell, and B cells **all have similar receptors able to dock onto the same pathogen's foreign antigen** /// during clonal selection memory cells are made to similar antigen but rest in lymph nodes*
- *Memory cells do not react to “current infection” but will respond immediately after a **second exposure** to similar pathogen. /// first exposure vs second exposure*

Why do we need cellular and humoral immunity?



Because the pathogen is either outside or inside our cells!

*Humoral Adaptive Immunity: B cell morph into plasma cells after activated // plasma cells make antibodies /// antibodies only attack antigens when they are **outside our cells**.*

*Cellular Adaptive Immunity: Cytotoxic T cells (i.e. cellular immunity) recognize foreign antigen when they are “hiding” **inside our cells**.*

Therefore, when we are infected by a bacteria, our acquired immune system must activate both T cells and B Cells. These cells have receptors matched to the same foreign antigen!

Each cell line (T and B) have receptors that are able to recognize the same foreign antigen /// waiting in our lymph nodes are “billions” of naive immunocompetent T and B cells just waiting to become activated /// each pair of cells will have a unique receptor

*Note: When T and B cells are educated “**each B and T cell pair**” will receive just one out of a possible billion different foreign antigen receptors. This means we have billions of “B cells and billions of T cell forming pairs” that share a common foreign antigen receptor unique to a pathogen's antigen.*



Key Factoids

Immune system differentiate between self and non-self antigens

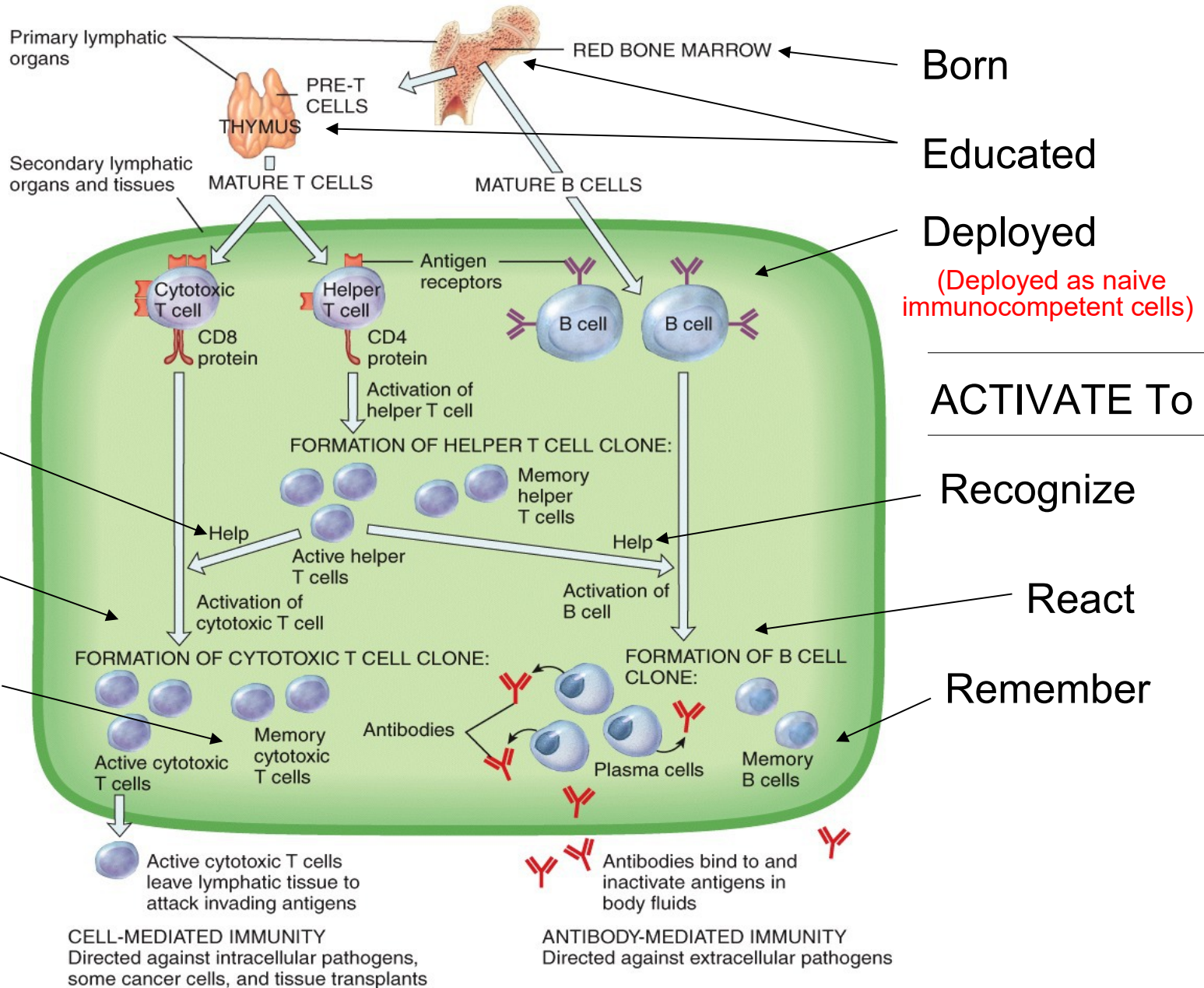
Immune system function is to eliminate pathogens

Cytotoxic T cells are able to kill infected host cells

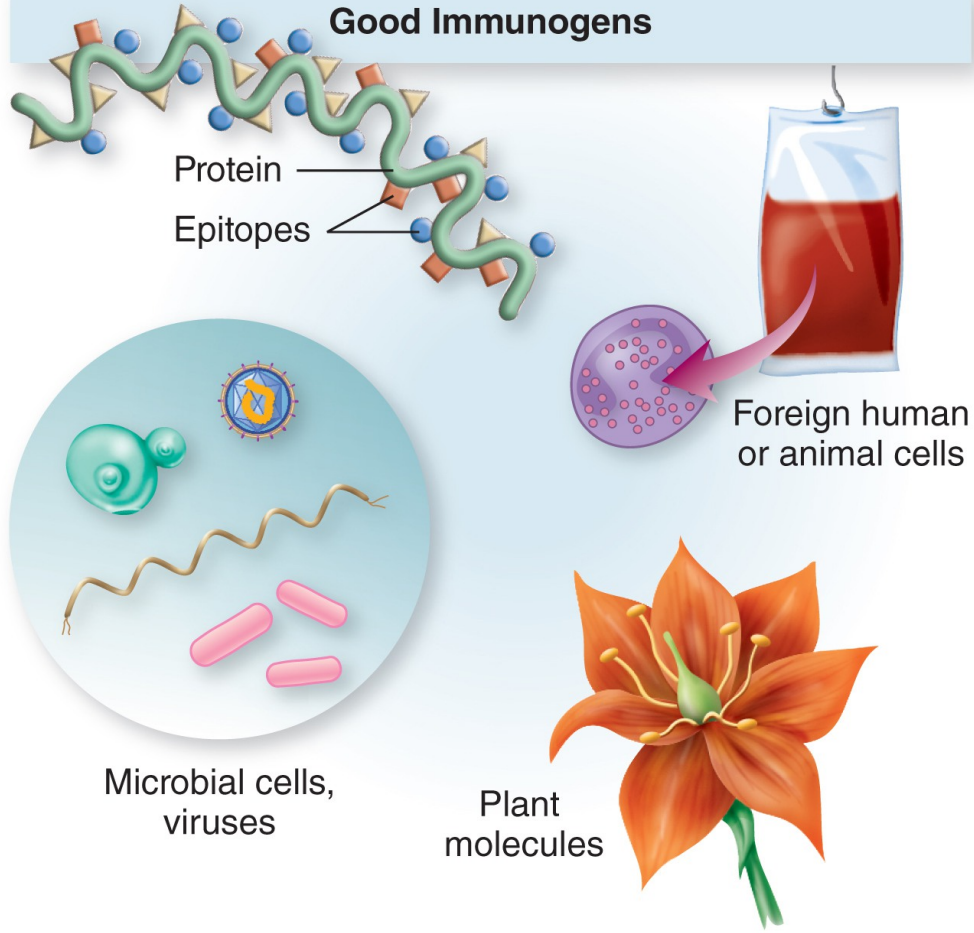
Plasma cells (made from B cells) produce antibodies to render pathogen harmless and tag pathogen for destruction /// this occurs in body fluids // antibodies made by plasma cells

Another lymphocyte called Natural Killer Cells (NK cell) are able to kill infected host cells but uses a different types of receptors // evolved to kill host cells infected by cancer or virus as well as cells infected with bacteria /// NK cells do require to be activated by a pathogen's antigen but may recognize MHCP Holding non self proteins // NK cells perform immune surveillance

Outline for the structure and function of acquired immunity.



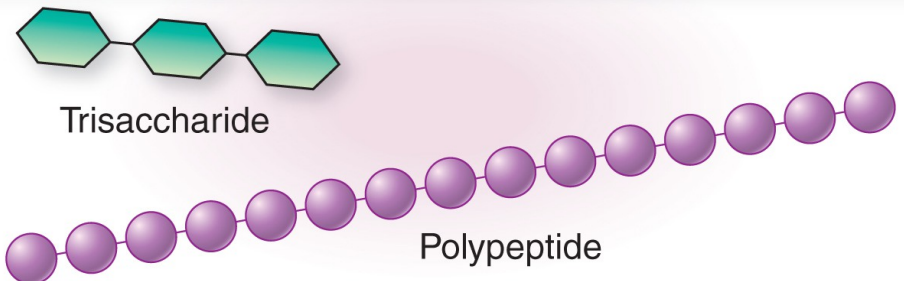
Good Immunogens



Foreign antigens (i.e. non-self antigens) are also known as immunogens!

Antigens are large molecules.

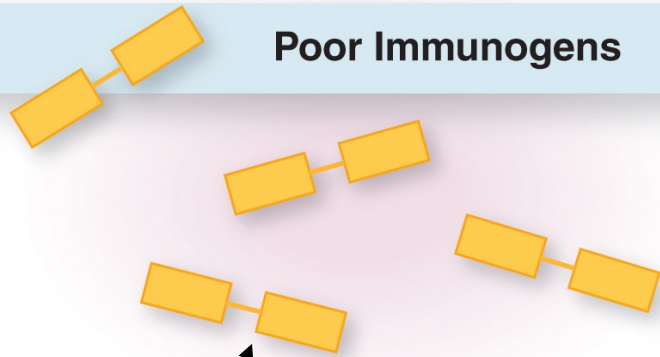
Poor Immunogens



Haptens

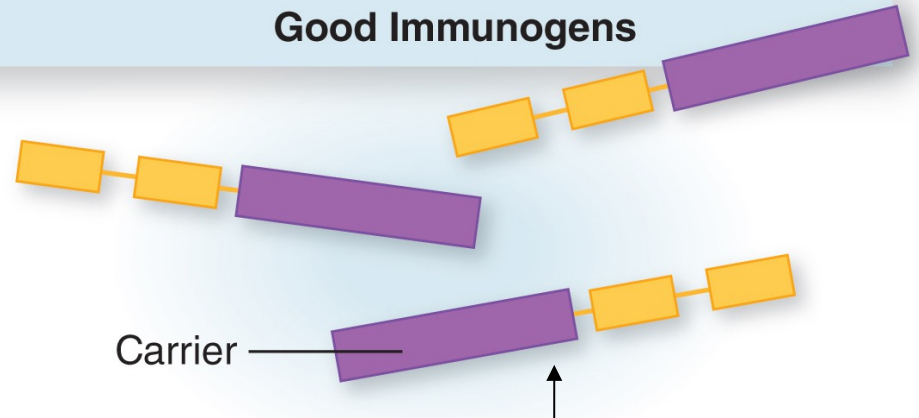
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Poor Immunogens



Haptens are too small to act as an antigen.

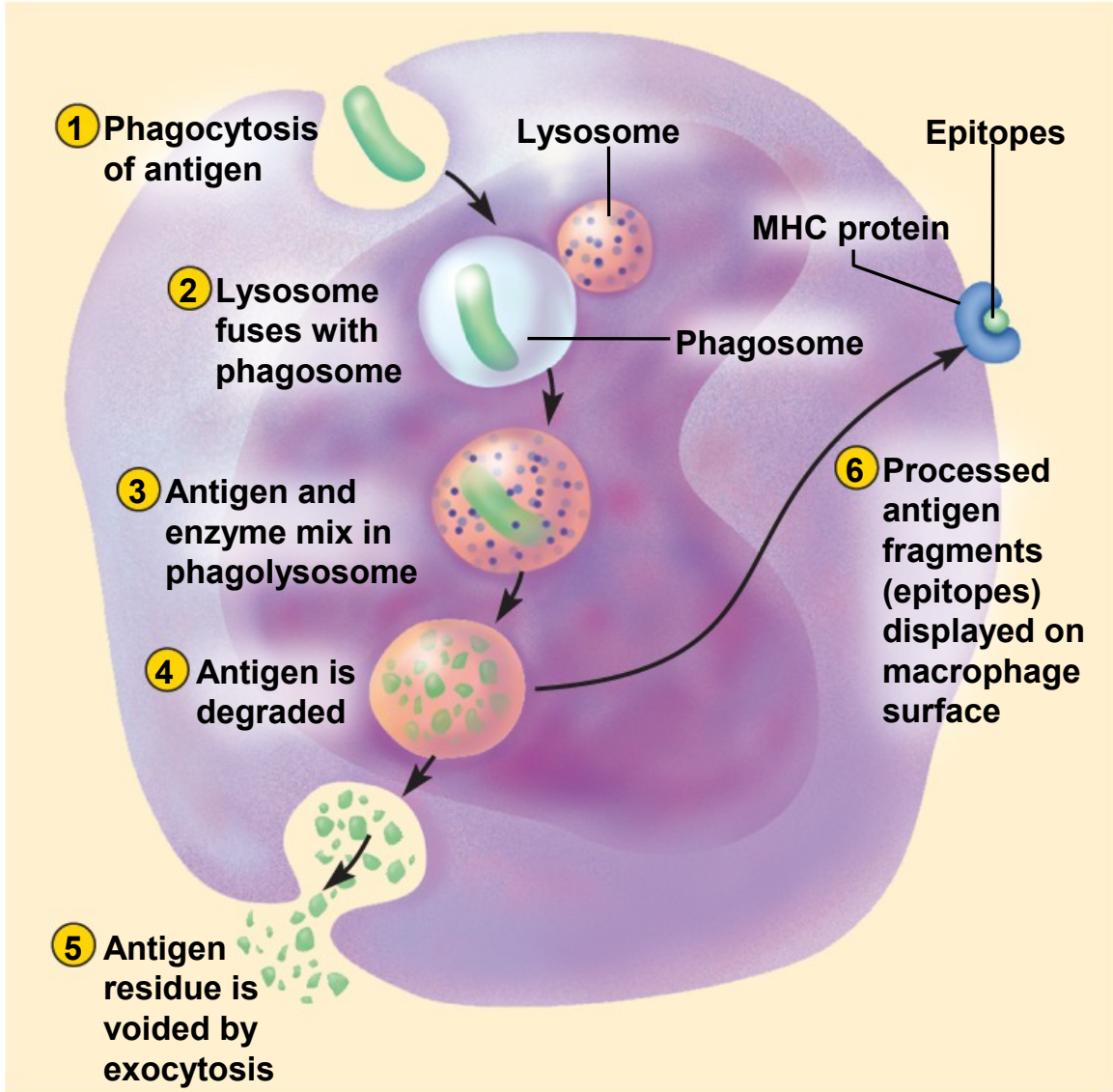
Good Immunogens



After haptens joined to a “carrier” (e.g. albumin) they can now be recognized as an antigen.



How Do Antigen Processing Cells Turn Antigens into Epitope and then Display Epitope on Outer Surface of the Plasma Membrane?



MHC protein hold the epitope and may be either type-I or type-II

Macrophage and B cells have MHCP-II // both are APCs

Dendritic cells = APC //// MHCP Class-I and Class II

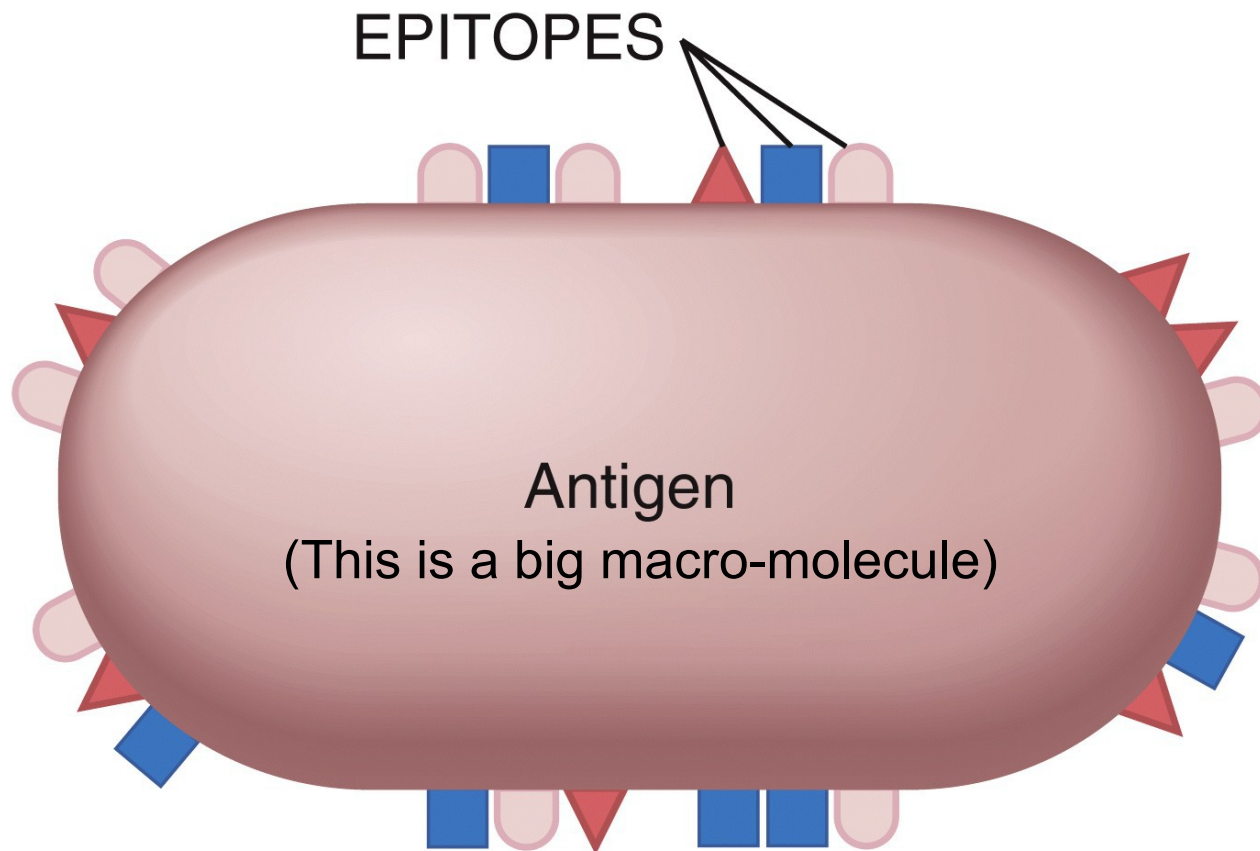
Helper T-cells receptors only bind to MHCP-II // must occur to activate H-Tc // macrophage and dendritic cells have MHCP II

Cytotoxic-T-cells receptors only bind to MHCP-I // must occur to activate C-Tc // dendritic cells have MHCP-I

NK cells receptors use different clusters of differentiation to recognize virus or cancer // when NK engage with markers take 3 days to reach peak activity

All nucleated host cells have only MHC-I

A single antigen molecule may generate many epitopes. The proteasome will degrade the antigen and create protein fragments that are processed by the endoplasmic reticulum. The endoplasmic reticulum put epitopes into vesicles that are then inserted into the host's plasma membrane.



Major Histocompatibility Proteins (MHCP-1 VS MHCP-2)

Cells use proteosomes to degrade cytoplasmic proteins into fragments // foreign cell's protein fragments (called epitopes) are displayed on the outer surface of the plasma membrane in MHCP which maybe type-I or type-II (the epitopes are like the pathogens “finger prints”)

Cytoplasmic proteins fragments displayed by host cells maybe “normal” host cell proteins (endogenous) or from unusual proteins associated with cancer, bacteria, or virus. /// Host cells only have MHCP-1 /// Protein fragments are picked up by MHCP-1 and inserted on the outer surface of the host's plasma membrane

Now we know what cells are infected (if they have epitopes). The next step is to activate naive immunocompetent C-Tc and naive immunocompetent H-Tc with receptors matched to the epitopes of infected host cells.

This will require antigen presenting cells (APC). These cells help naive T and H cells (specific naive immune cells with receptors only able to bind to the displayed epitope) recognize the pathogen inside our cells.

C-Tc cells have receptors only able to dock with MHCP-I and H-Tc cells have receptors only able to dock with MHCP-II (now it becomes confusing so keep the type I and type II separate).

Major Histocompatibility Proteins (MHCP-1 VS MHCP-2)

APC (macrophage and dendritic cells) capture the bacteria infecting our cells, process the epitopes, then deliver this info to the lymph nodes

Macrophage MHCP-II dock with naive Th cells with matching receptor to activate Th cells

Dendritic cells have both MHCP-I and MHCP-II. Dendritic cells may activate both Tc (recognize type I) or Th cells (recognize type II) .

Now we have activated both Tc and Th cells which have specific receptors match to the bacteria that is infecting the host cell. Tc receptors now may engage directly with the infected host cells.

The Th secretes cytokines are required to finalize the activation of the Tc cell.

