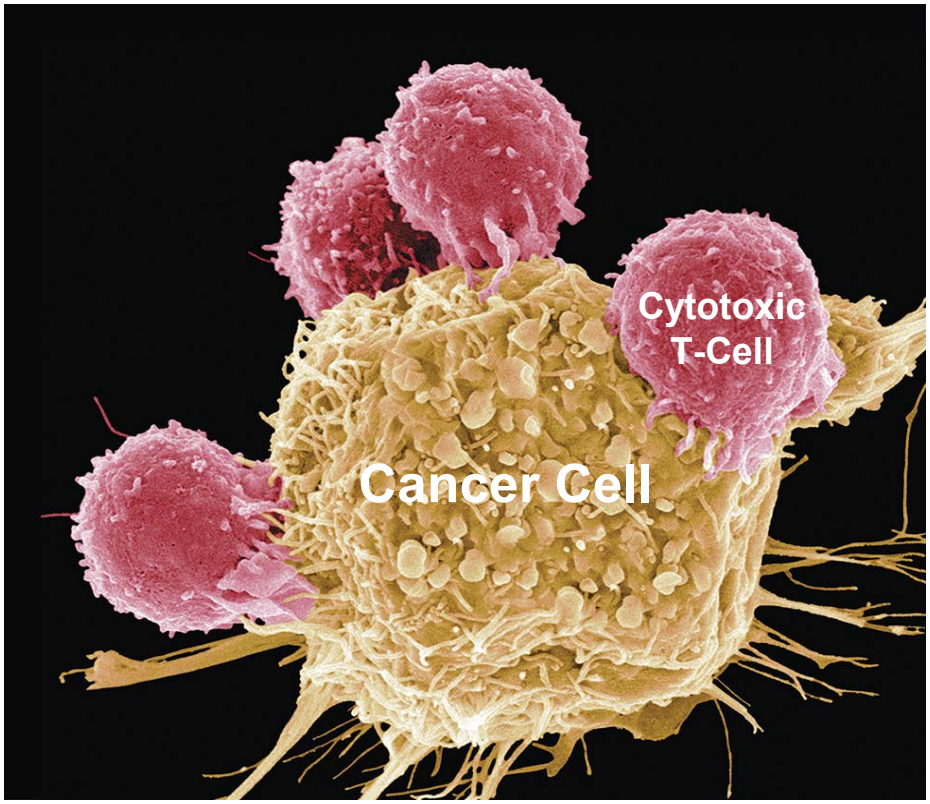
C21.5

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" // cellular response to pathogens*
- *We fight infections by using three lines of defenses:*
  - *#1 - Physical barriers*
  - *#2 - Non-specific resistance*
  - *#3 - Acquired immunity*

(innate)

(not innate)

What makes acquired immunity so special?

Two important characteristics = "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)

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 naive immunocompetent T and B cells are activated by Antigen Presenting Cells /// results in rapid mitosis of T and B cell // both T and B cells have similar receptors matched to a specific antigen on the 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 to a second exposure to similar pathogen. /// first exposure vs second exposure*

Why do we need cellular and humoral immunity?

Because the pathogens maybe 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 receoptor

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 the same pathogen's antigen.