Fully activated CTc receptor now may dock to the host cell MHCP-I-epitope and kills the cell with the kiss of death // CTc cell then undocks and goes to next infected cell to kill it. After all infected host cells killed, this group of CTc die by apoptosis.

Major Histocompatibility Proteins (MHCP-1 VS MHCP-2)

B cells provide humoral immunity. B cells function as their own APC.

Naive immunocompetent B cells have D class antibodies as receptors. Matching B cell receptors may dock to bacteria's antigen. B cells then engulf the bacteria and process the epitope. //

B cells use MHCP-II to display bacteria's epitope on B cell plasma membrane // at this point the B cells are only partially (weakly) activated and produce some plasma cells which make few antibodies and no memory cells

If these B cells dock with H-T cell (activated by similar epitope) the H-T cells secrete cytokines and the B cells are now fully activated /// B cell now morphs into plasma cell /// These plasma cells make many more antibodies as well as memory B cells // more on this topic later

Antibodies neutralize bacteria outside of our cells by rendering the bacteria harmless and tag them for destruction. Complement will destroy the tagged pathogen.

Major Histocompatibility Proteins (MHCP-1 VS MHCP-2)

NK cells receptors use different clusters of differentiation to recognize host cells infected with virus, cancer, or bacteria

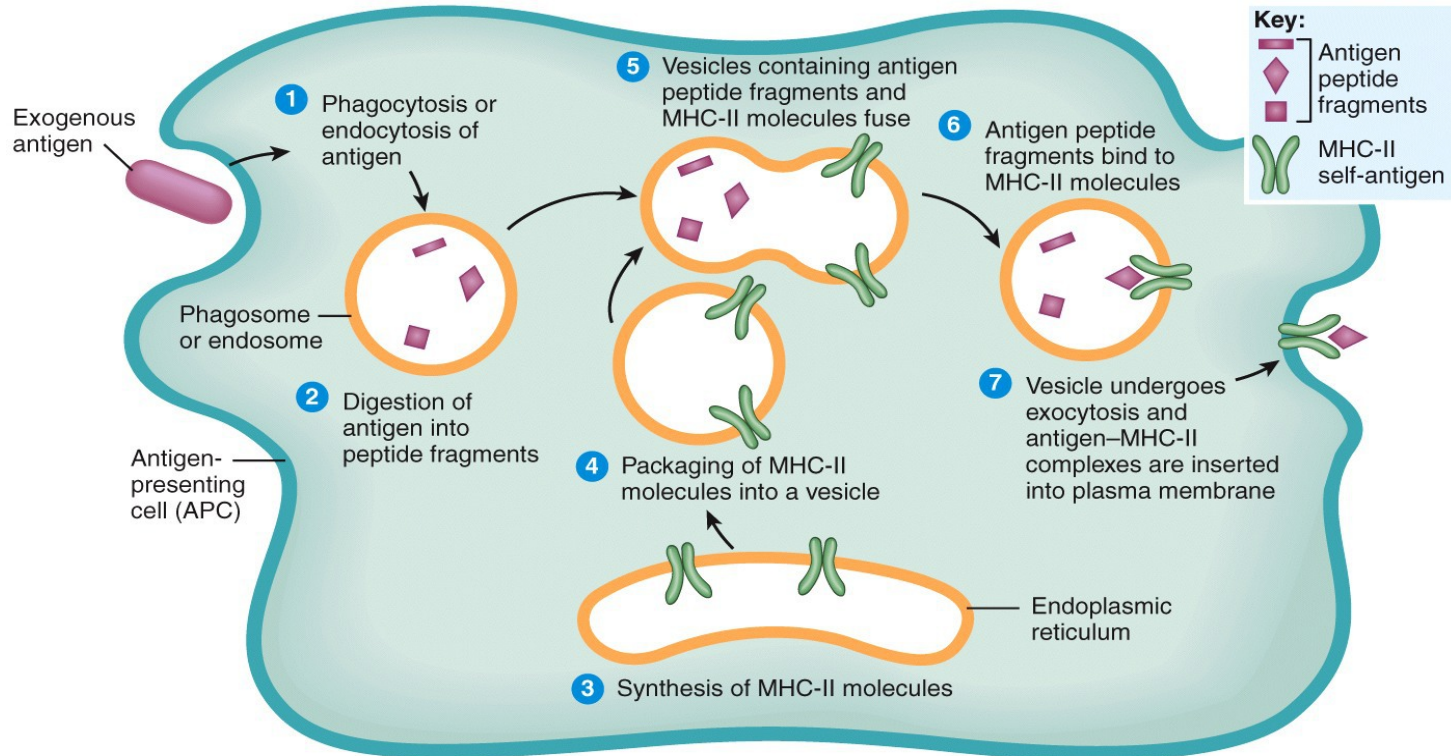
After NK engage with host cells epitope then it will take 3 days to reach peak activity

In conclusion, immunity is complicated! /// more slides to illustrate these steps.

Antigen Processed Cells Using MHC-II



Macrophage and dendritic cells are antigen processing cells that have MHC-II proteins. The APCs engulf exogenous antigen and present their epitope-MHC-II complex in the plasma membrane. Naïve immunocompetent helper T cells (CD4) with matched receptors bind to the MHC-II-complex. This activates the helper T cell.

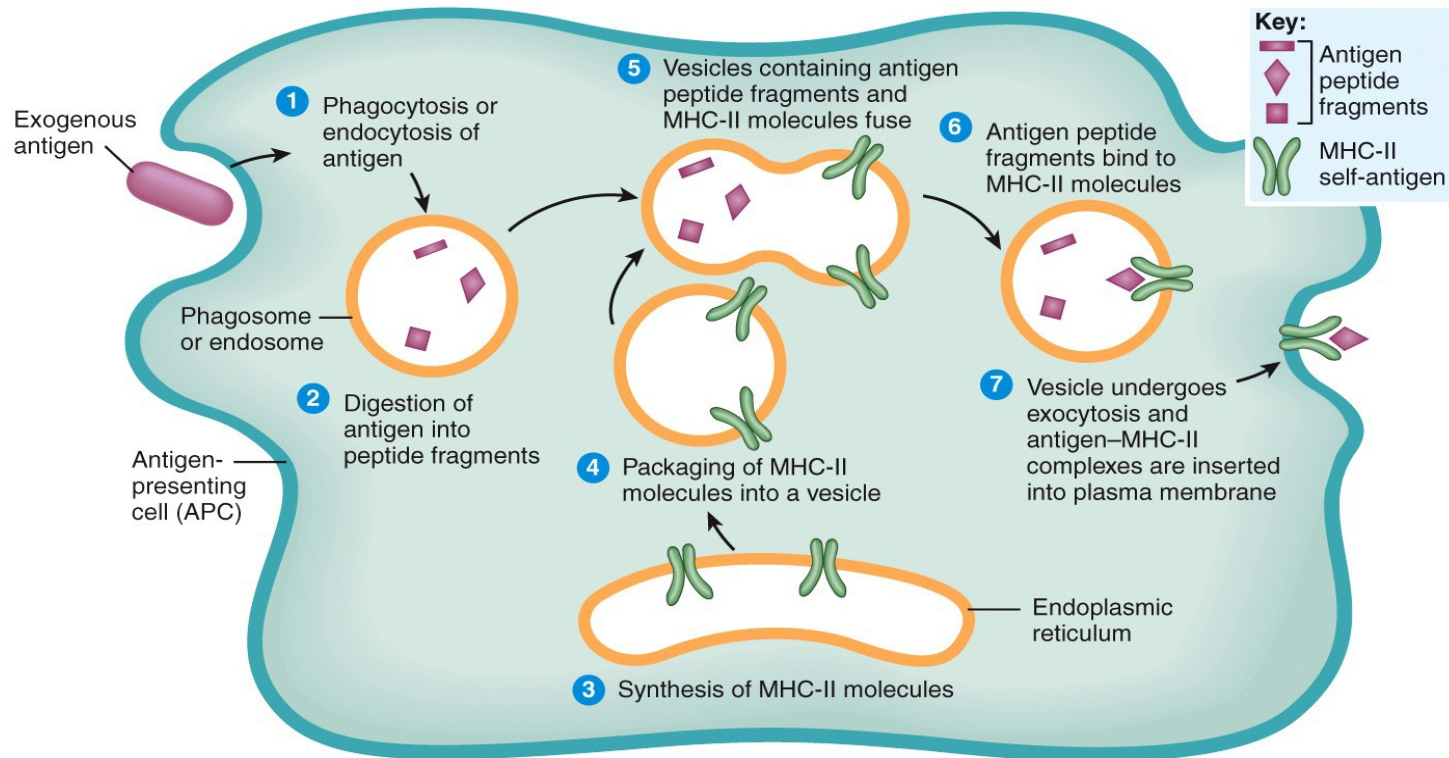


APCs present exogenous antigens in association with MHC-II molecules

Antigen Processed Using MHC-I by Dendritic APC



Dendritic cells are antigen processing cells that have both MHC-I and MHC-II proteins. This means dendritic cells may activate both naive cytotoxic Tc as well as naive helper T cells



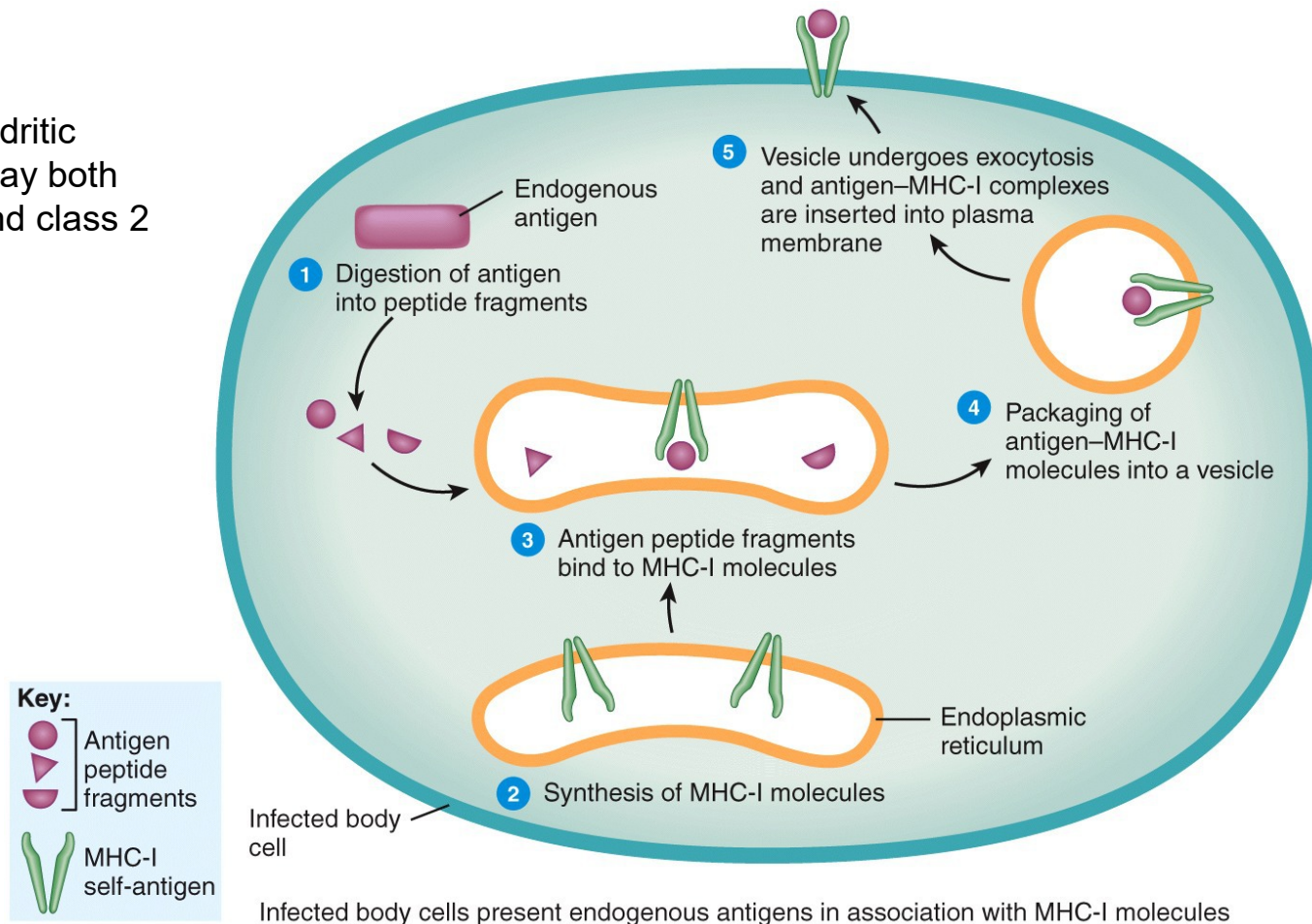
APCs present exogenous antigens in association with MHC-II molecules

How Host Cells Process and Display Foreign Antigen Using MHC-I

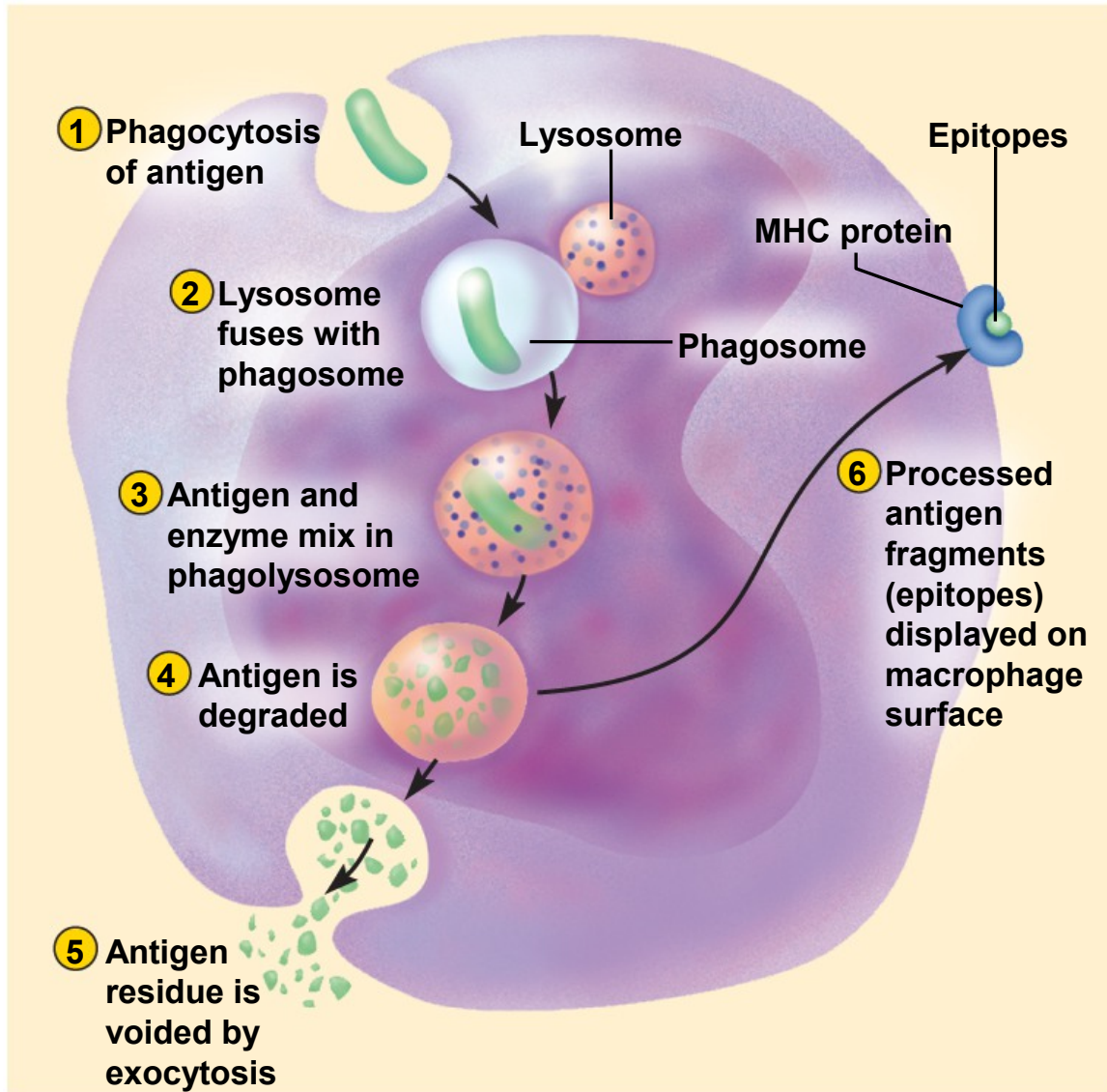


Placing epitope into the **host cell's plasma membrane** will allow activated cytotoxic T cell receptors to recognize infected cells. If the cell displays bacterial epitope in MHC-I complex then cytotoxic T cell will form a c-T-cell-receptor-MHC-1 complex. Now the c-T-cell kills the infected cell with the “kiss of death”. Endogenous implies that the proteins are from the cell's cytoplasm. // Only cytotoxic T cell receptors recognize host cell's MHC-I type molecules.

Note: dendritic cells display both class 1 and class 2 MHCP.



How Do Antigen Processing Cells Turn Antigens into Epitope and then Display Epitope on Outer Surface of the Plasma Membrane?



MHC protein may be either type-I or type-II

Macrophage and B cells have MHCP-II // both are APCs

Dendritic cells = APC and have both MHCP Class-I and Class II

Helper T-cells receptors only bind to MHC-II // must occur to activate H-Tc

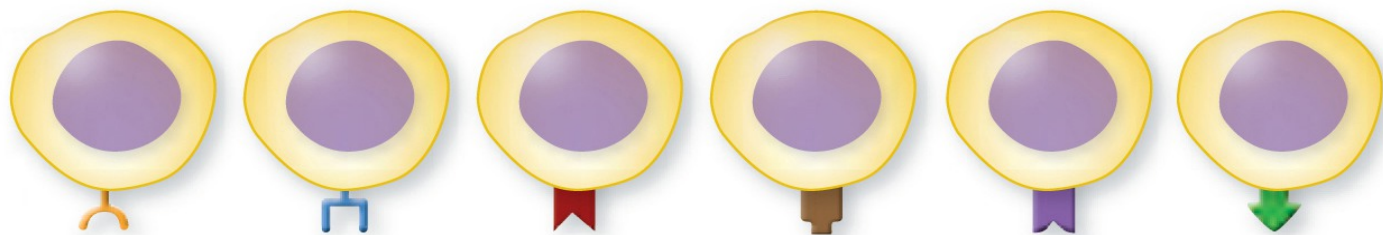
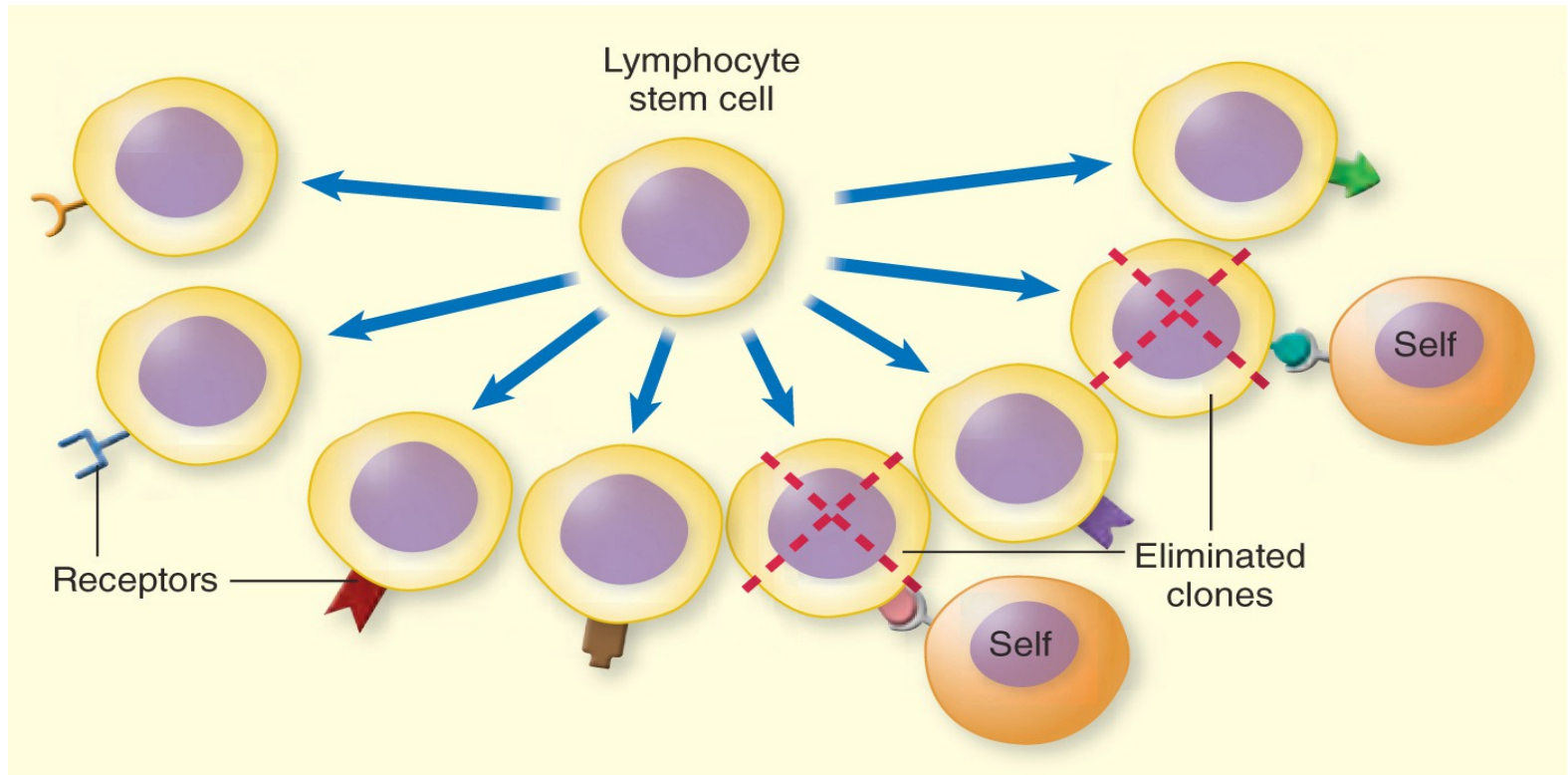
Cytotoxic-T-cells receptors only bind to MHC-I // must occur to activate C-Tc // Dendritic cell activate C-Tc

NK cells receptors use different clusters of differentiation to recognize virus or cancer // when NK engage with markers take 3 days to reach peak activity

All nucleated host cells have only MHC-I

How Naïve Immunocompetent T and B Cells Are Selected

Clonal Selection and Expansion of T and B Cells



Repertoire of lymphocyte clones, each with unique receptor display

Activation of Helper T Cells

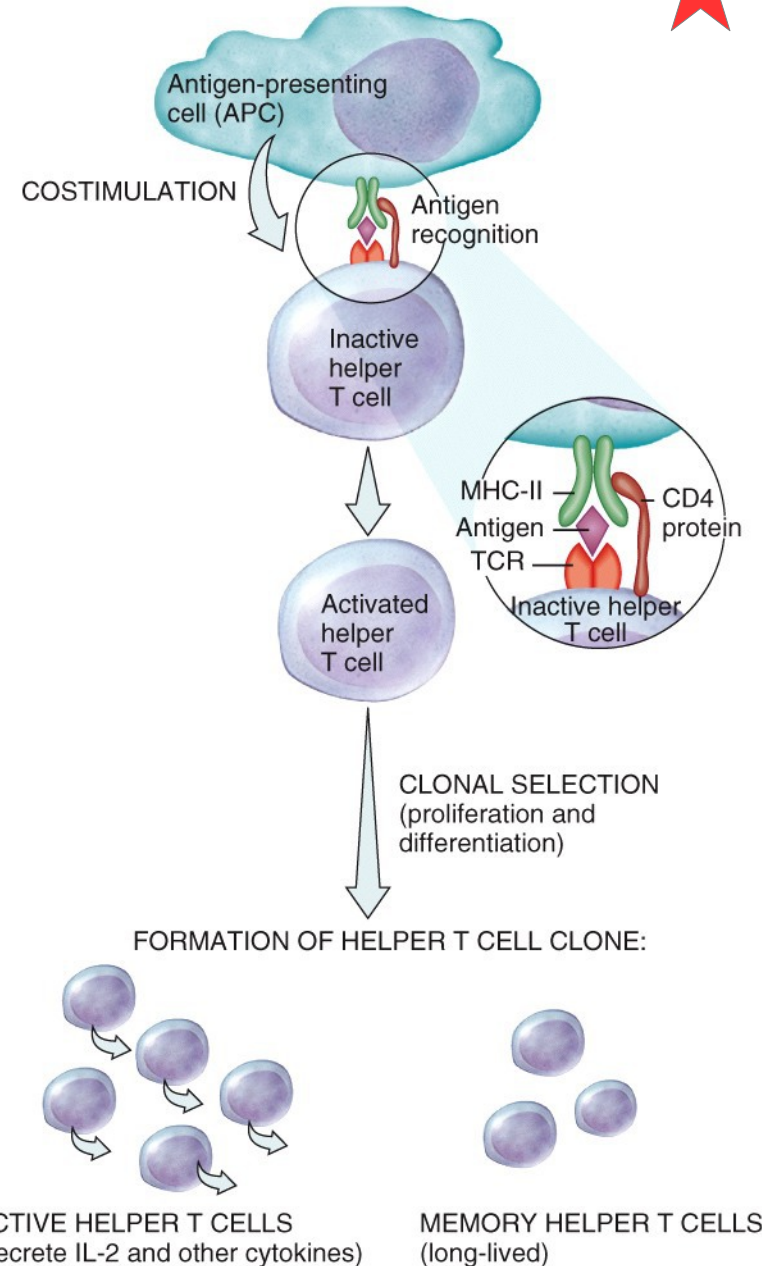


Immune system must activate helper T cells using Antigen Presentation Cells // HTc only have receptors for MHCP-II (APC maybe either Dendritic Cells or Macrophage)

Activated Helper T cell must secrete cytokines (interleukin 2) to complete the activation of both cytotoxic T cells and B cells.

Helper T cells **will also attract to area of infection macrophage, NK cells, and other inflammation responses**

*Note: the **CD4 protein** on helper T Cell functions as a costimulatory factor in the activation of helper T Cell*



How Are H-Tc Activated?

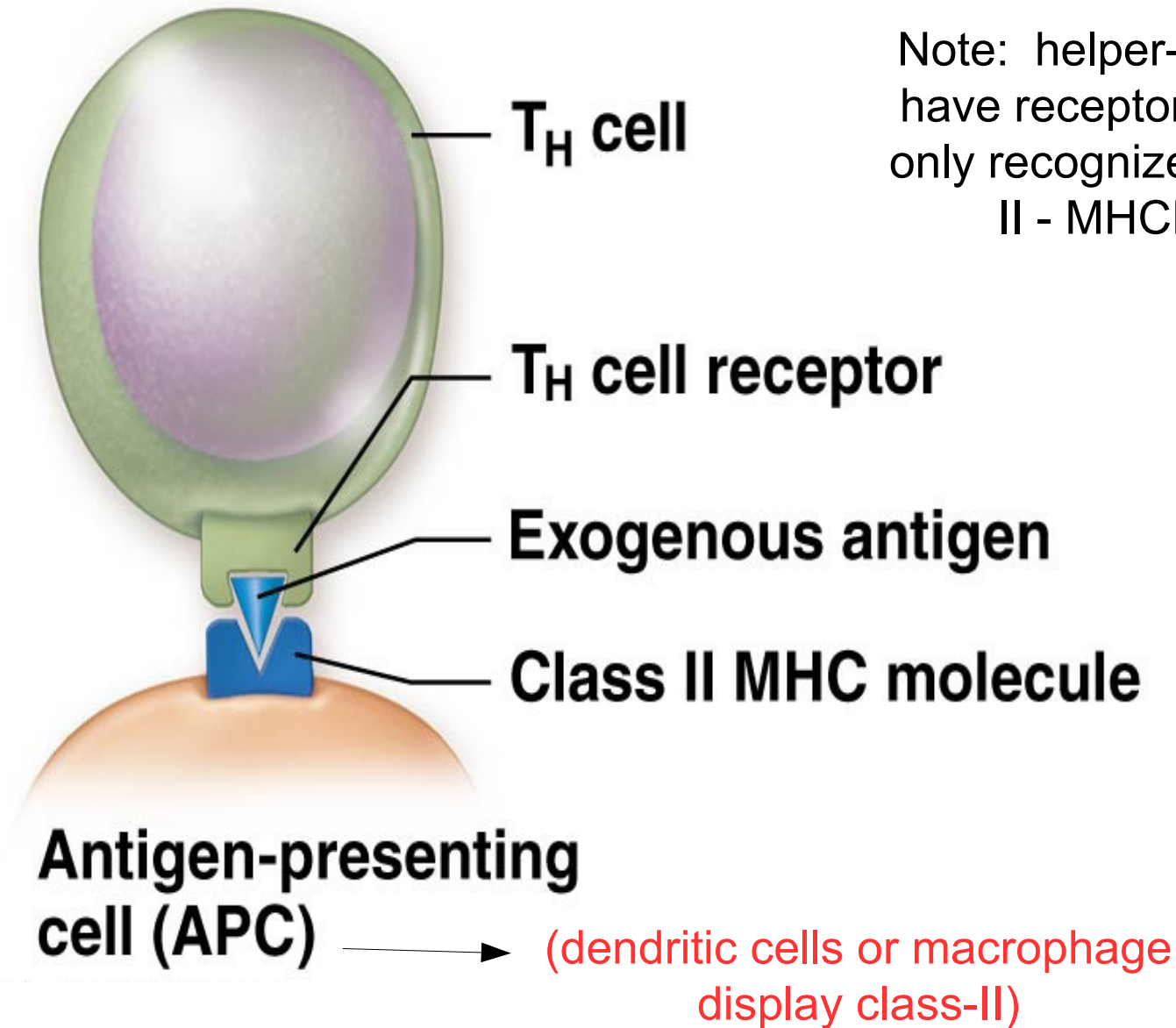


- **Helper T Cells receptors** bind to the epitope-MHC-II-complex of an antigen presenting cell (APC) /// e.g. macrophage or dendritic cell
- If APC docks to a macrophage, then the macrophage then the macrophage secretes **interleukin-1** (this then stimulates and activates H-Tc)
- Activated H-Tc responds by secreting **interleukin-2** // interleukin-2 stimulates macrophage to secrete more interleukin-1 /// this creates **positive feedback loop** /// macrophage continues to secrete more interleukin-1 /// **this is a key step in the overall activation of acquired immunity**
- Activated Helper T Cells now themselves undergoes **clonal selection** /// H-Tc continues to secrete interleukin-2 with following outcomes.....
 - Make many more hTc (with same receptor type)
 - H-Tc cytokines required to complete activation of cytotoxic Tc
 - H-Tc cytokines required to fully activate B-cells to plasma cells
 - Form memory H-T cells – saved and rest for future use
 - Form regulatory T cells – controls intensity of immune response
- Activated T Helper cells will also **stimulate non-specific defenses** /// stimulate more **macrophage and NK cells to emigrate into the area and initiates inflammation**

This is how a naive immunocompetent helper T cell is activated to initiate clonal selection.



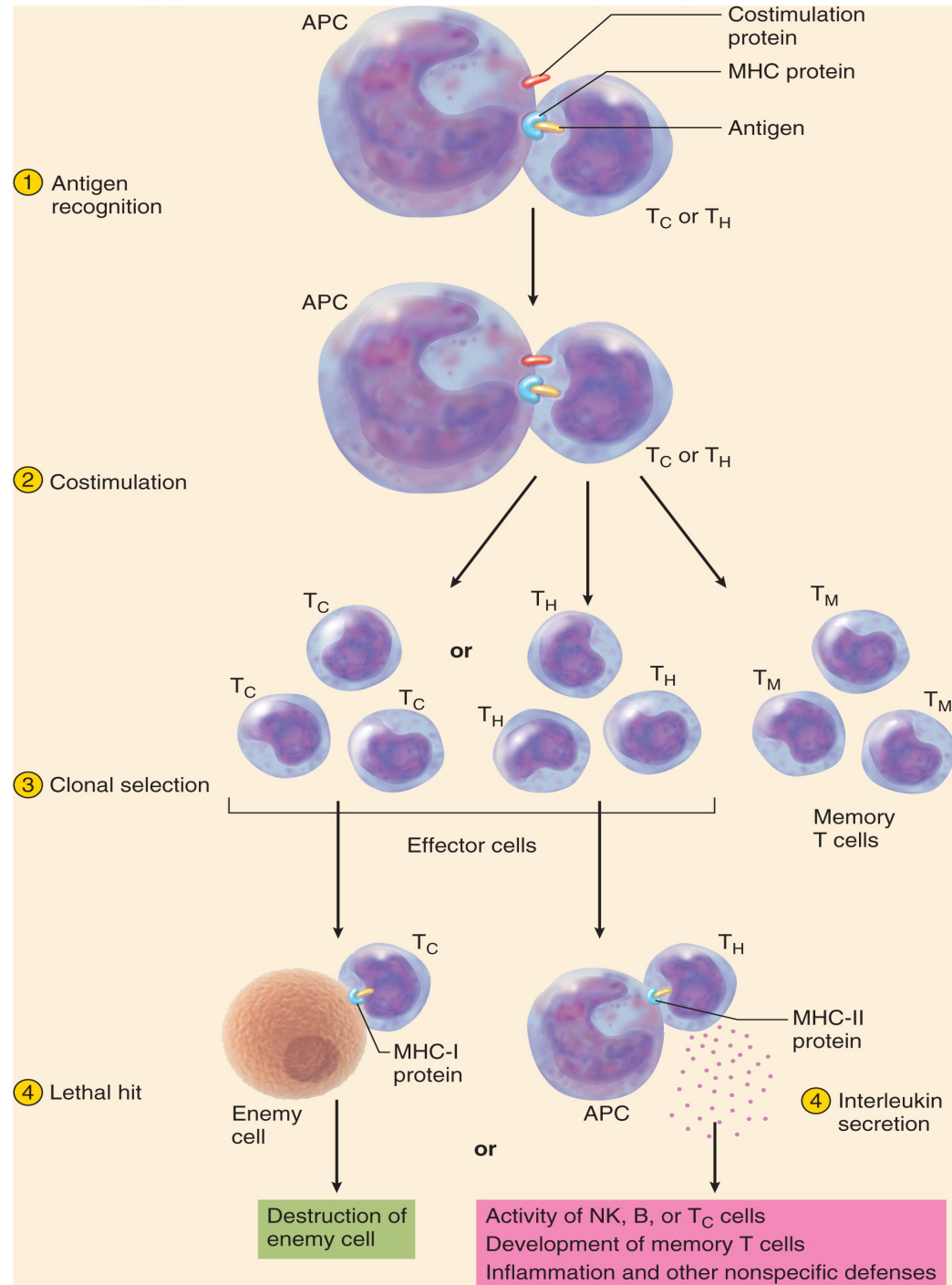
After activation this H-Tc will secrete cytokines to complete activation of both cellular immunity (C-Tc) and humoral immunity (H-Tc)



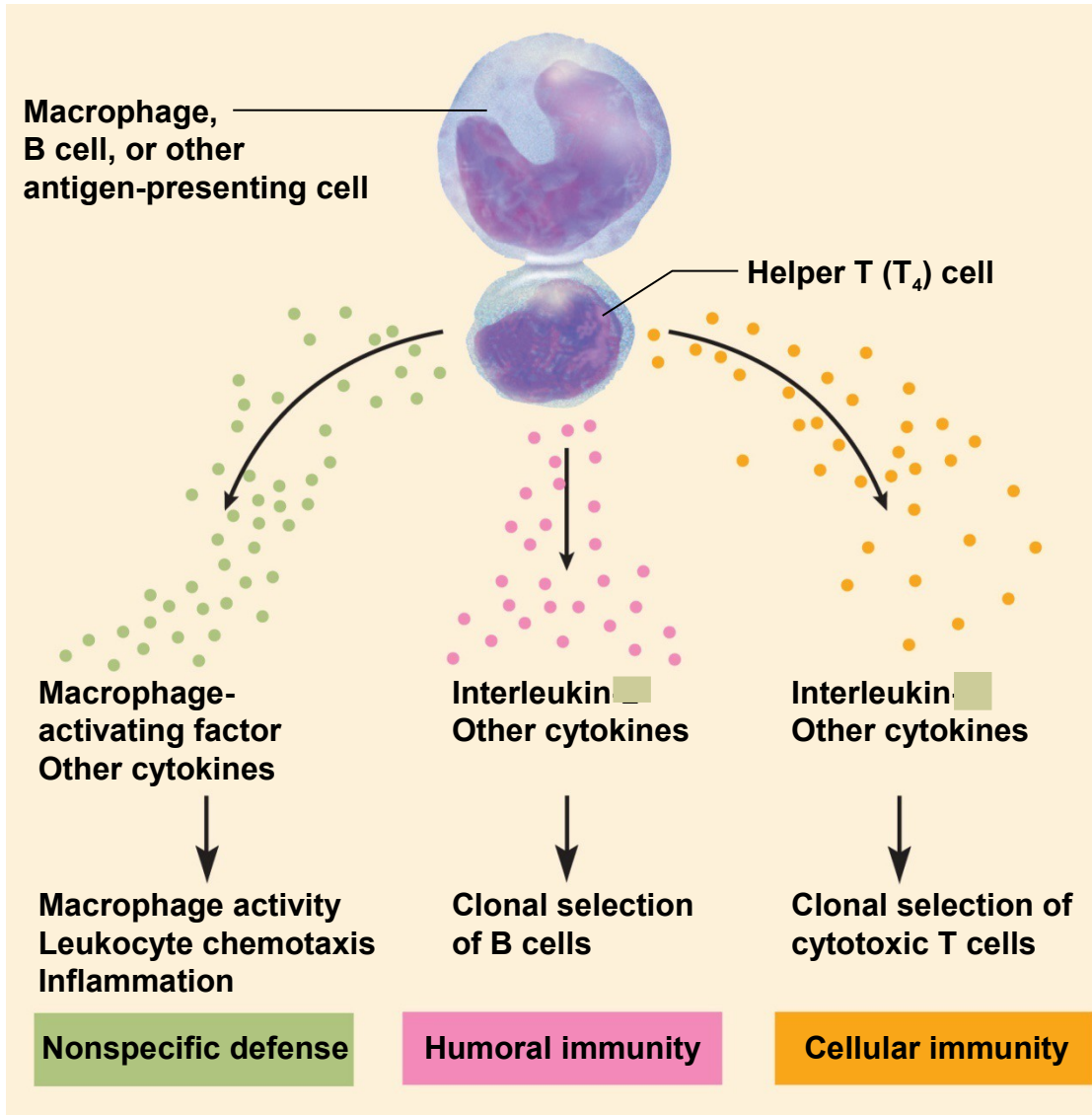
Note: helper-Tcells have receptors that only recognize class II - MHCP

Activation of Cytotoxic T Cells

- The **first step to activate** CD8-Tc occurs when they bind to a dendritic cell that displays foreign epitope in Class-I MHC (note: dendritic cells have both class I and II)
- Note CD8 protein on T cell binds to dendritic cell costimulation protein = “second check” for proper MHC-I receptor complex = costimulation
- Now cytotoxic T cell (Tc) starts clonal selection and at same time makes memory Tc
- Clonal selection make “attack” cytotoxic T cells /// These cytotoxic cells = killer cells /// These **activated cytotoxic T cells are now able to dock and but to kill infected cells need a secretion of interleukin-2 from Helper-T cells (also activated by similar epitope)**



Helper T Cell's Perform a Pivotal Role in all Three Forms of Immunology



T_H Cells are required to activate both humoral and cellular immunity

T_H Cells release cytokines that increase the activity of macrophage, leukocyte chemotaxis and inflammation.

Without activated H- T_c you will lack both the 2nd and 3rd line of defenses against pathogens!

This is how a naive cytotoxic T cell is activated and initiates clonal selection.