Key Factoids

Immune system differentiate between self and non-self antigens

Immune system function is to eliminate pathogens

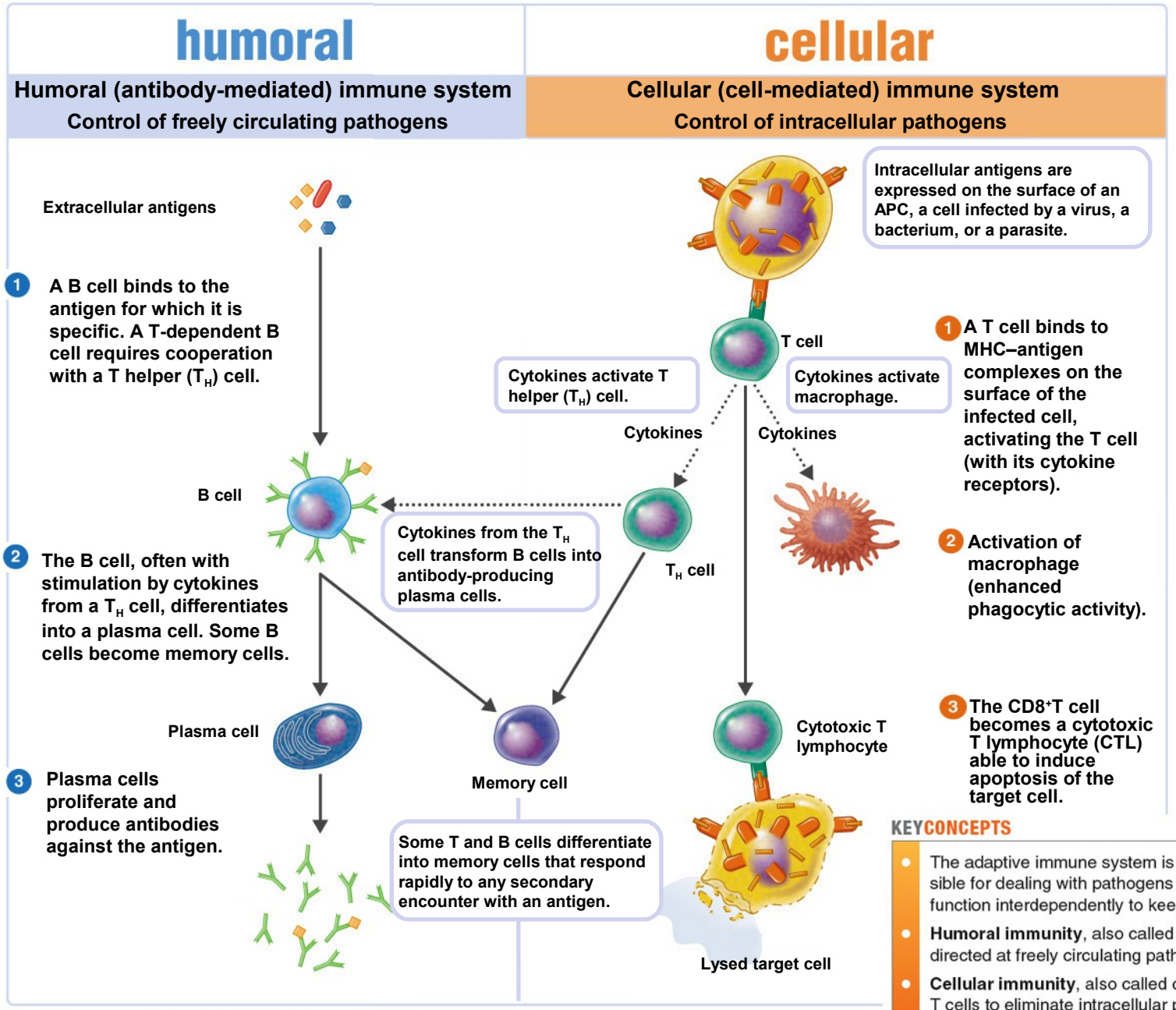
Cytotoxic T cells are able to kill infected host cells with a kiss of death

Plasma cells (B cells when activated morph into plasma cells) produce Antibodies. Antibodies do not kill pathogens, but render pathogen harmless and tag pathogens for destruction by complement /// this occurs in body fluids //

Another lymphocyte called Natural Killer Cells (NK cell) are able to kill infected host cells but use a different types of receptors

- Increase number in response to inflammation cytokines
- Evolved to kill host cells infected by cancer or virus (but also bacteria)
- KN cells are activated by a pathogen's antigen using different process
- NK cells perform immune surveillance
- Part of the second line of immune defense // innate

The dual nature of the adaptive immune system.



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 (helper T cells = hTc and cytotoxic T cells = cTc) and B-cells are the key cells responsible for acquired immunity

These cells must first be born, educated, deployed // all formed elements are born in the red bone marrow // education means the T cells and B cells acquire unique receptors matched to pathogen's antigens // B cells are educated in bone marrow and T cells are eduated in thymus // after T cells and B cells receive their receptors the move into the blood where they are “deployed as naive immunocompetent cells”.

After being deployed these cells will “rest” until a pathogen enters the body

If the pathogen's antigen is “presented” to the T and B cells, then these cells will enter their second phase: recognize, react, remember

How is acquired immunity managed?

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 a pathogen enters the tissue which initiates the three "R"s. (recognize, react, remember)

How is acquired immunity managed?

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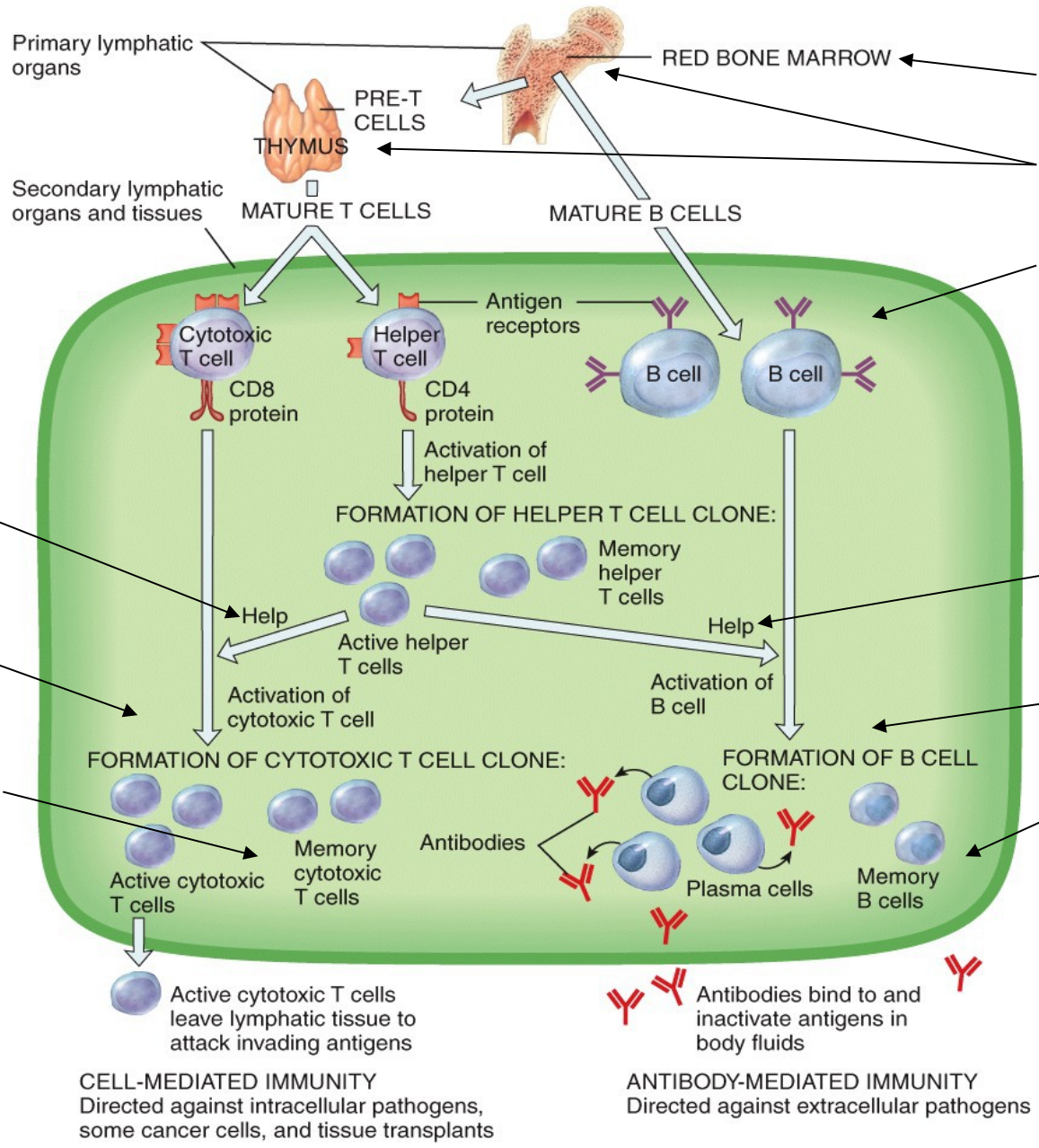
Recognize = naive immunocompetent T and B cells are not able to "see the pathogen" until after an antigen presenting cells "shows" the T and B cells the pathogen now invading the Body // these cells are no longer naive but are now "turned on"

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.

All formed elements made in red bone marrow



Born

Educated

Deployed

(Deployed as naive immunocompetent cells)