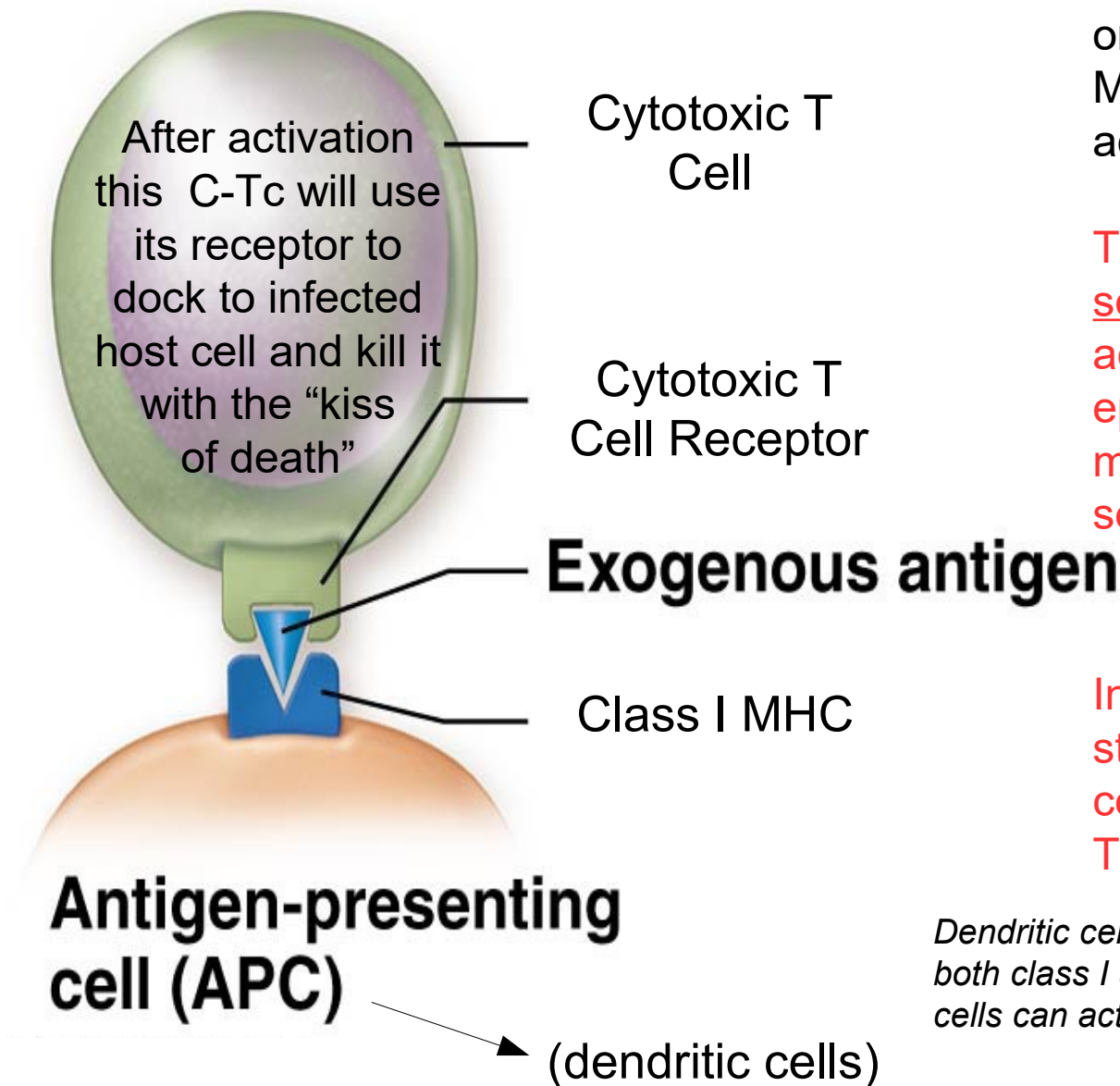


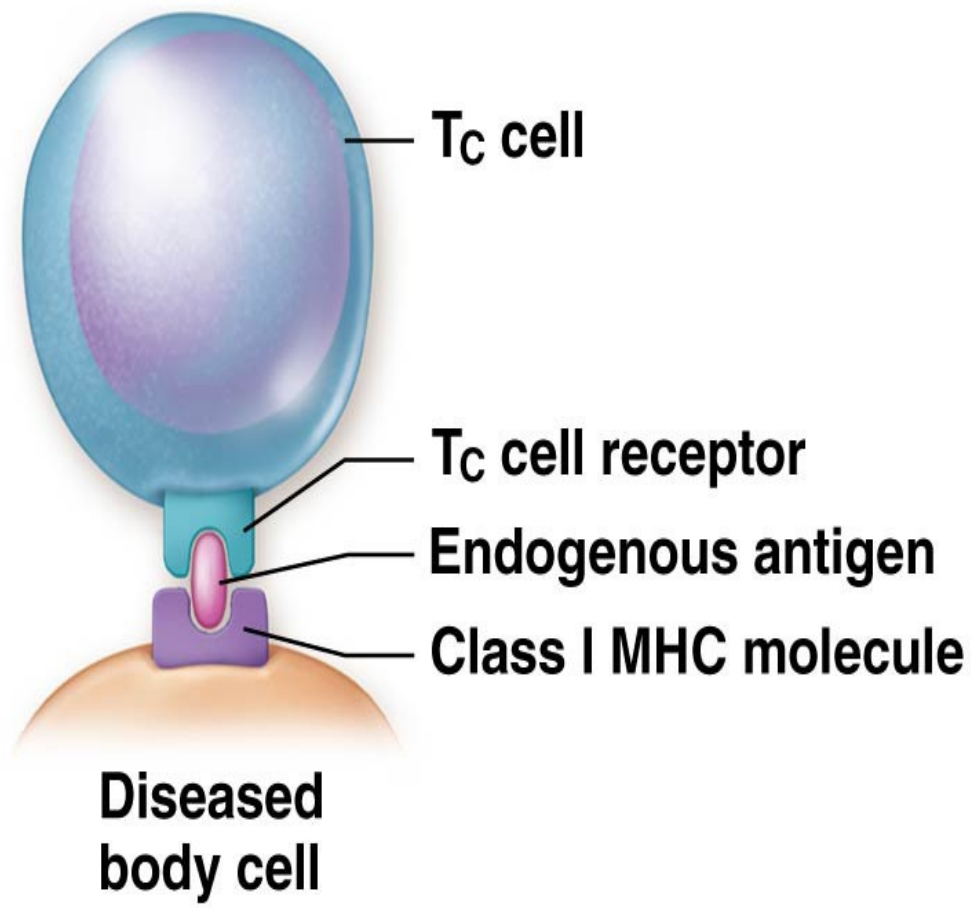
Naive C-Tcells receptors only recognize class I-MHCP // must be activated by dendritic cell

To complete clonal selection of C-Tc // activated H-Tc (by same epitope in a separate mechanism) must secrete interleukin 2

Interleukin 2 is required to start clonal selection // complete activation of C-Tc

Dendritic cells are unique because they have both class I and class II MHCP // dendritic cells can activate both C-Tc and H-Tc





After a Cytotoxic-T cell is activated and undergoes clonal selection the host will now have millions of “killer” cytotoxic-T-cells

These fully activated C-Tc may now directly dock onto diseased body cells showing epitope in class-I-MHC and kill these infected cells

After docking the C-Tc gives the “kiss of death”

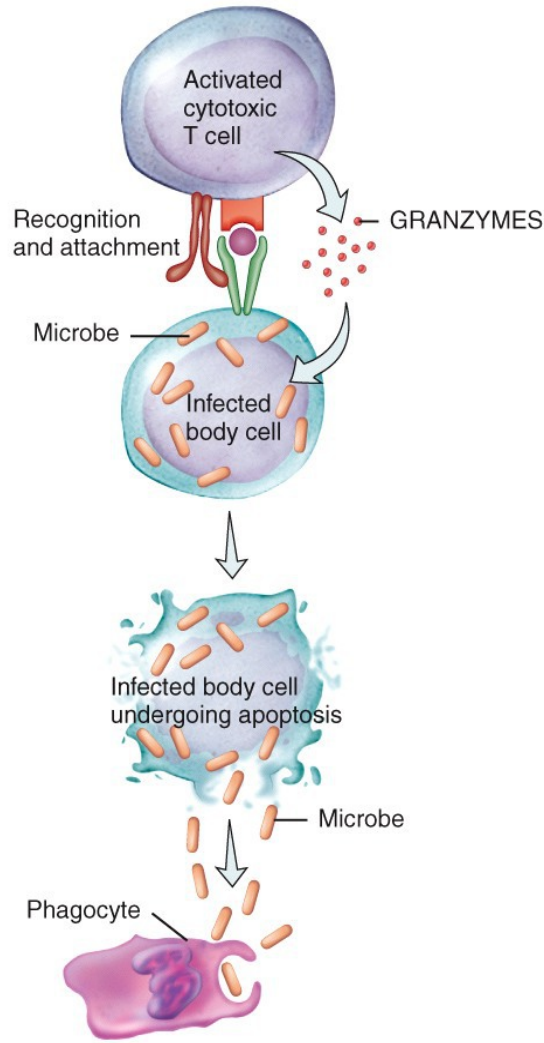
Endogenous means these proteins are from the host cells' cytoplasm

The Kiss of Death Delivered by the Cytotoxic T Cells

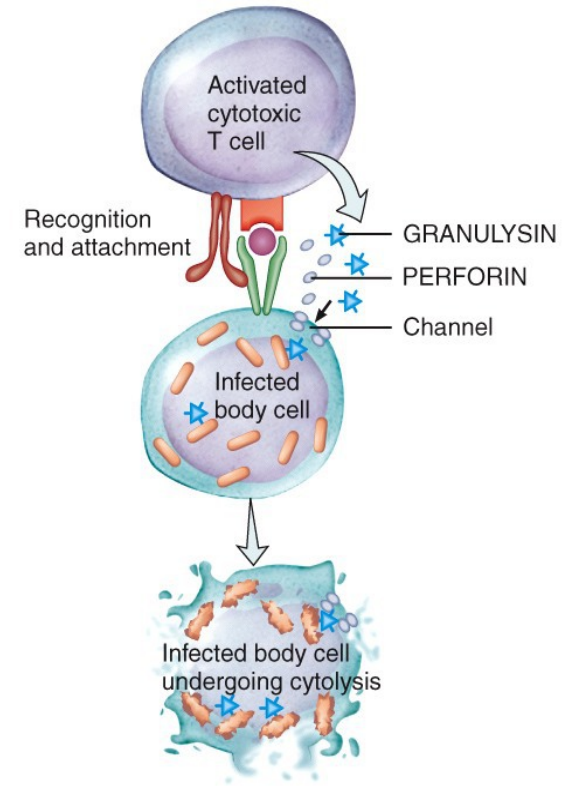
This is the react stage of the “three R”

Two different methods maybe used to destroy infected cells with endogenous foreign antigen

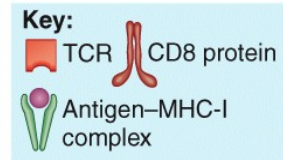
There is also a third way for C-Tc to kill host cells by releasing cytokines (e.g. cytokine storm)



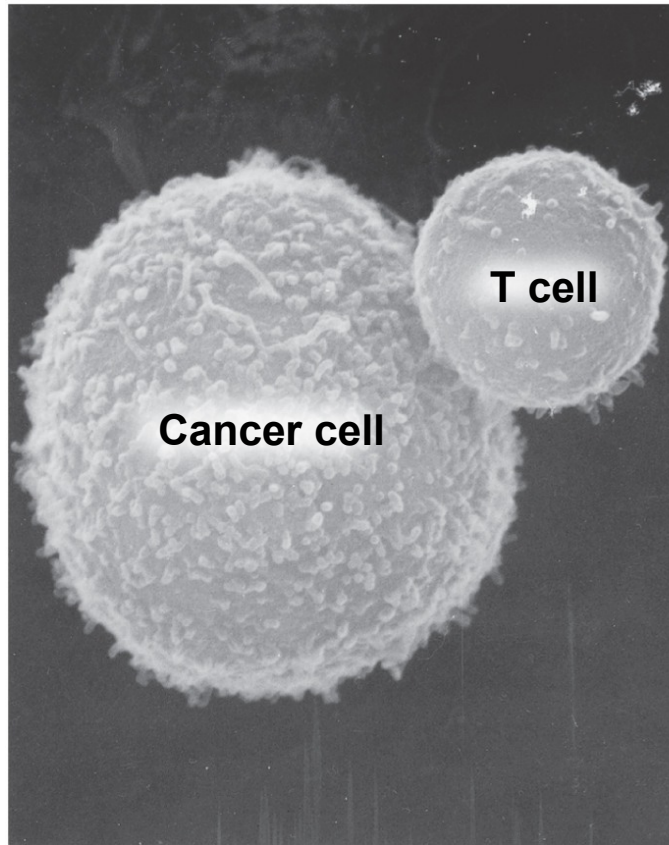
(a) Cytotoxic T cell destruction of infected cell by release of granzymes that cause apoptosis; released microbes are destroyed by phagocyte



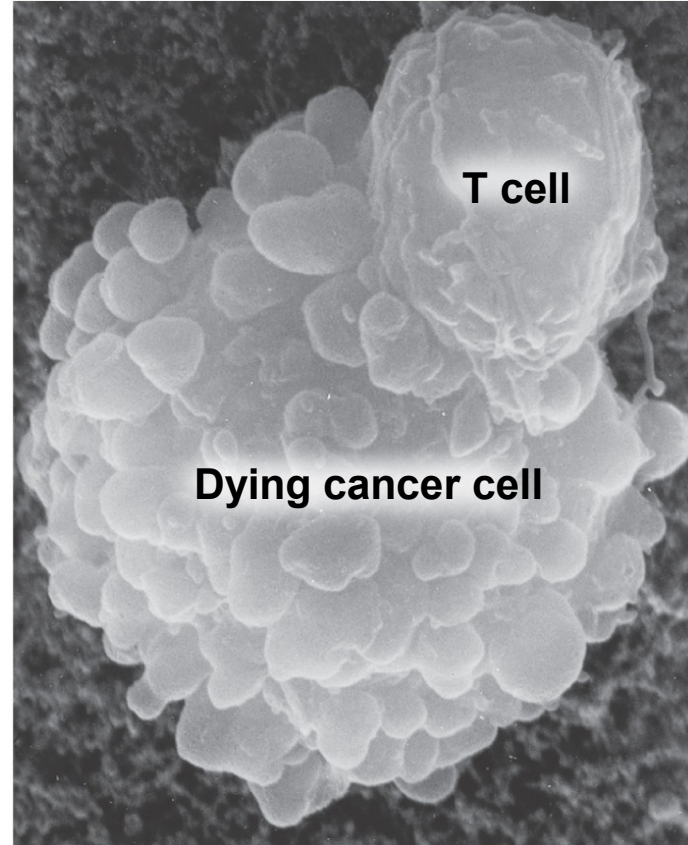
(b) Cytotoxic T cell destruction of infected cell by release of perforins that cause cytolysis; microbes are destroyed by granzysin



Cytotoxic T Cell Function



(a)

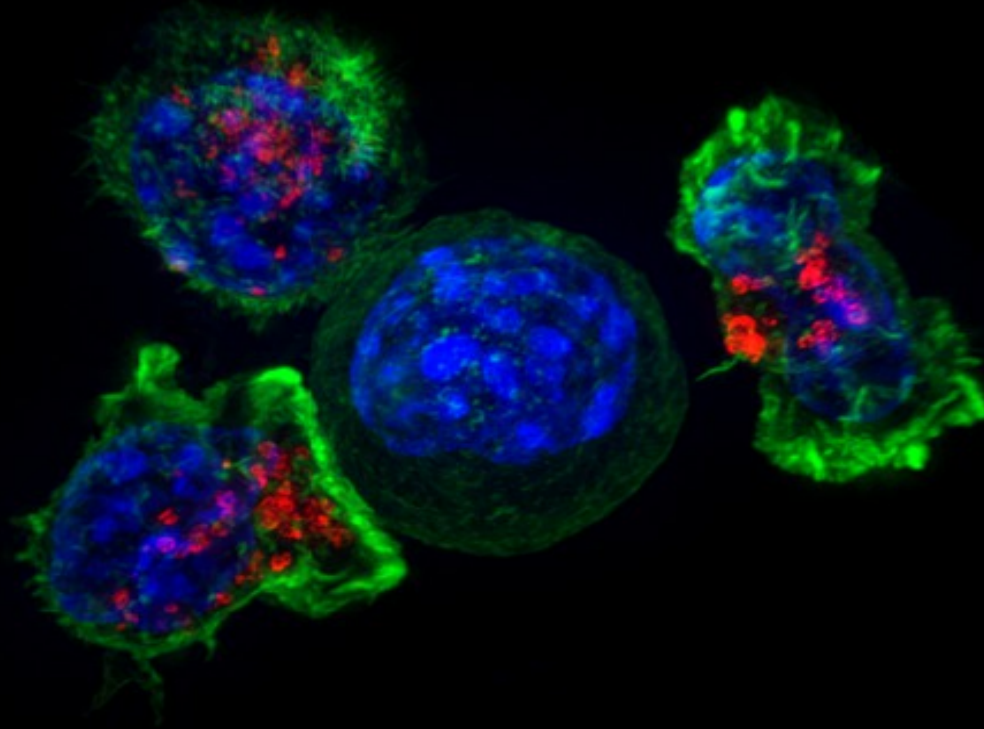


(b)

Dr. Andrejs Liepins

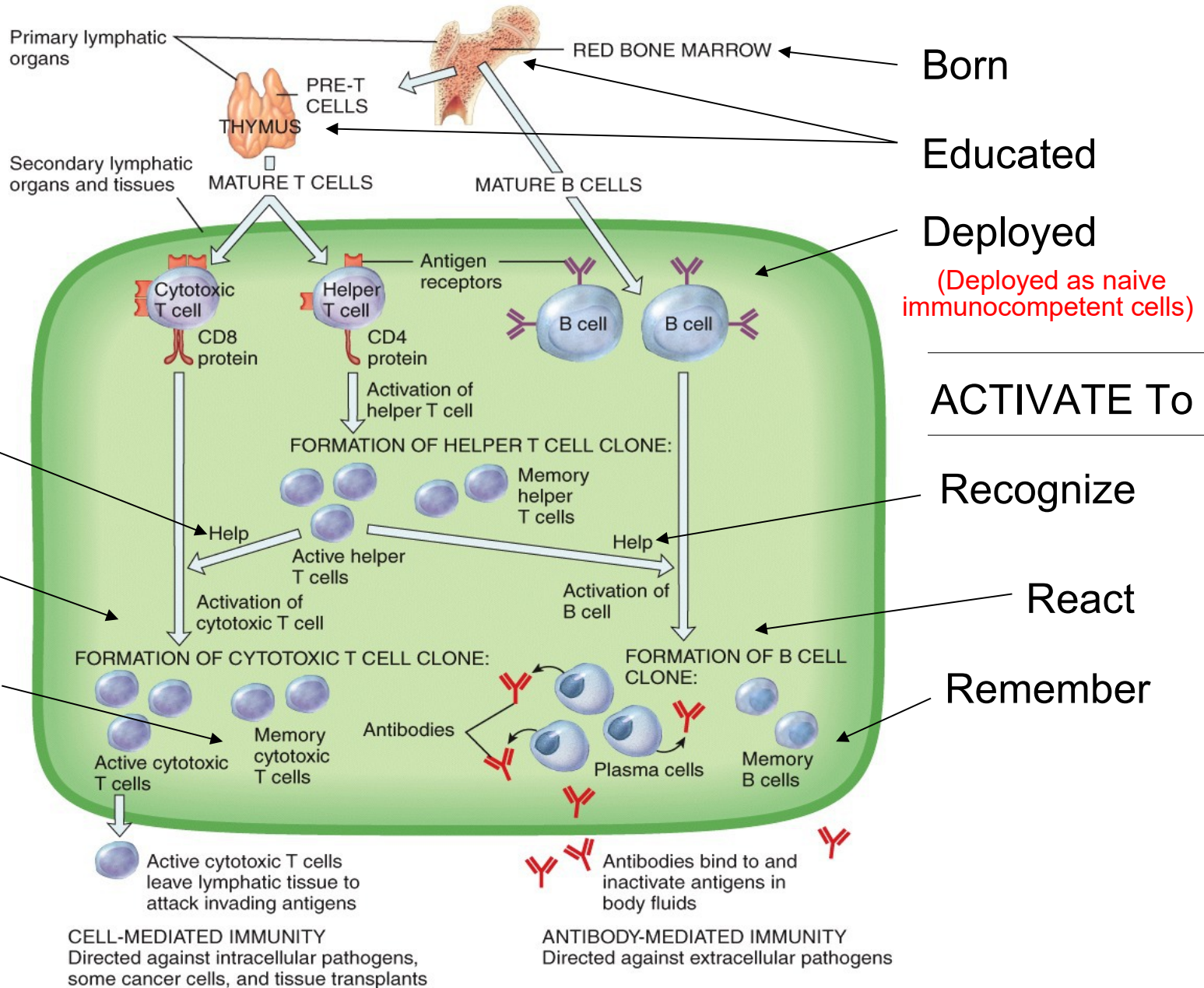
- cytotoxic T cell binding to cancer cell

Cytotoxic T Cells Attacking Cancer Cell



In this immunofluorescence image, a group of killer T cells (outer three) are engaging a cancer cell (centered one). A patch of signaling molecules (pink) that gathers at the site of cell-cell contact indicates that the CTL has identified a target. Lytic granules (red) that contain cytotoxic components then travel along the microtubule cytoskeleton (green) to the contact site and are secreted, thus killing the target.

Outline for the structure and function of acquired immunity.



How are B cells activated?



Humoral immunity requires the action of B cells

Different classes of B cells (plasma cells, memory B cells, regulatory B cells)

Each class has a special function

*Plasma cells are formed from B cells /// **it is the plasma cells that make antibodies** // each plasma cell make **2,000 antibodies per second for approximately 7 days***

*Antibodies attach to foreign antigen /// **render foreign antigen harmless and tag pathogen for destruction***

*Note: **antibodies don't kill anything** /// antibodies **activate complement** and **complement kills the pathogen***

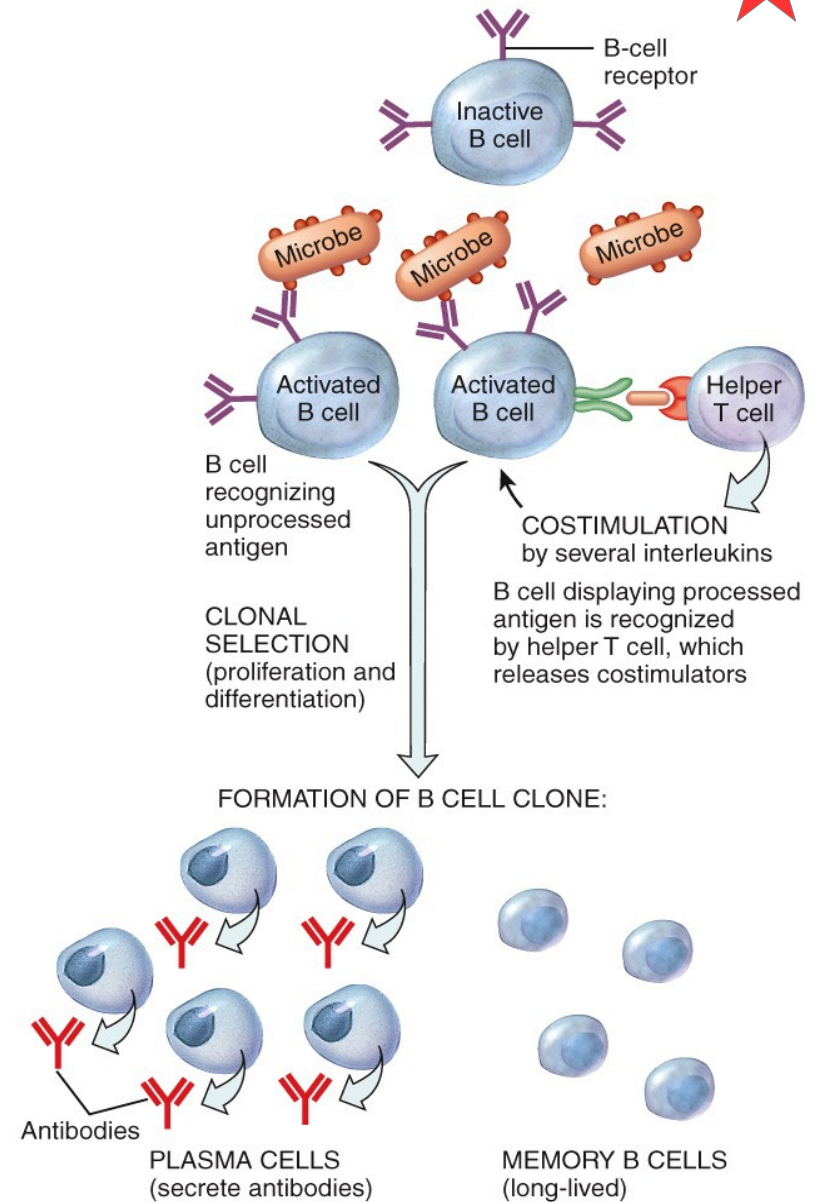
Activation of B Cells

The B cell “recognition” process for activation is different than the Tc process.