ACTIVATE To

Recognize

React

Remember

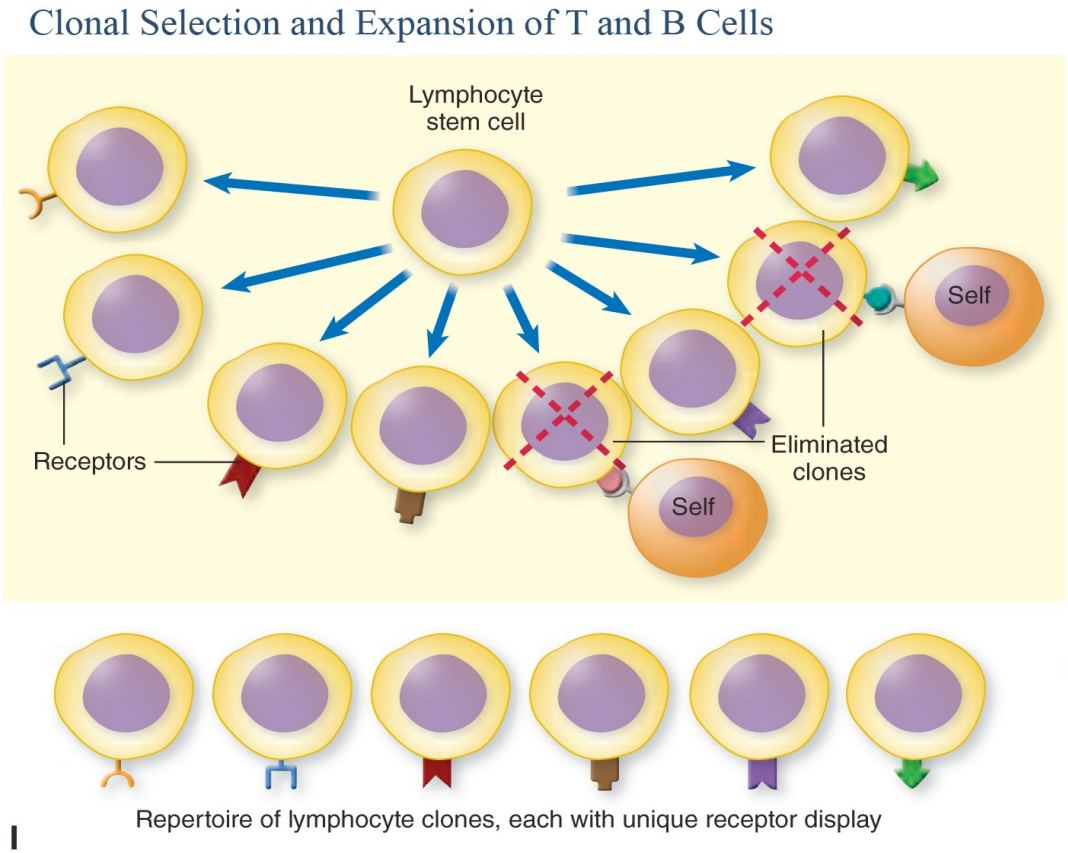
Recognize

React

Remember

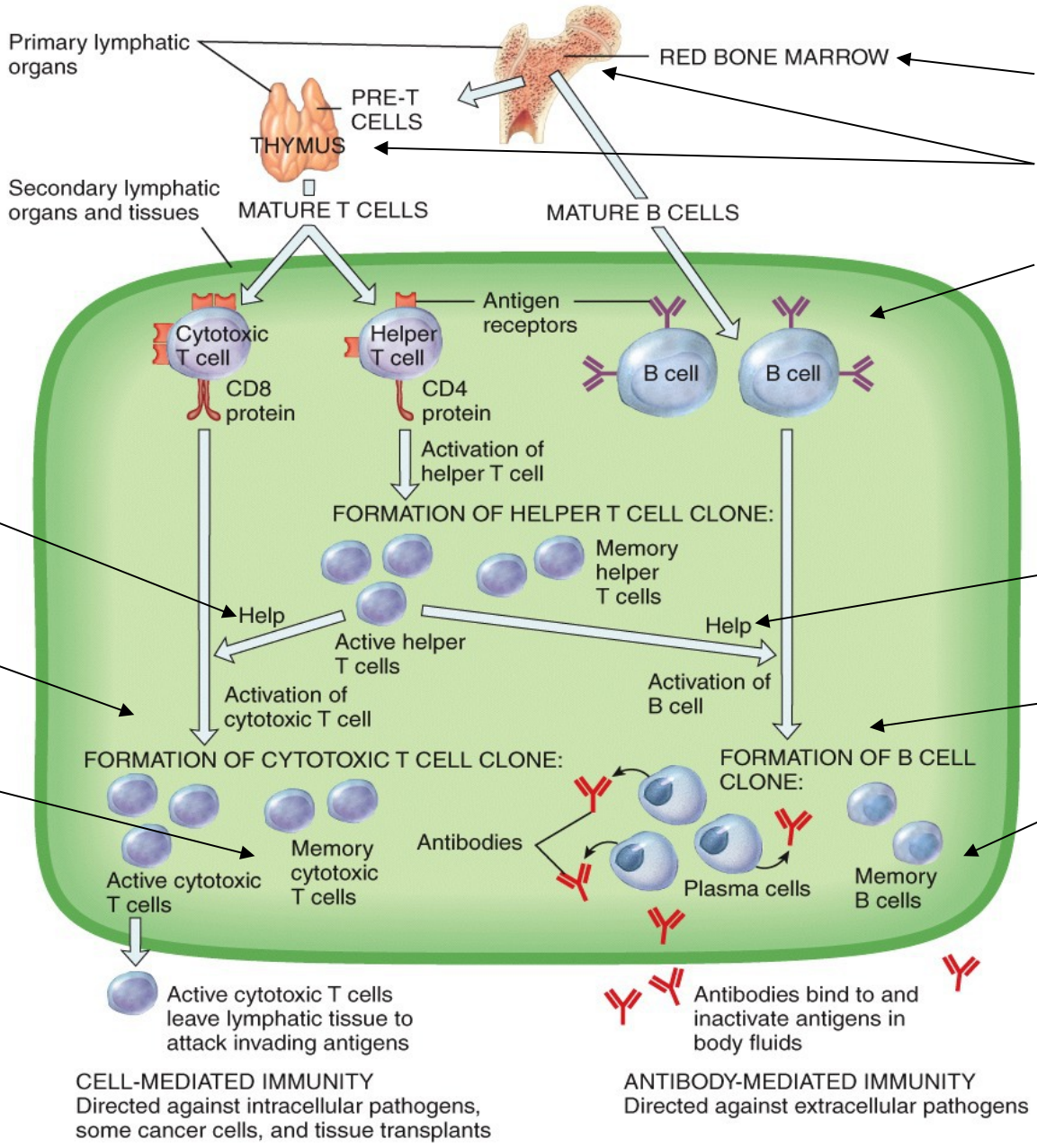
Clonal selection occurs during the education phase.

Rapid mitosis of B and T cells occurs during the "education phase". Each group of three (helper T cells, cytotoxic T cells, and B cells) undergo rapid cell division all with similar receptors match to a specific pathogen antigen . There are billions of possible foreign antigens and billions of cell sets



During clonal selection mitosis produces millions of similar cells all receiving similar receptors. If a new clonal cell binds to a host self antigen then the cell is eliminated. Clonal cells bind only to non-self antigens.

Outline for the structure and function of acquired immunity.