Naïve immunocompetent B cells have two distinct activation pathways with different outcomes // **H-T cell dependent** and **H-T cell independent**.

If B cells enter clonal selection without the Helper T cell – (no costimulation known as H-T cell independent) then... /// the B cell activation is less robust /// results in fewer plasma cells and less antibodies /// but **no B memory cells are formed**

If B cells enter clonal selection with the assistance of Helper T cells – with costimulation - then.... /// stronger response with many more plasma cells formed, more antibodies formed and **memory B cells formed**.



Activation of B Cells

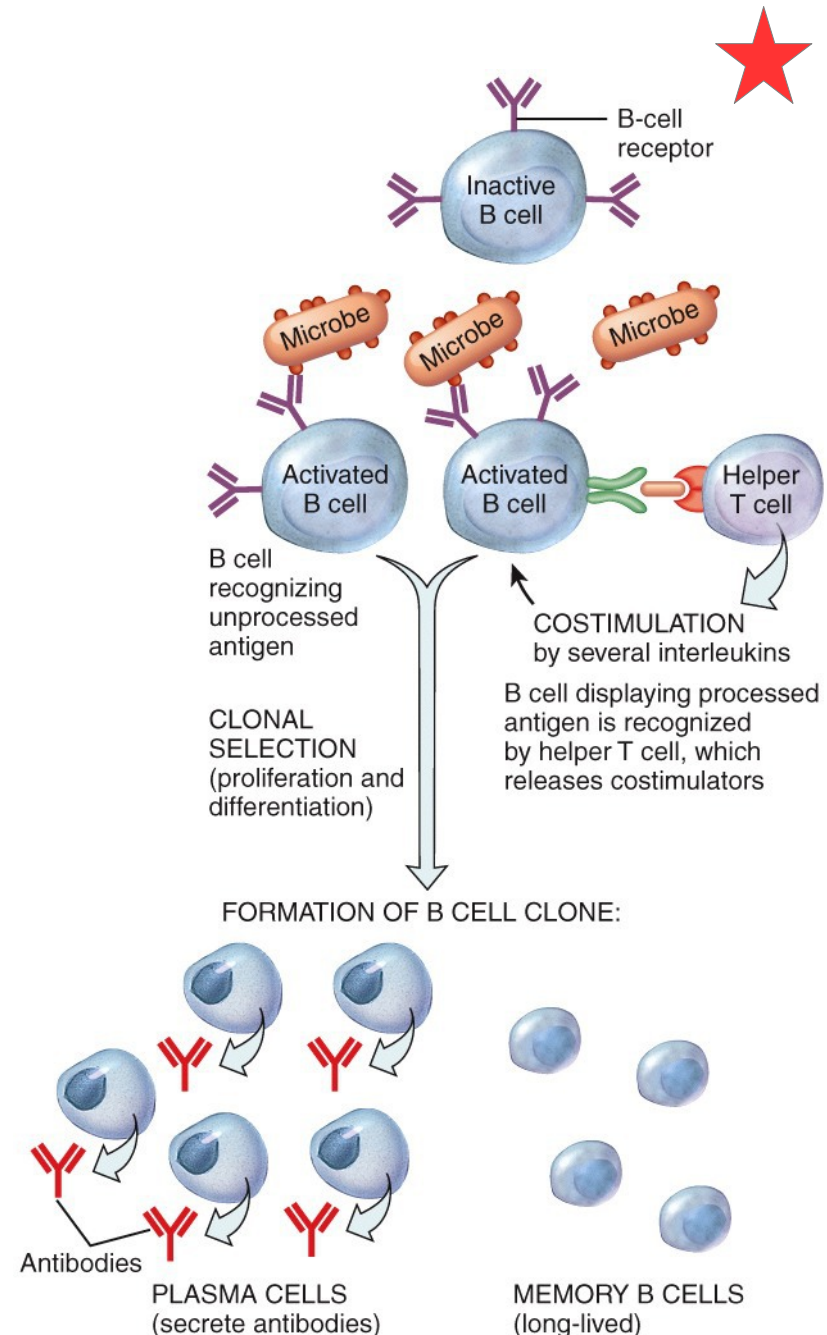
First step in “recognition” (activation) is pathogen binds to a B cell receptor.

B cell now will act as an APC and engulphs pathogen /// processes antigen and presents epitope on its plasma membrane

Previously activated Helper T cell with similar pathogen now binds it's T cell receptor with MHCP-II-epitope complex
(second step)

If Helper T cell and B cell complex receives interleukin 2 and other secretions from T_H itthen B cell undergoes costimulation

Plasma cells and memory B cells formed // Plasma cells make 2,000 antibodies per second per cell for 7 days.



B Cells to Plasma Cells

Plasma cells make antibodies – What are the functions of antibodies?

1 Antigen recognition
Immunocompetent B cells exposed to antigen. Antigen binds only to B cells with complementary receptors.

2 Antigen presentation
B cell internalizes antigen and displays processed epitope. Helper T cell binds to B cell and secretes interleukin.

3 Clonal selection
Interleukin stimulates B cell to divide repeatedly and form a clone.

4 Differentiation
Some cells of the clone become memory B cells. Most differentiate into plasma cells.

5 Attack
Plasma cells synthesize and secrete antibody. Antibody employs various means to render antigen harmless.

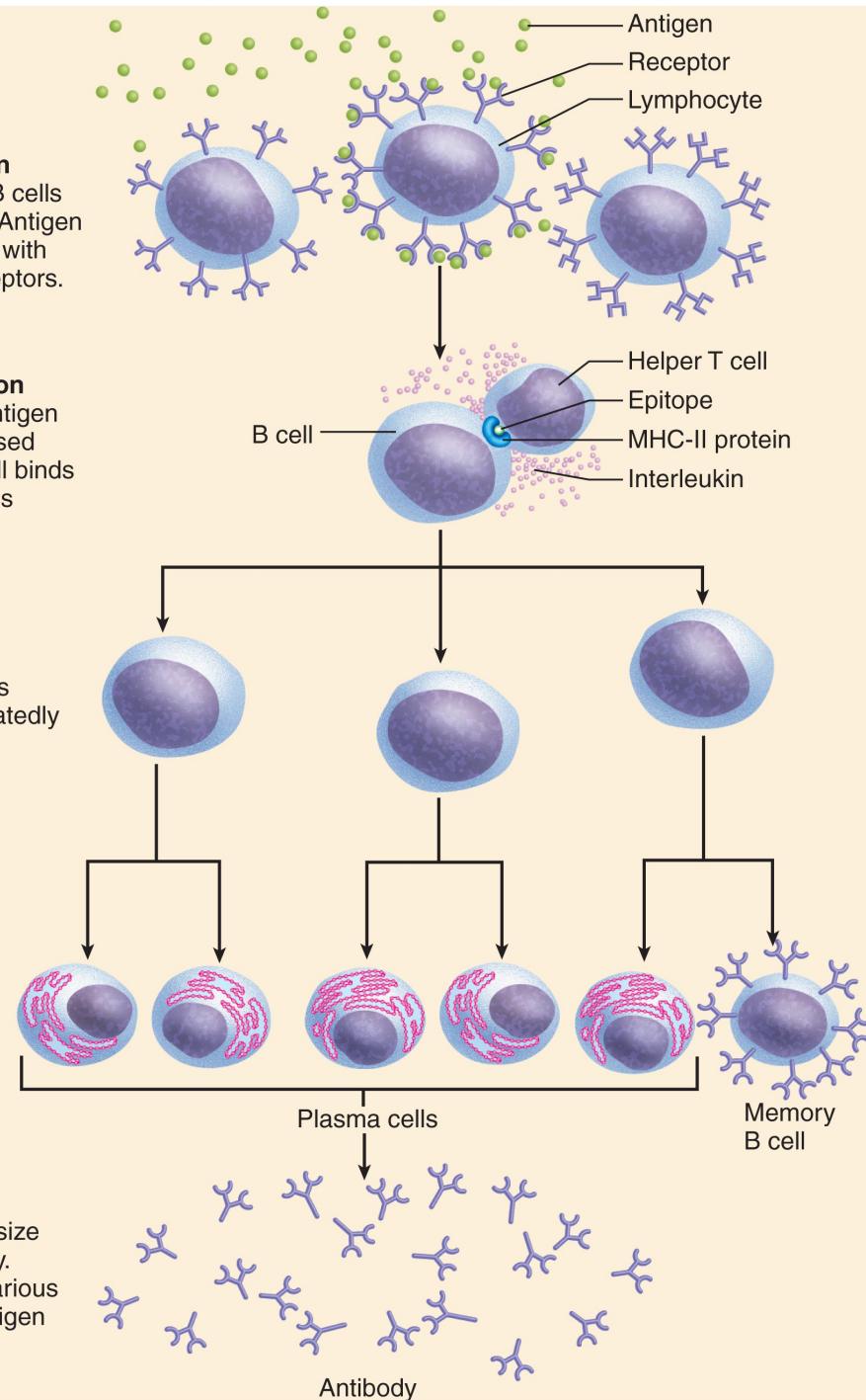
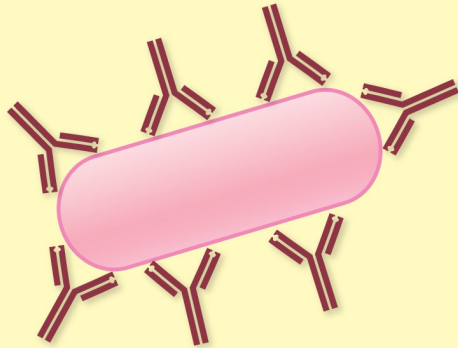
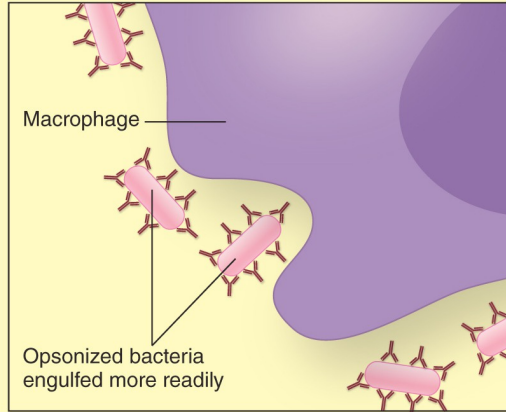


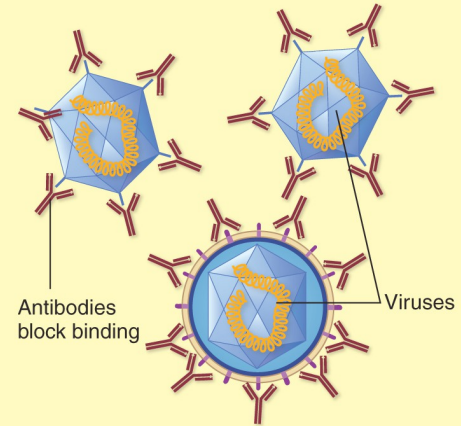
Table 13.7 Summary of Antibody Functions



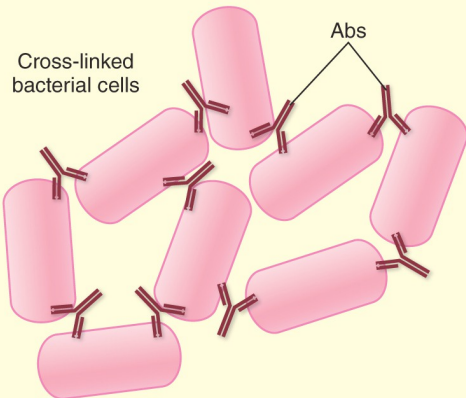
Antibodies coat the surface of a bacterium, preventing its normal function and reproduction in various ways.



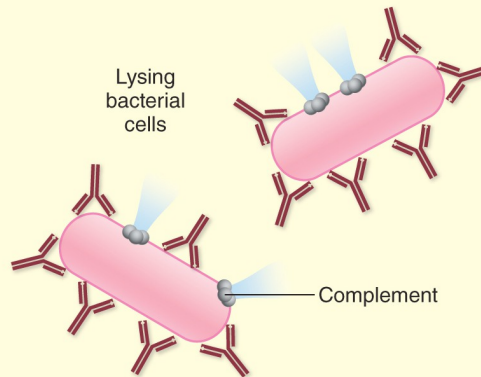
Antibodies called opsonins stimulate **opsonization** (ahp^{oo}-son-uh-zaz'-shun), a process that makes microbes more readily recognized by phagocytes, which dispose of them. Opsonization has been likened to putting handles on a slippery object to provide phagocytes a better grip.



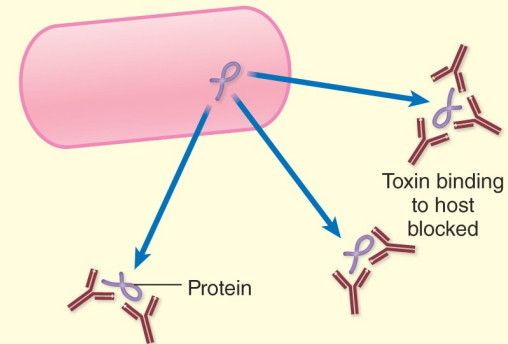
In **neutralization** reactions, antibodies fill the surface receptors on a virus or the active site on a microbial enzyme to prevent it from attaching normally.



The capacity for antibodies to aggregate, or **agglutinate**, antigens is the consequence of their cross-linking cells or particles into large clumps. Agglutination renders microbes immobile and enhances their phagocytosis. This is a principle behind certain immune tests discussed in chapter 15.

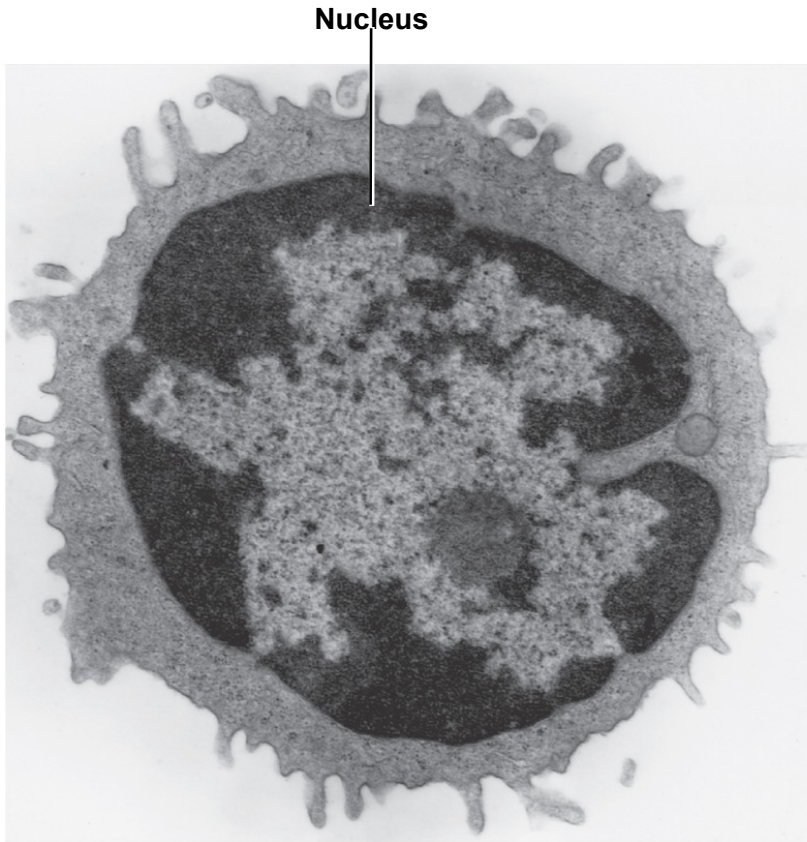


The interaction of an antibody with complement can result in the specific rupturing of cells and some viruses.



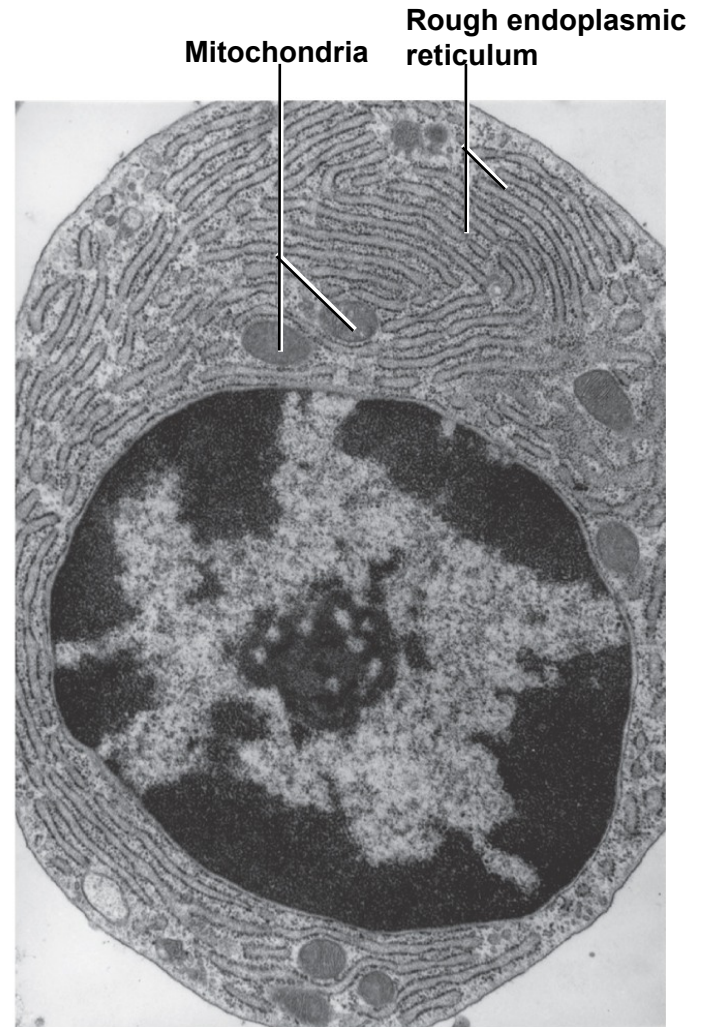
An **antitoxin** is a special type of antibody that neutralizes bacterial exotoxins.

B cells to Plasma cells



(a) B cell

2 μm



(b) Plasma cell

2 μm

Can you explain the structure and function relationship?

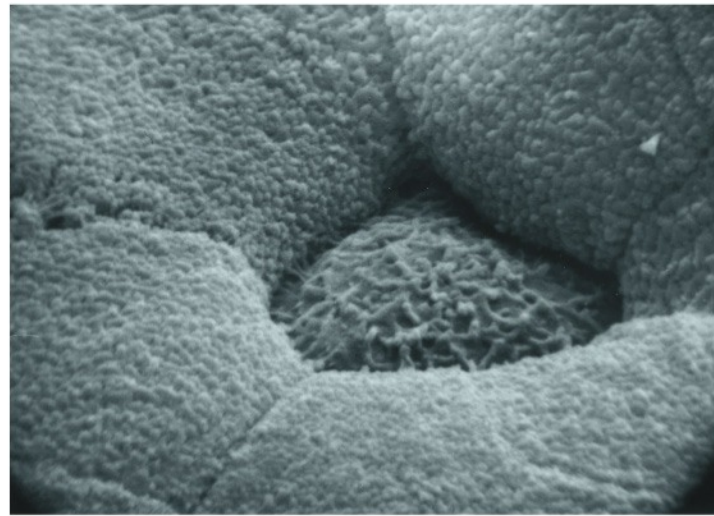
M Cells

This is how immune cells try to find out (i.e. recognize) what type of pathogens may “break into” the sterile compartments of your body.

Immune system recognize bacteria even before it is in our bodies

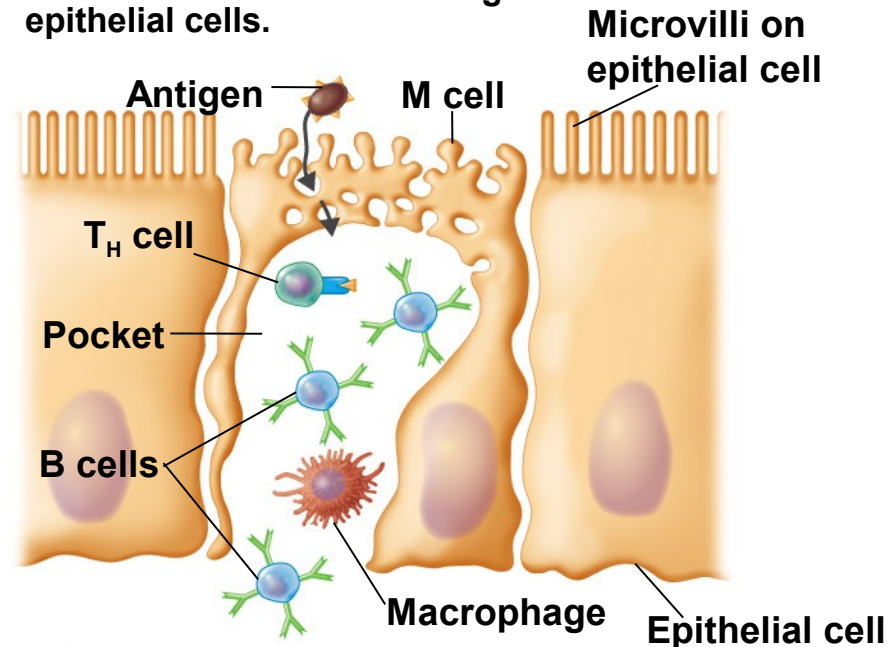
Immune system starts to prepare defenses against bacteria.