Born

Educated

Deployed

(Deployed as naive immunocompetent cells)

ACTIVATE To

Recognize

React

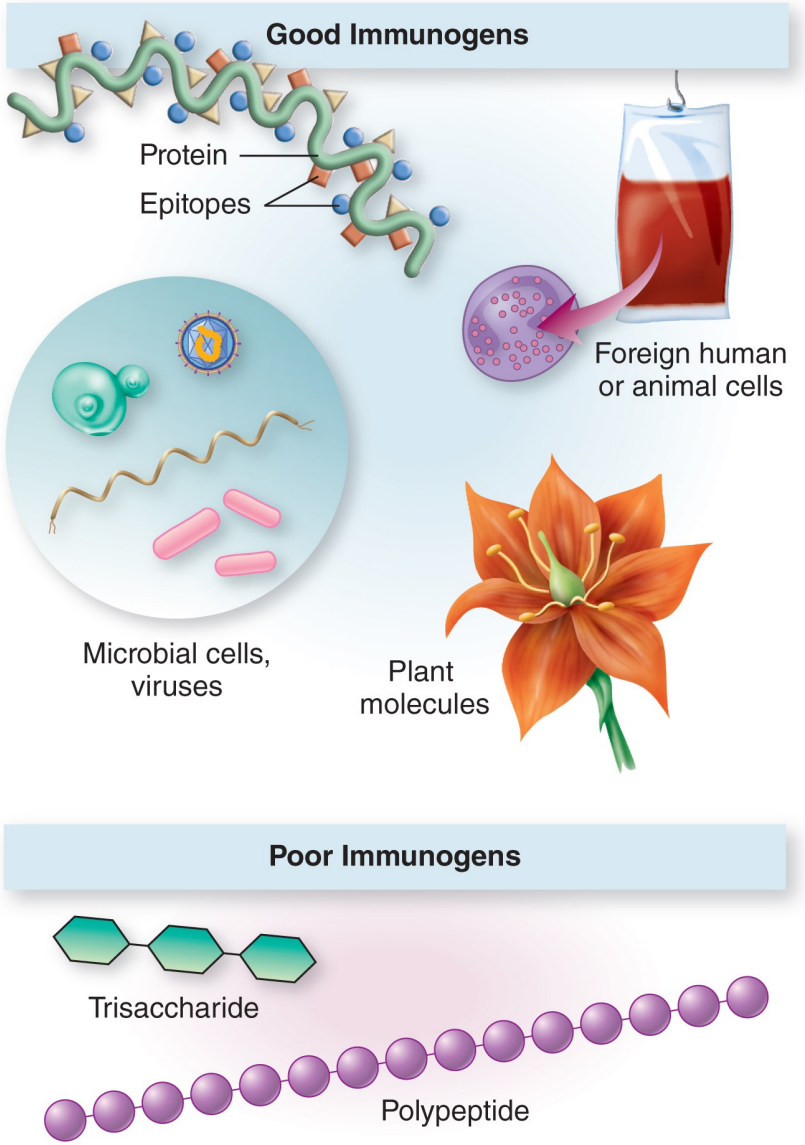
Remember

Recognize

React

Remember

What makes a good antigen?



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

Antigens are large molecules.

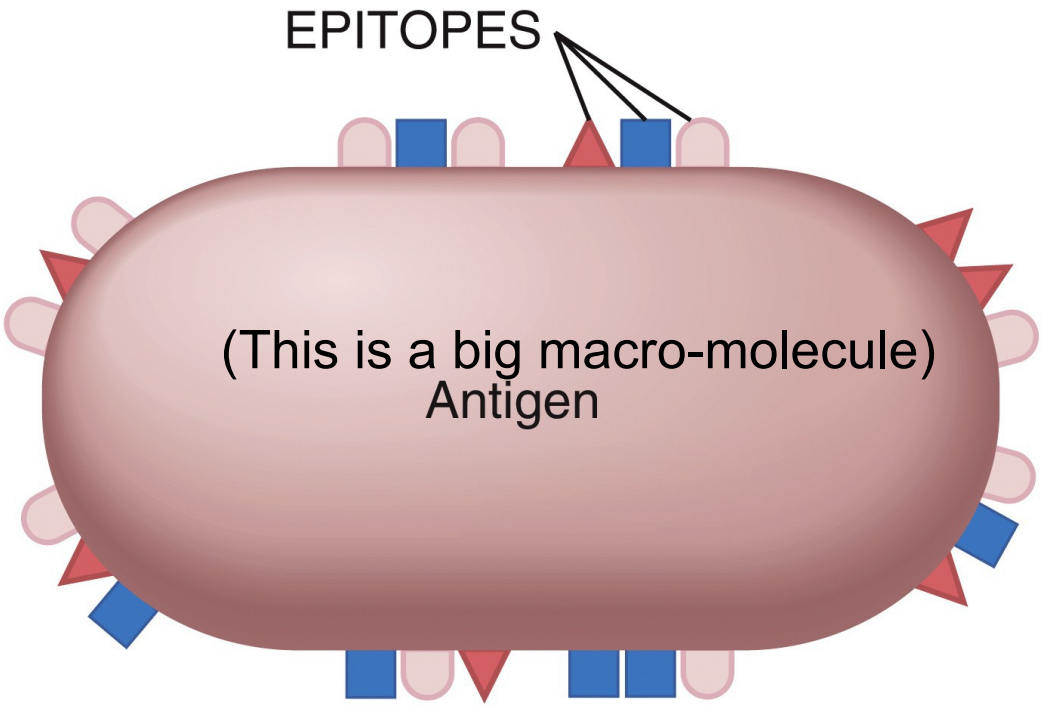
Antibodies = also called aglutinin

> A single antigen molecule may generate many epitopes.