Tonsils have a similar function in bucal cavity!



(a) M cell on Peyer's patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells.

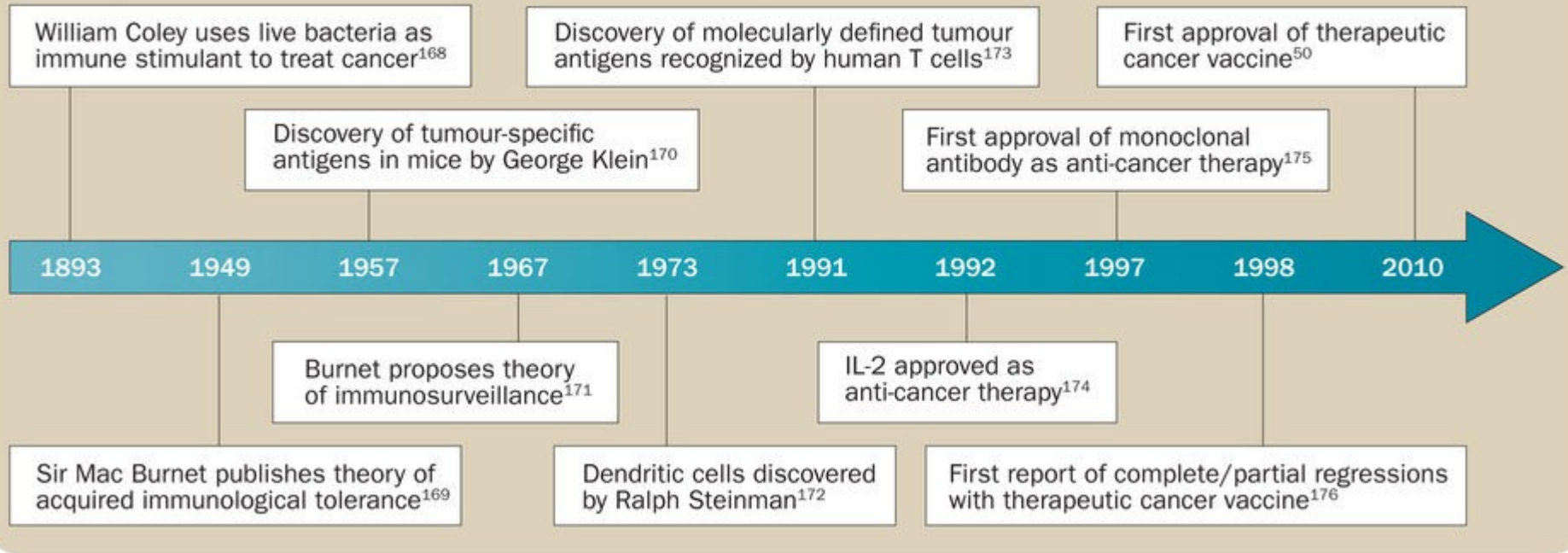
SEM 1 μm



(b) M cells facilitate contact between the antigens passing through the intestinal tract and cells of the body's immune system.

The History of Immunotherapy

Timeline | Milestones in the development of active immunotherapy

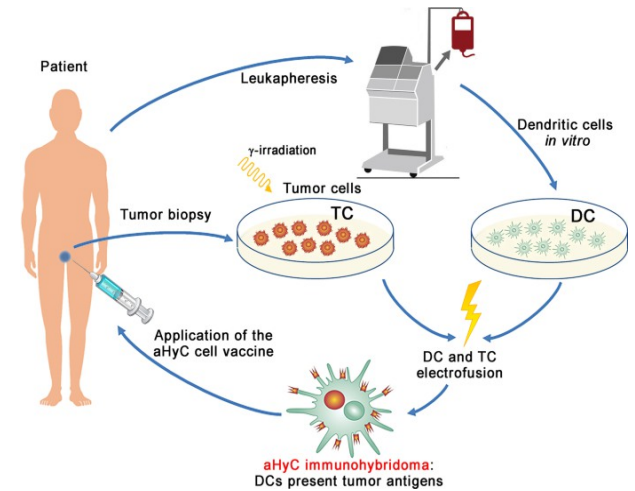
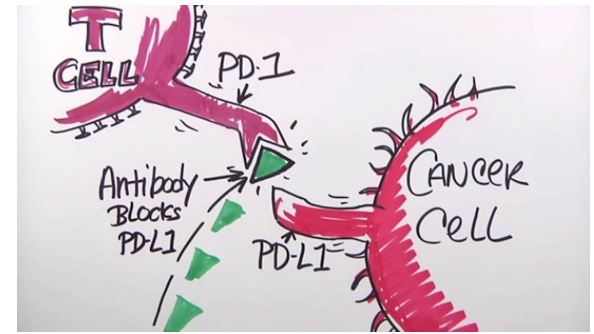


Three Immune Strategies

The Old Strategy:
surgery, radiation and chemo-therapy
(not a cure)

Today's New Strategy:
Immunotherapy

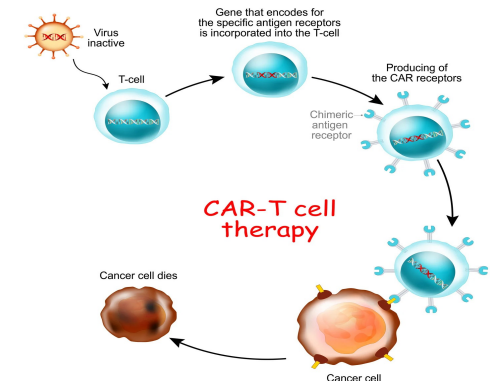
Using the specificity of the immune system
we now have a cure for some forms of
cancer.



Checkpoint Inhibitors

Dendritic Cell Vaccine

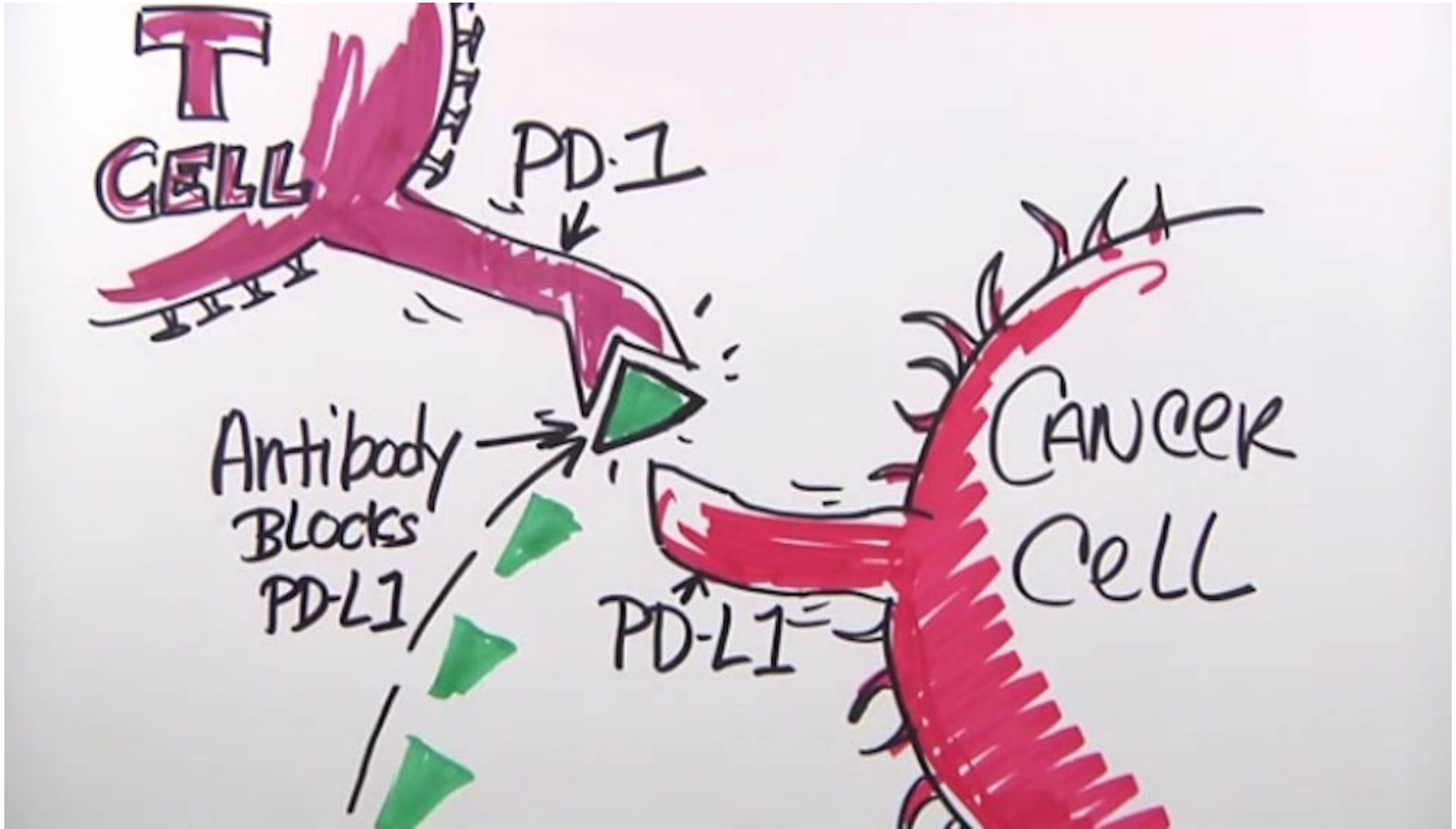
CAR-T Cells



How Can We Use This Knowledge to Cure Cancer

- For decades we have tried to cure cancer with surgery, radiation, and chemotherapy. These options have often caused significant damage to the patient and failed to provide a lasting cure.
- Today we are on the threshold of understanding how to use our cytotoxic T cells and antibodies to cure some forms of cancer.
- Cancer immunotherapy is able to leverage our knowledge about the immune system to direct the immune system cells to identify “specific types of molecules only found on cancer cells” and inhibit cancer cells ability to turn off our immune cells from attacking cancerous cells.
- Immunotherapy targets and kill only cancer cells.
- Early “clinical trials” have demonstrated that we can kill some types of cancer cells using our immune cells. These new therapies now offer some people diagnosed with cancer a real cure.
- Three New Therapies = Checkpoint Inhibition, Dendritic Cell Vaccines, and CAR T Cells

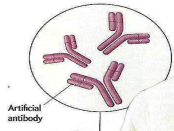
Checkpoint Inhibitors



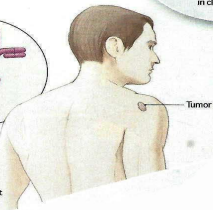
Checkpoint Inhibitors

Checkpoint Inhibitors

Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor. Now drugs—called checkpoint inhibitors—disable the cancer cells' immune-dampening signals, allowing the immune system to do its job.



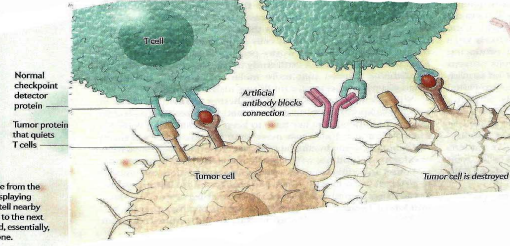
The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.



How is immunotherapy changing the treatment of solid tumors?

Cancers of the skin, lungs and other tissues are called solid tumors because they form a mass that creates its own protective environment. Checkpoint inhibitors help to disrupt this environment, eliminating advanced skin tumors for one in five patients in clinical trials.

Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.



Could intestinal bacteria boost the effectiveness of immune treatments?

Studies in mice suggest that the presence of specific bacterial species in the intestine (part of the body's so-called microbiome) may boost the immune system's ability to slow the growth of certain types of tumors. Also, checkpoint inhibitors do a better job of eliminating cancer in rodents that harbor these bacteria.

By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.

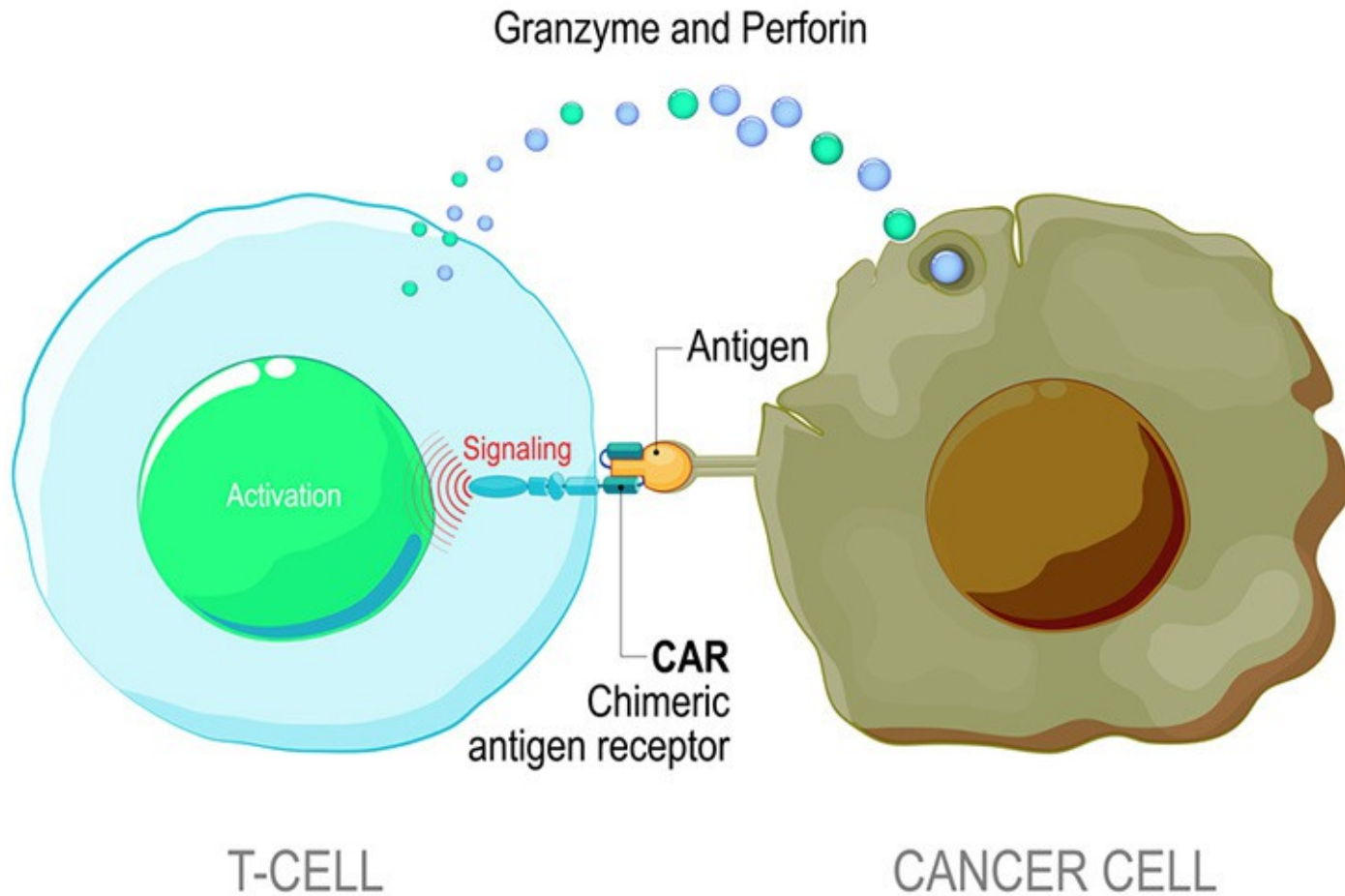
Left unchecked, immune responses can be so powerful that they will destroy healthy tissue. Thus, specialized immune cells called T-cells must pass several biological checkpoints before achieving full strength. Cancer cells often act on these checkpoints in a way that prevents the immune system from attacking the tumor.

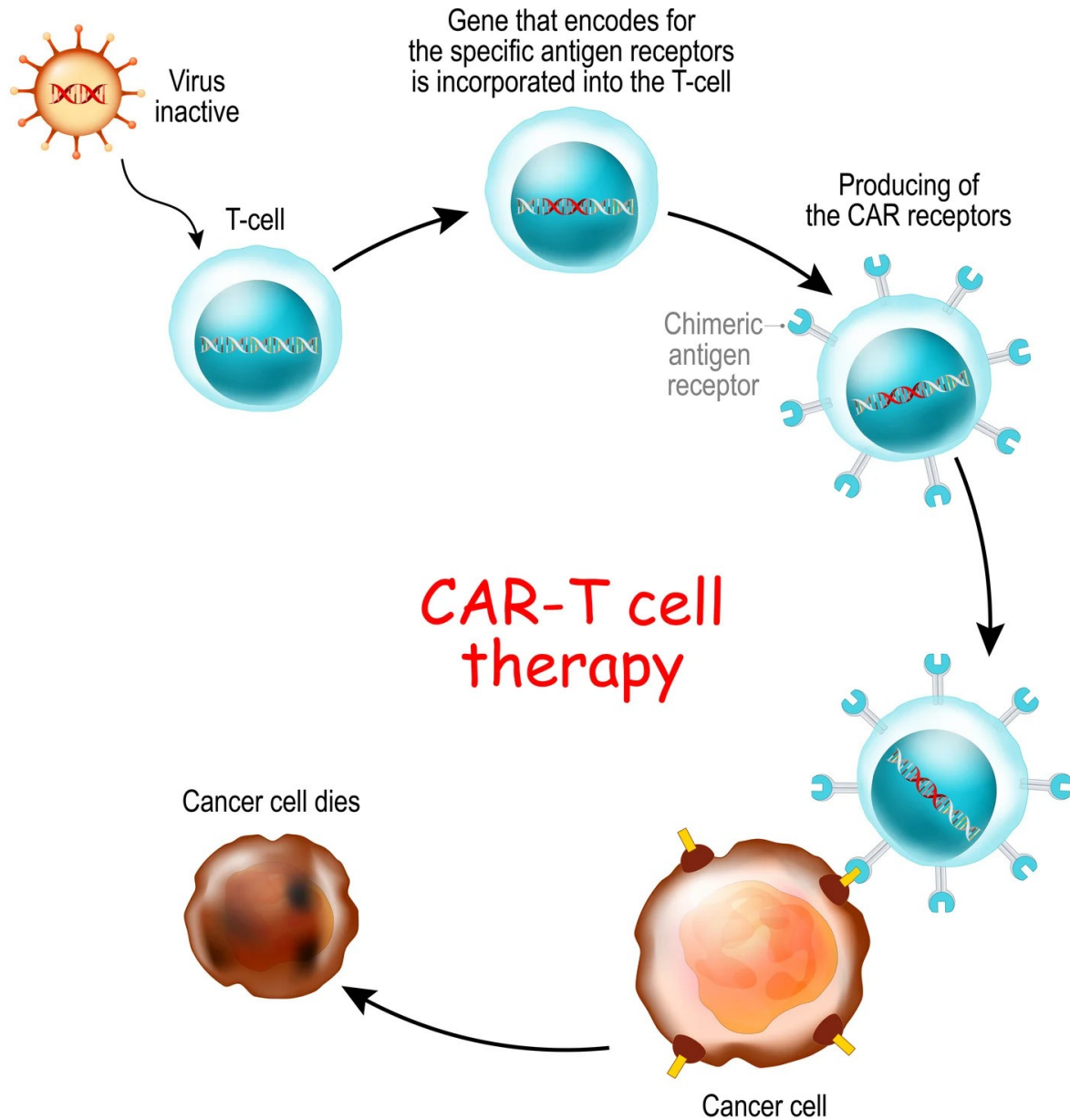
New drugs called checkpoint inhibitors, disable the cancer's immune dampening signals to allow the immune system to do its job. The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.

Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next state of activation and essentially, to leave the tumor alone. By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.

Cancer of the skin and other tissue are called solid tumors and create its own protective environment. Checkpoint inhibitors disrupt this environment to eliminate these solid tumors in 20% in clinical trials.

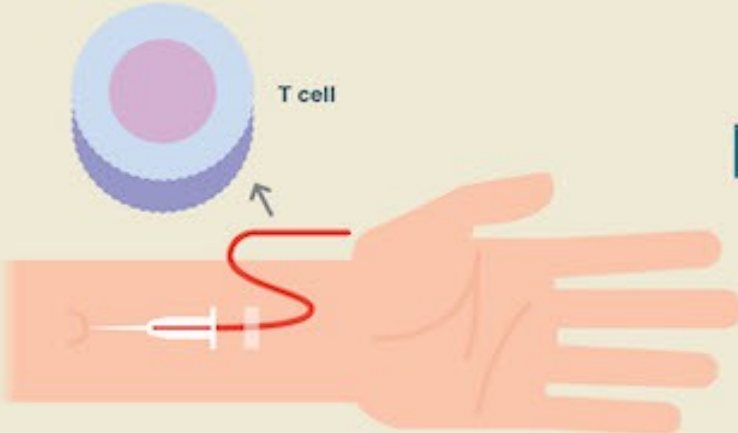
CAR T-cell therapy





CAR T-cell Therapy

Get blood with T cells from patient

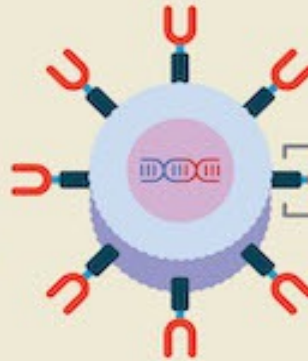


Create CAR T cells that react to cancer cells

Insert gene for CAR



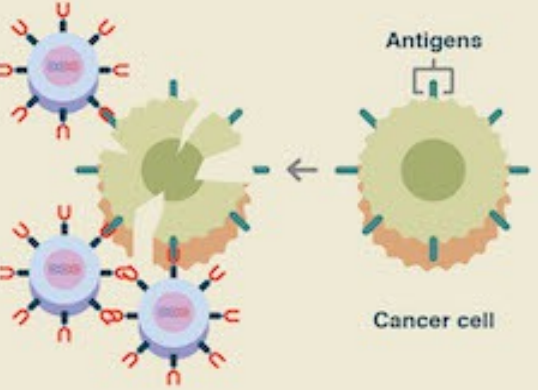
T cell



Chimeric antigen receptor (CAR)

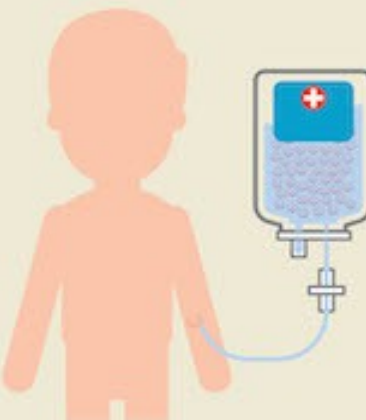
CAR T cell

CAR T cells attack cancer cells

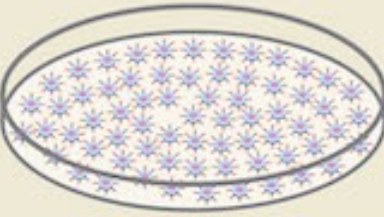


Cancer cell

Inject CAR T cells into patient



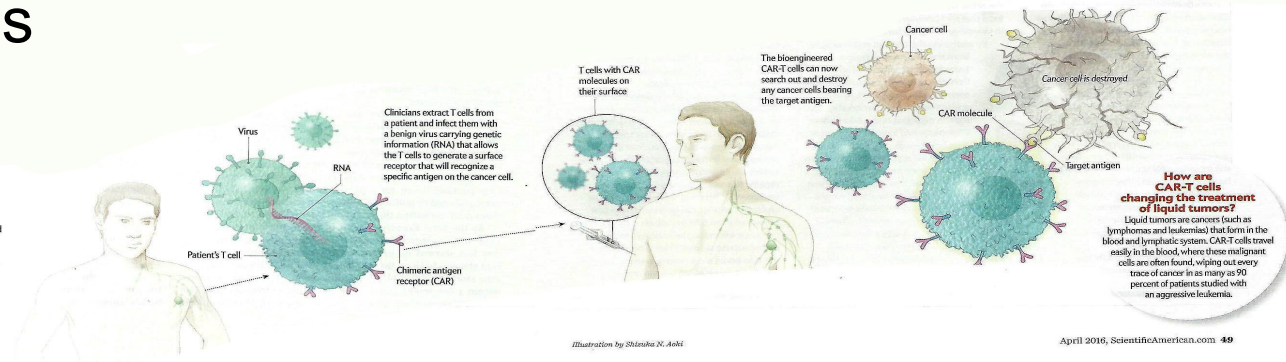
Grow many CAR T cells



CAR-T Cells

CAR-T Cells

Chimeric antigen receptor (CAR) T cells combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy any cells that bear the target antigen. This mishmash eliminates intermediate steps typically taken by B and T cells, making CAR-T cells virtually unstoppable.



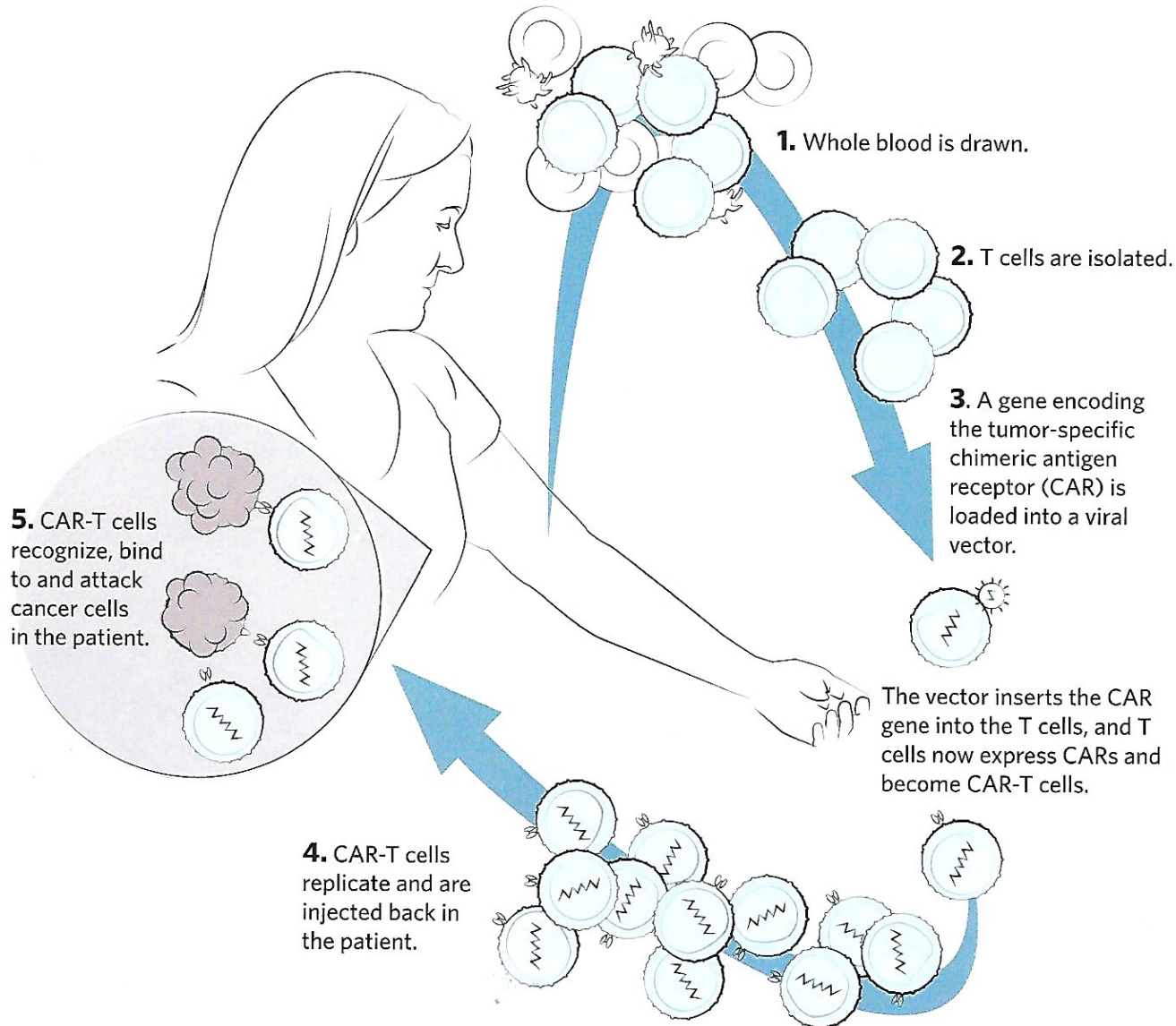
Chimeric antigen receptor cells (CAR-T Cells) combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy any cells that bear the target antigen. This mishmash eliminates intermediate steps typically taken by B and T cells, making CAR-T cells virtually unstoppable

Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (mRNA) that allows the T cell to generate a surface receptor that will recognize a specific antigen on the cancer cell. The bioengineered CAR-T cells can now be injected back into the patient and search out and destroy any cancer cells bearing the target antigen.

Liquid tumors are cancers (lymphomas and leukemias) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer with 90 percent success.

How CAR-T Therapy Works

CAR-T—the initial class of T cell therapies—harnesses the patient’s own immune system to fight certain types of cancer

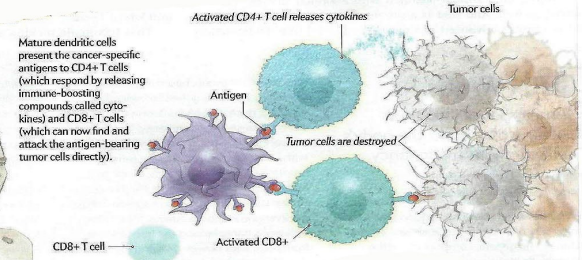
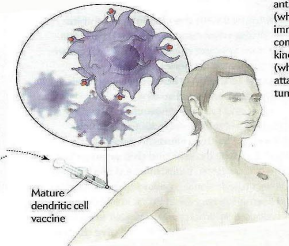
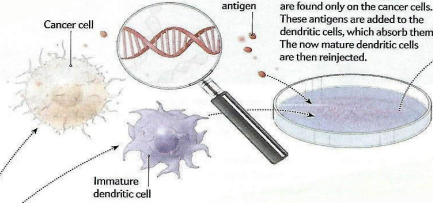
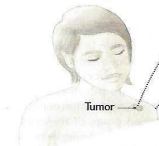


Dendritic Cell Vaccines

Dendritic Cell Vaccine

Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dendritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.

Researchers extract healthy cells, cancer cells and immature dendritic cells from a patient.

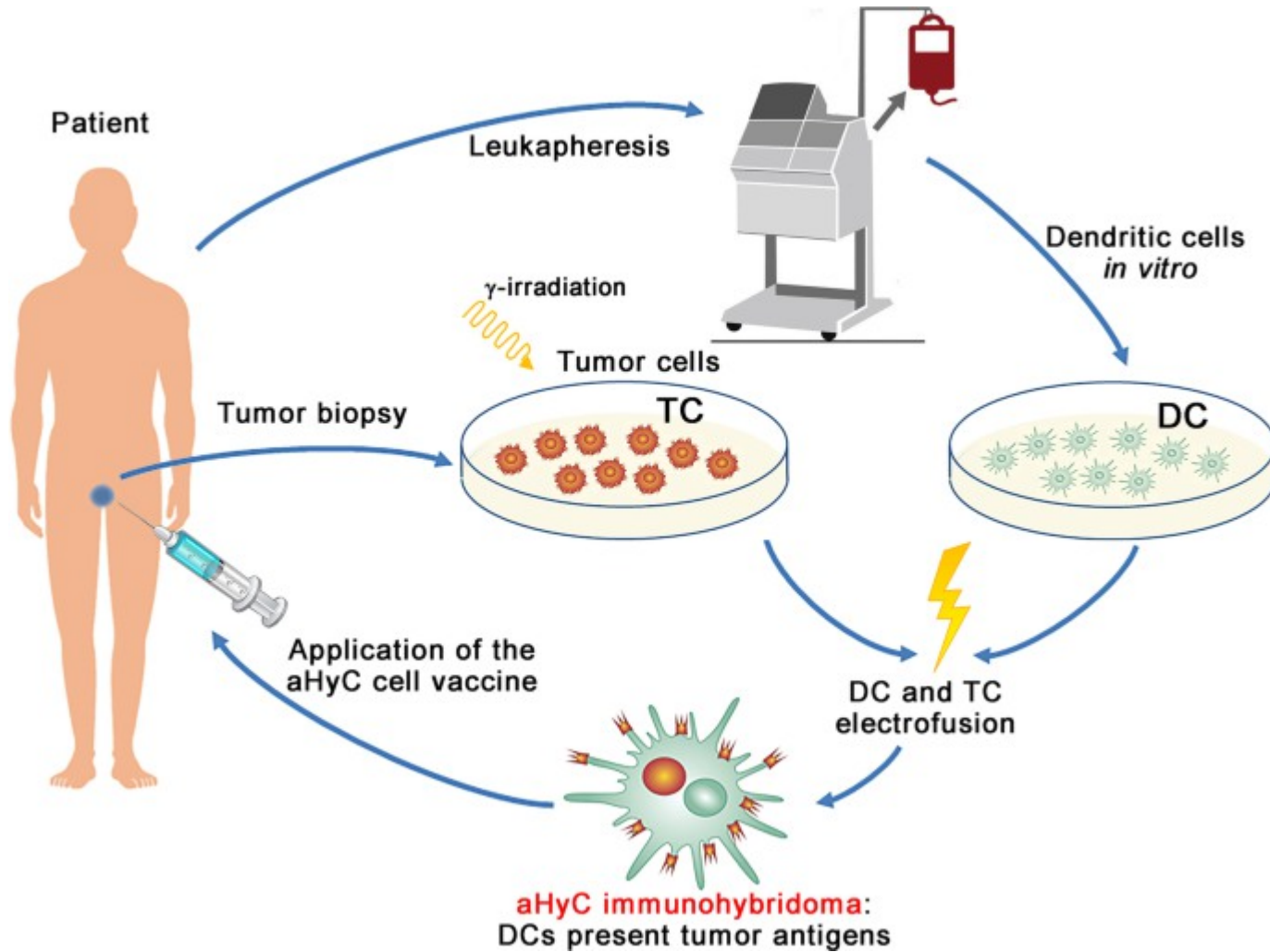


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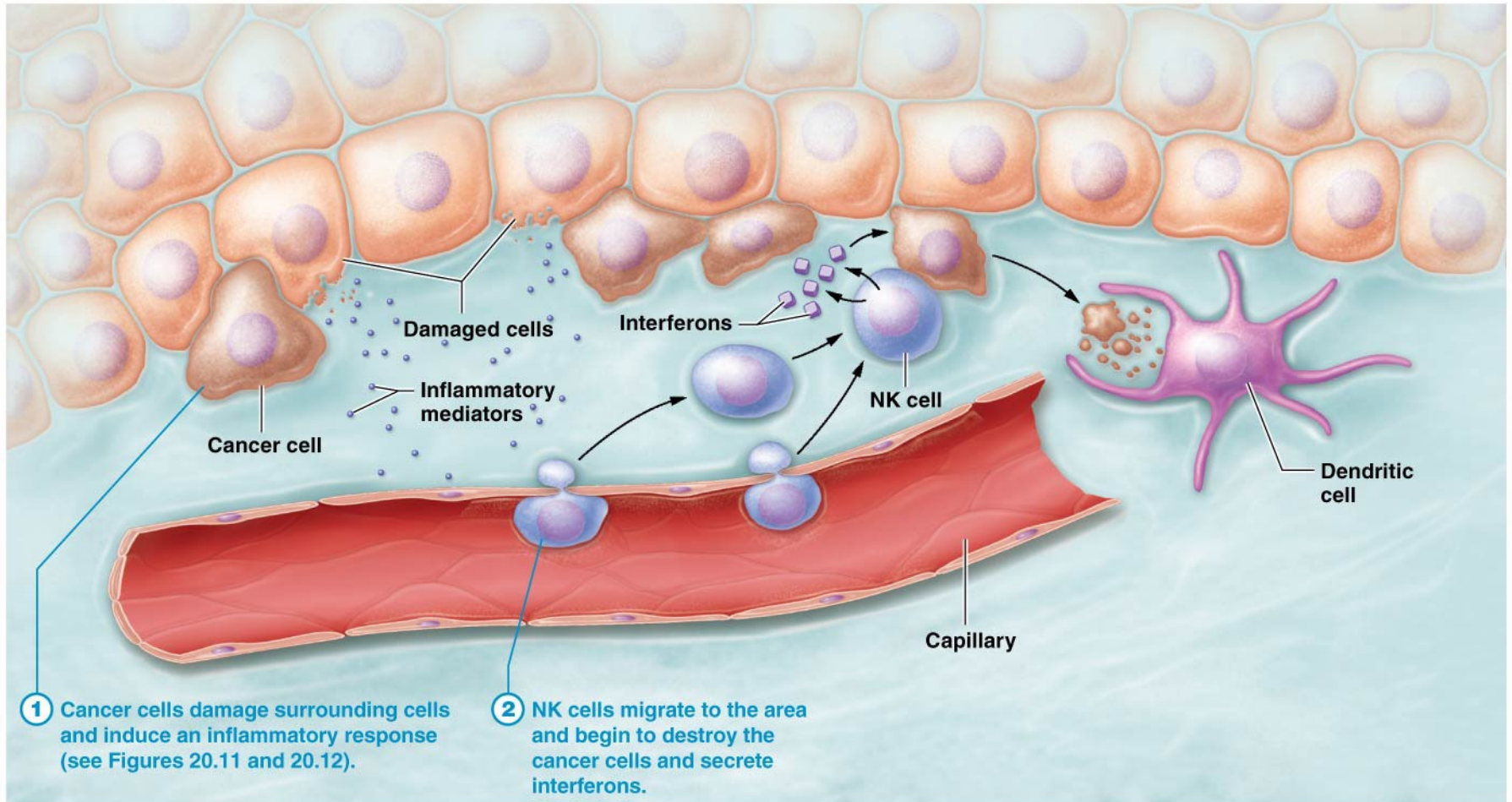
Researchers extract healthy cells, cancer cells and immune dendritic cells from a patient. Researchers look for antigens only found on cancer cells. These antigens are added to the dendritic cells invitro and the dendritic cells absorb the cancer antigen. Now the dendritic cells are injected back into the patient. These now mature dendritic cells present the cancer antigen to helper and cytotoxic T cells. These immune cells now initiate an specific immune response to the cancer cells.

Dendritic Cell Vaccines



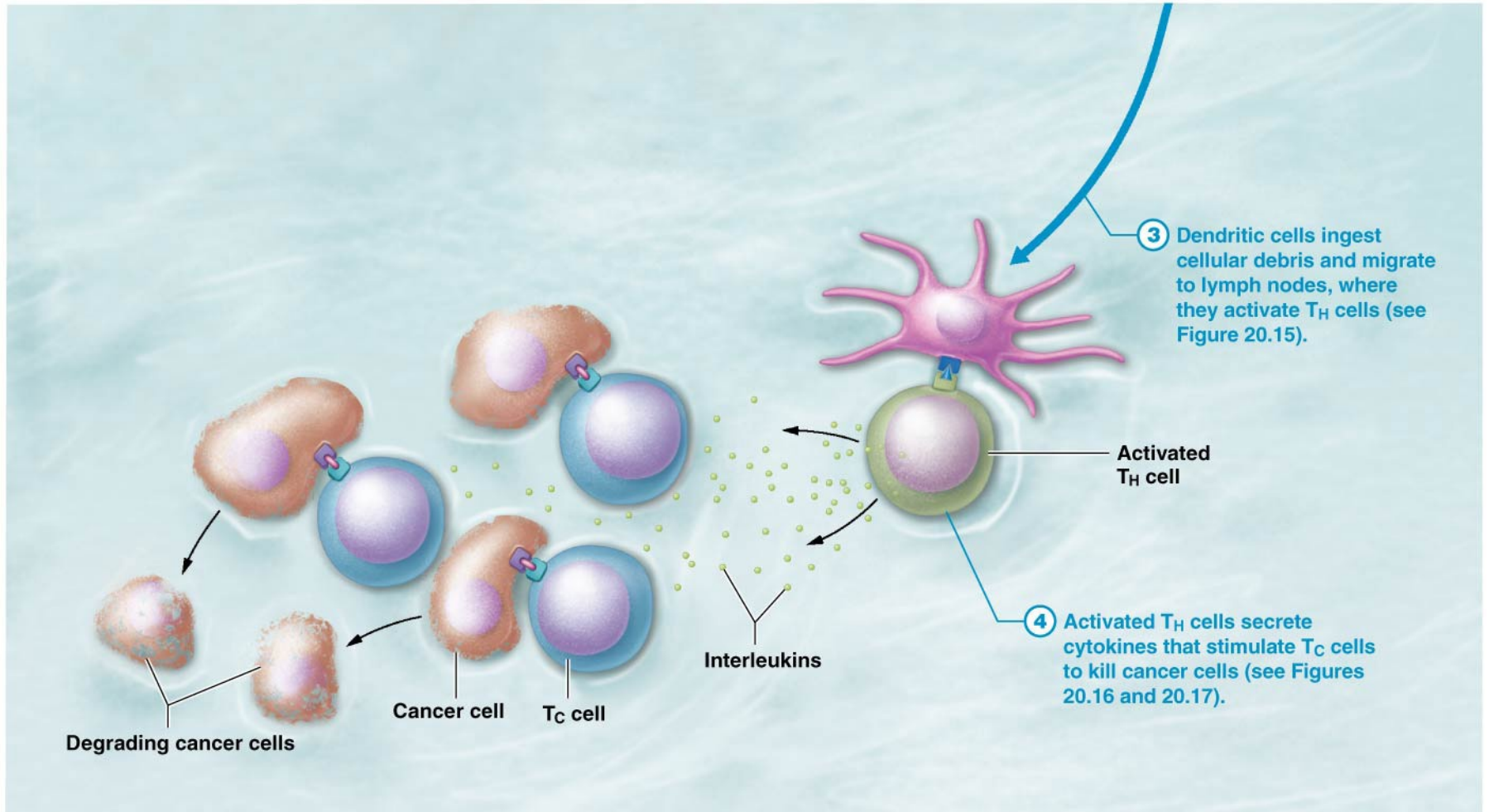
The Big Picture

Using the Immune Response to Cancer Cells. (slide 1 fo 2)