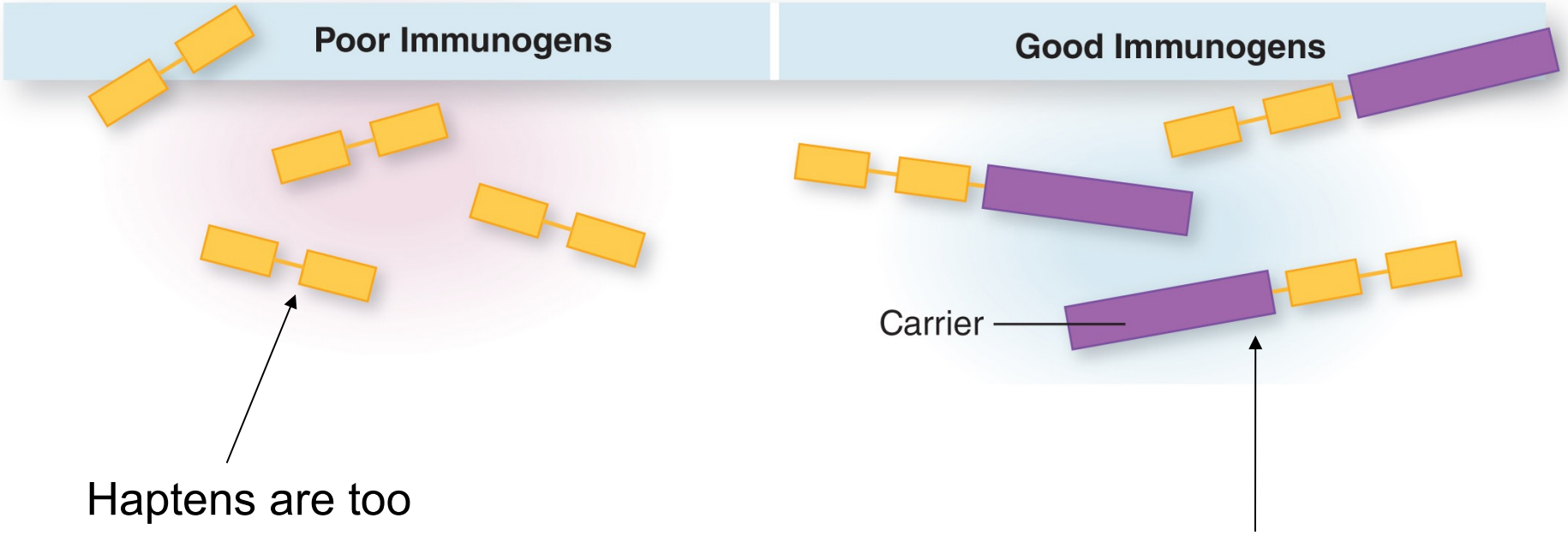
> A proteosome will degrade the antigen to create protein fragments called epitopes. These are processed by the endoplasmic reticulum.

> The endoplasmic reticulum put epitopes into vesicles with MHCP proteins.

> The MHCP with its epitope are inserted into the host's plasma membrane or antigen presenting cells.



Haptens are poor immunogens, however!



Haptens are too small to act as an antigen.

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

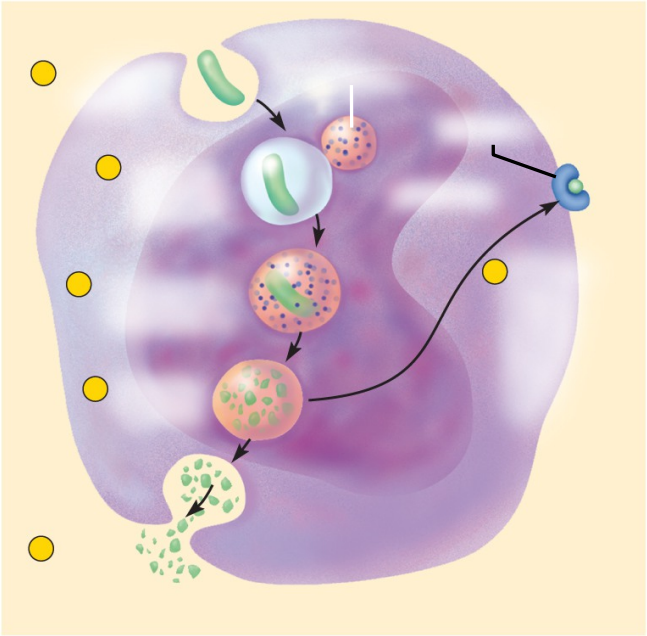
What is antigen presentation?

How do antigen processing cells capture antigens?

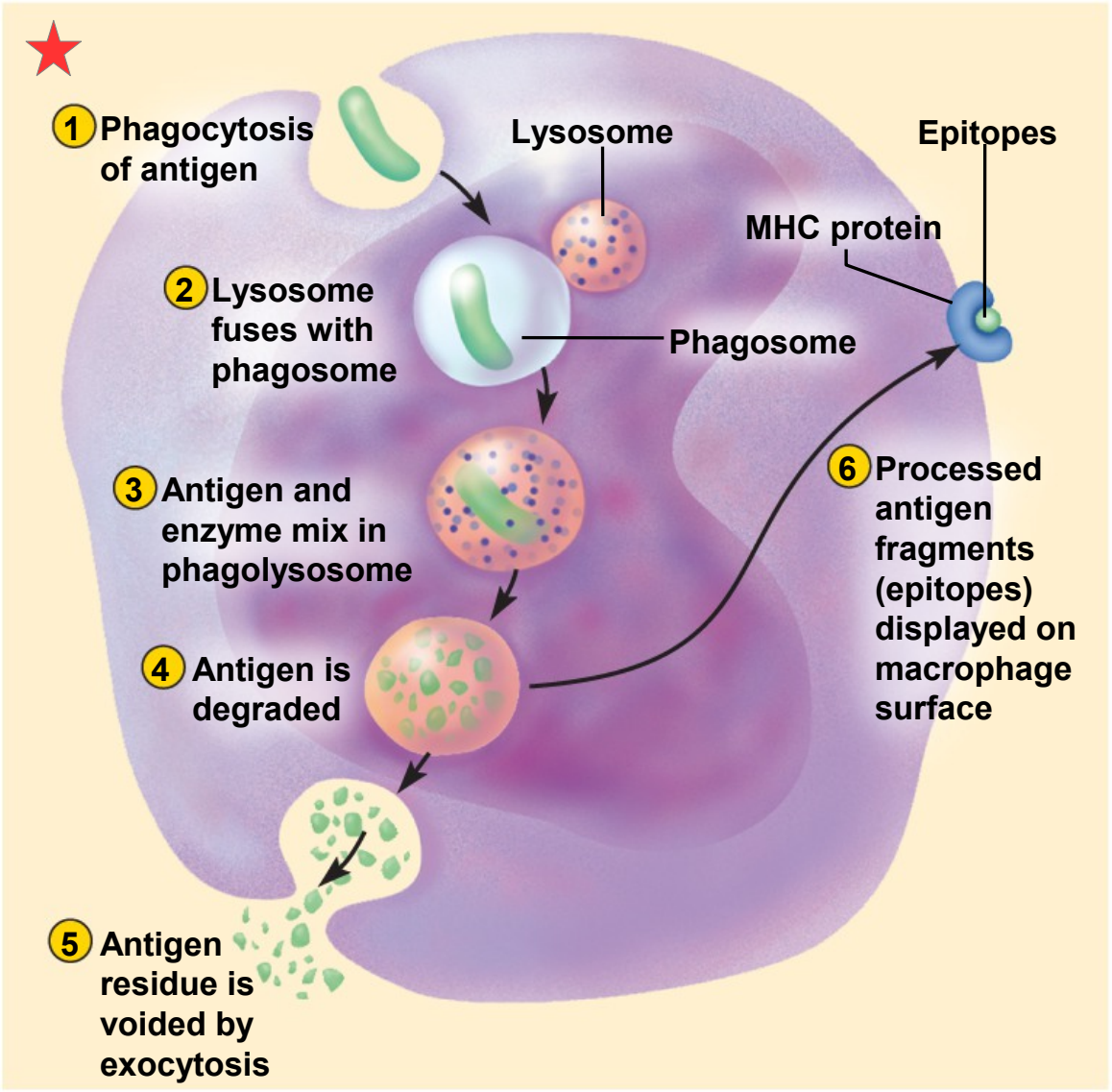
What is the difference between an antigens and an epitope?

How do APC display epitope on outer surface of the plasma membrane?

What is the difference between MHCP-I and MHCP-II?



How Do Antigen Processing Cells Turn Antigens into Epitope? How do APC 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

Major Histocompatability 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

Cells are infected with patogens if the “show” foreign 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 Histocompatability Proteins
(MHCP-1 VS MHCP-2)

APC (macrophage, dendritic cells, and B cells) capture the bacteria infecting our cells, process the epitopes, then deliver this info to the lymph nodes. *(B cells use a special process which will be covered later)*

Macrophage MHCP-II dock with naive hTc cells with matching hTc receptors to activate the hTh cells

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

Now both cTc and hTc with their specific receptors match to the bacteria are activated against bacteria infecting the host cell. cTc receptors may now dock onto host cell's MHCP-I epitope.

The hTc secretes cytokines to complete the activation of the cTc.

The now fully activated cTc may dock to the host cell MHCP-I-epitope and kills the cell with the kiss of death // CTc may then undock and go to next infected cell to kill it.

After all infected host cells are killed, this group of cTc die by apoptosis.

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

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

Naive immunocompetent B cell's use D class antibodies as receptors. Matched B cell receptors will dock to bacteria's antigen. B cells then engulfs the bacteria and processes the epitope.

Bell 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-Tcell (activated by similar epitope) the H-Tcells secrete cytokines and the B cells are now fully activated

B cell now morphs into plasma cell /// These plasma cells makes 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. Compliment will destroy the tagged pathogen.

Dendritic Cells Special Role in Immunity

Dendritic cells (DCs) are “special” antigen-presenting cells (APCs) because they present antigens on both **Major Histocompatibility Complex (MHC) class I and MHC class II molecules**.