The Big Picture

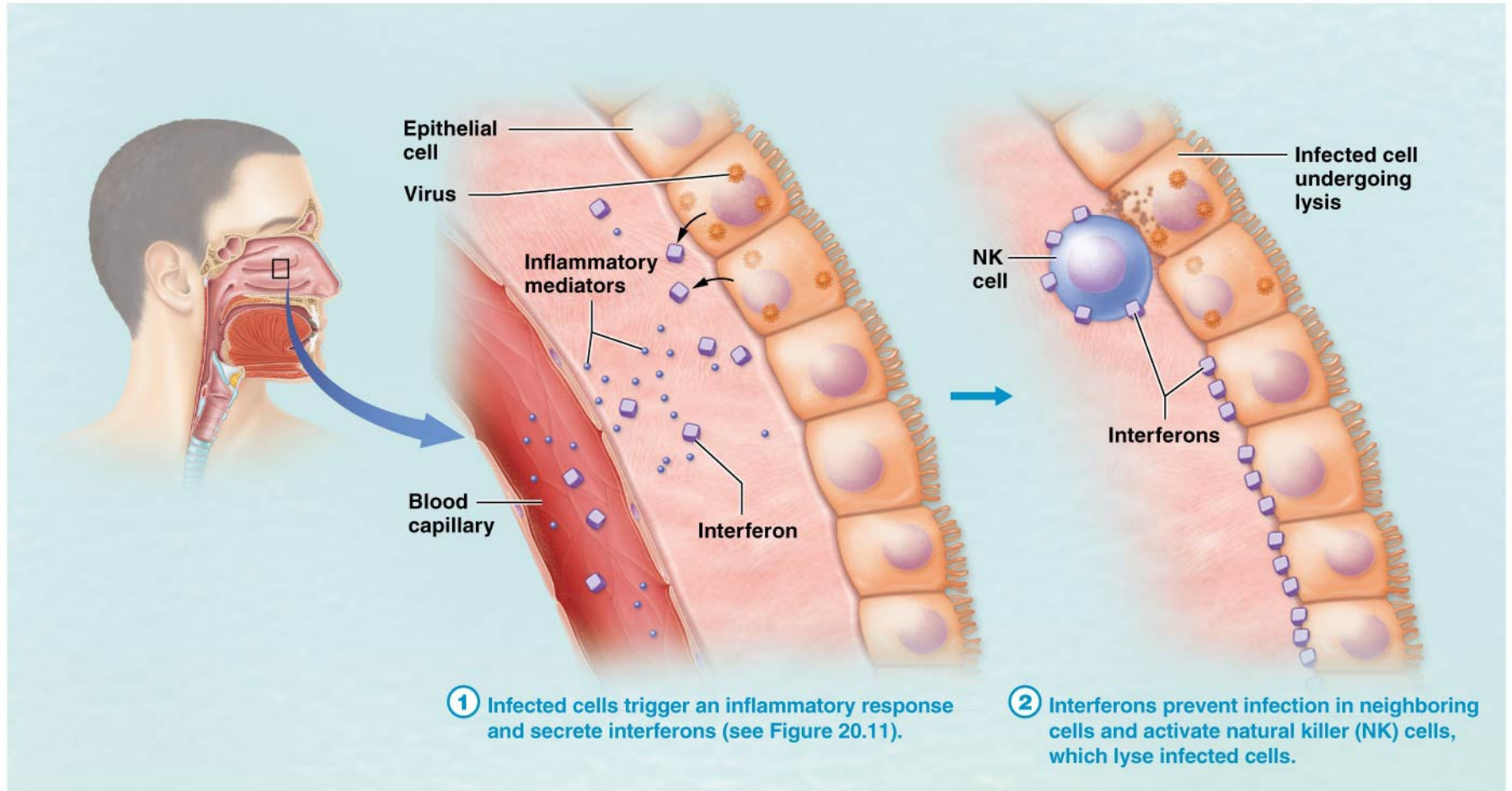
Using the Immune Response to Cancer Cells. (slide 2 of 2)



The Big Picture

Immune Response to the Common Cold.

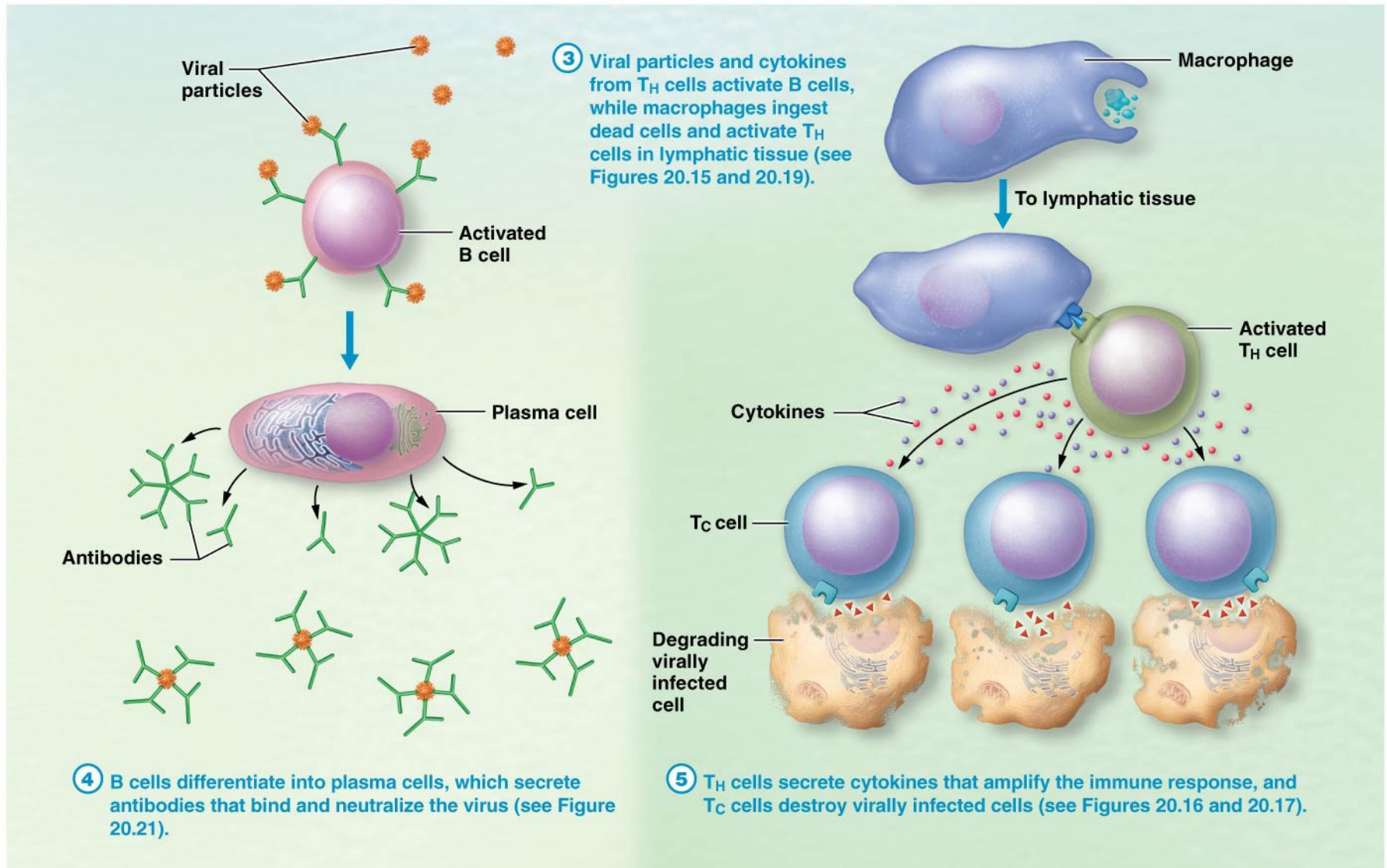
This is a viral infection. (slide 1 of 2)



The Big Picture

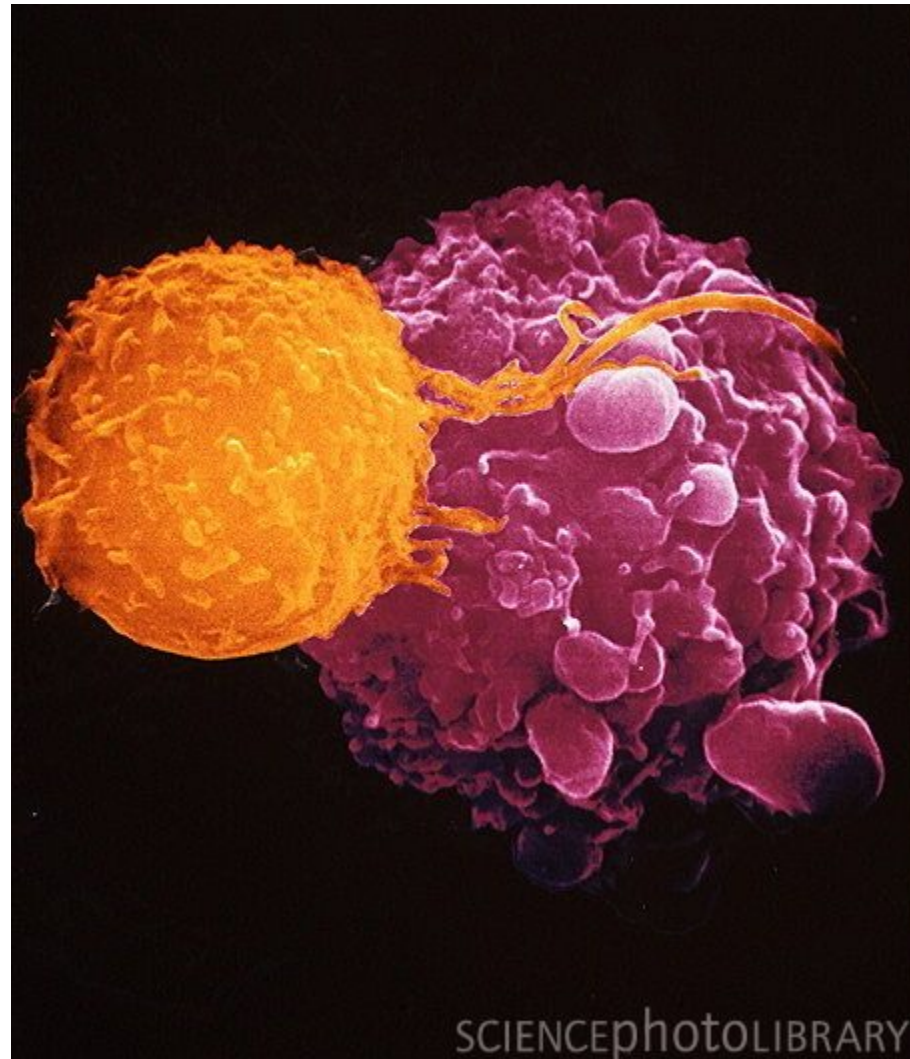
Using the Immune Response to the Common Cold.

This is a viral infection. (slide 2 of 2)

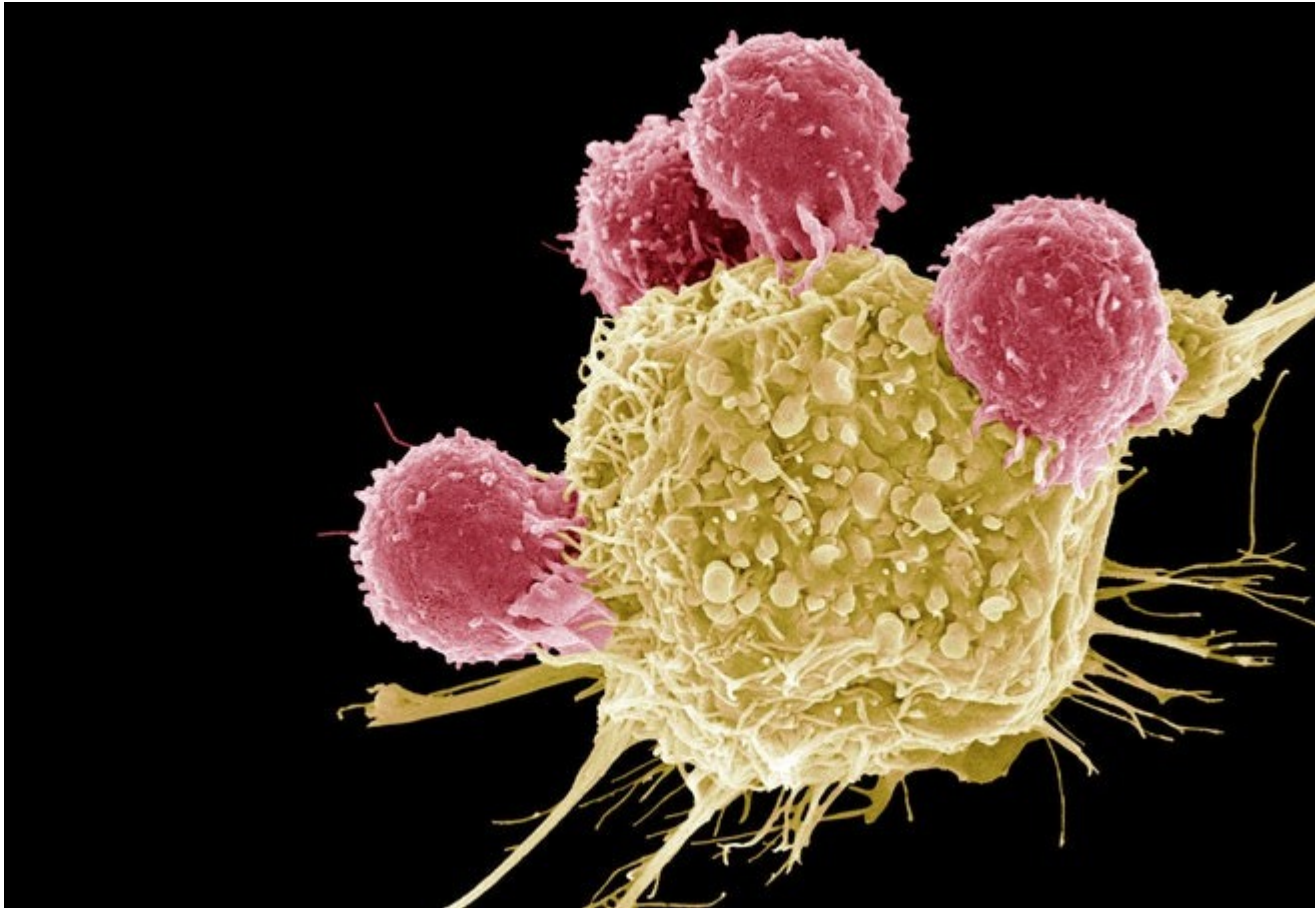


Immune system fighting a cancer cell.

A killer T-lymphocyte (orange) inducing a cancer cell to undergo Programmed Cell Death (apoptosis).



Coloured scanning electron micrograph of T cells (pink) attacking a cancer cell. Editing T cells' genes could soon enhance their cancer-attacking abilities.



Obesity contributes to development of diabetes and cardiovascular disease. Adipose tissue is composed of two main cell types, adipocytes and stromovascular mononuclear cells (i.e., resident leukocytes).

Adipose tissue macrophages (ATMs) are the most frequent leukocyte subtype in fat tissues. Normal adipose tissue is populated with the alternatively activated M2 ATMs. Persistent or frequent consumption of calorie-dense food results in obesity that is associated with increased adiposity which includes adipose tissue hypertrophy and influx of proinflammatory monocytes that mature to classically activated M1 ATMs.

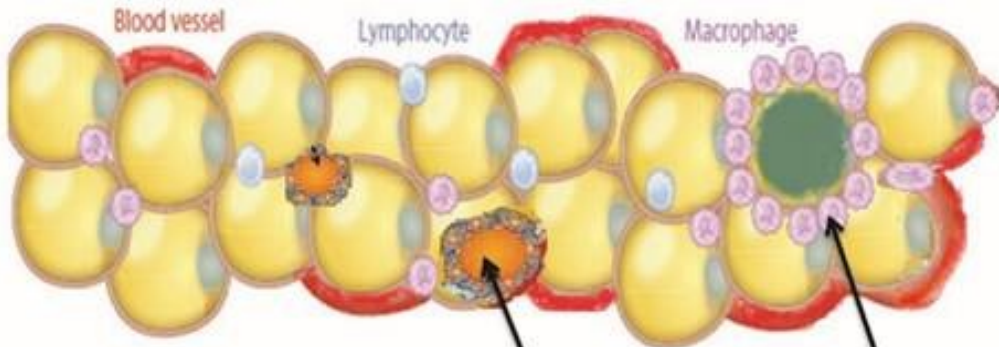
Obesity induces production of proinflammatory cytokines (i.e., IL-6, TNF α , and IL-1 β) and several chemokines including CCL2, CCL5, and CXCL5 among others by adipocytes and immune cells trigger adipose tissue inflammation, which when prolonged progresses to systemic inflammation that affects (i) vasculature increasing permeability of endothelium, thereby triggering plaque development and cardiovascular disease; (ii) anabolic actions of insulin and insulin signaling in metabolic tissues including liver and skeletal muscle, causing insulin resistance that manifests as impaired glucose disposal in muscle and altered cholesterol and glucose metabolism in the liver, which in turn triggers hyperinsulinemia, hyperglycemia, and hyperlipidemia that all contribute to type 2 diabetes and cardiovascular disease; and (iii) pancreas, decreasing insulin secretion that leads to hyperglycemia, which is a hallmark of diabetes.

Lean adipose tissue



↓
Obesity

Hyperplasia and hypertrophy



Blood vessel

Lymphocyte

Macrophage

Group of adipo-angiogenic cells (angiogenesis and adipoangiogenesis)

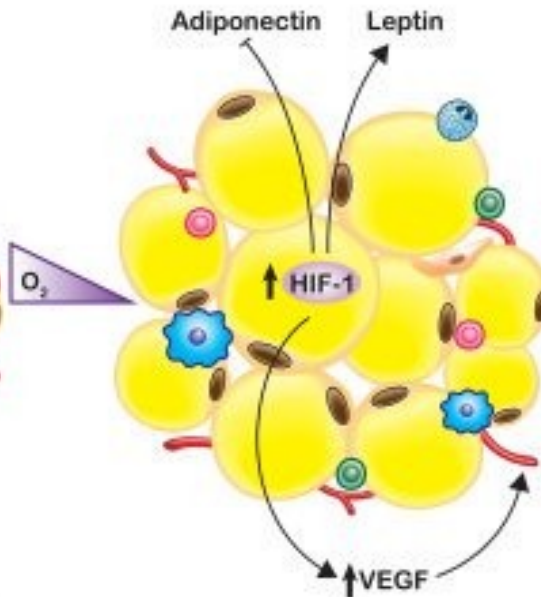
Crown structure (died adipocytes and macrophages M1)

LEAN ADIPOSE TISSUE

Anti-inflammatory Profile

↑ Adiponectin
↓ Leptin
↑ IL-4
↑ IL-10
↑ IL-13
↑ TGF-β

↑ Adiponectin
↓ Leptin

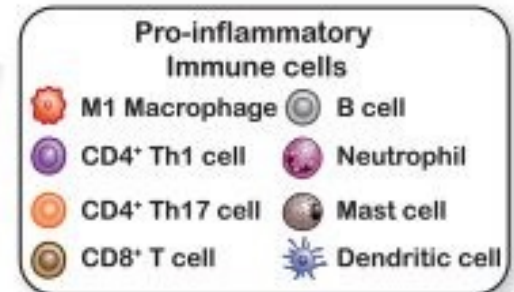
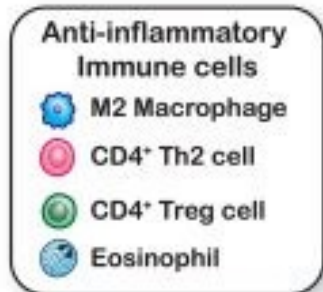
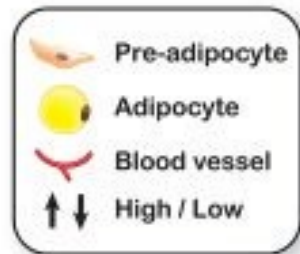
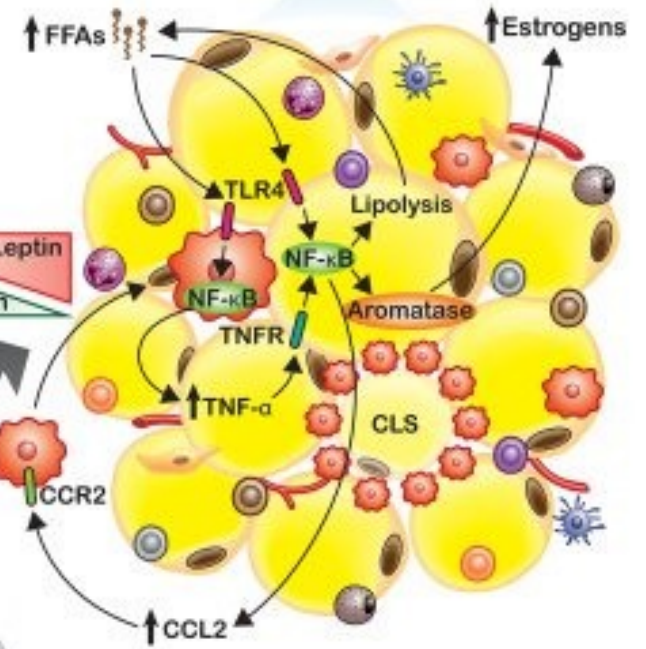


Leptin
Adiponectin

OBESE ADIPOSE TISSUE

Pro-inflammatory Profile

↓ Adiponectin
↑ Leptin
↑ TNF-α
↑ IL-1β
↑ IFN-γ
↑ IL-6
↑ IL-8
↑ IL-17
↑ CCL2
↑ CCL5



WEIGHT GAIN