MHC Class I:

MHC class I molecules are expressed by all nucleated host cells.

DCs can present internalized antigens on MHC class I molecules through **cross-presentation**. // Cross-presentation starts immune responses against pathogens like viruses and tumors.

This process involves moving antigens from endosomes to the cytosol for degradation, then loading the resulting peptides onto MHC class I molecules.

Dendritic Cells Special Role in Immunity

MHC Class II:

DCs constitutively express MHC class II molecules in macrophage and B cells. /// In immature DCs, MHC class II is stored in late endocytic compartments and is quickly degraded.

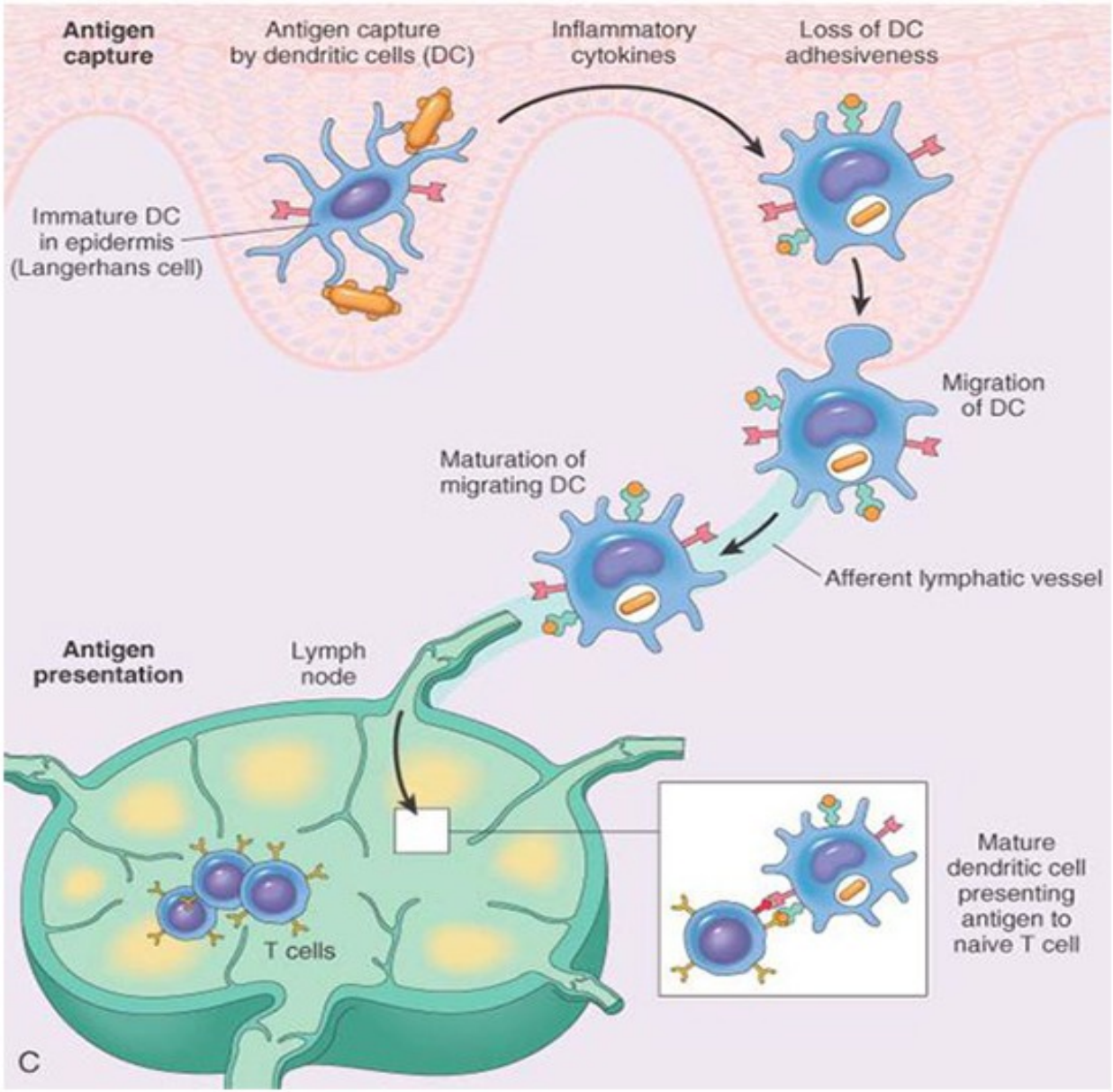
When activated, DCs load MHC class II with epitope, transporting these complexes to the cell surface.

MHC class II molecules with epitope are then presented to CD4+ T helper cells, initiating the adaptive immune response.

In summary: **Immature DCs:** Express MHC class II but keep it primarily in intracellular compartments. /// **Mature DCs:** Increase surface expression of both MHC class I and MHC class II, along with costimulatory molecules like CD86, becoming efficient APCs.

The presence of both MHC class I and MHC class II on DCs allows them to activate both CD8+ cytotoxic T cells (via MHC class I) and CD4+ T helper cells (via MHC class II). This is essential for a strong adaptive immune response.

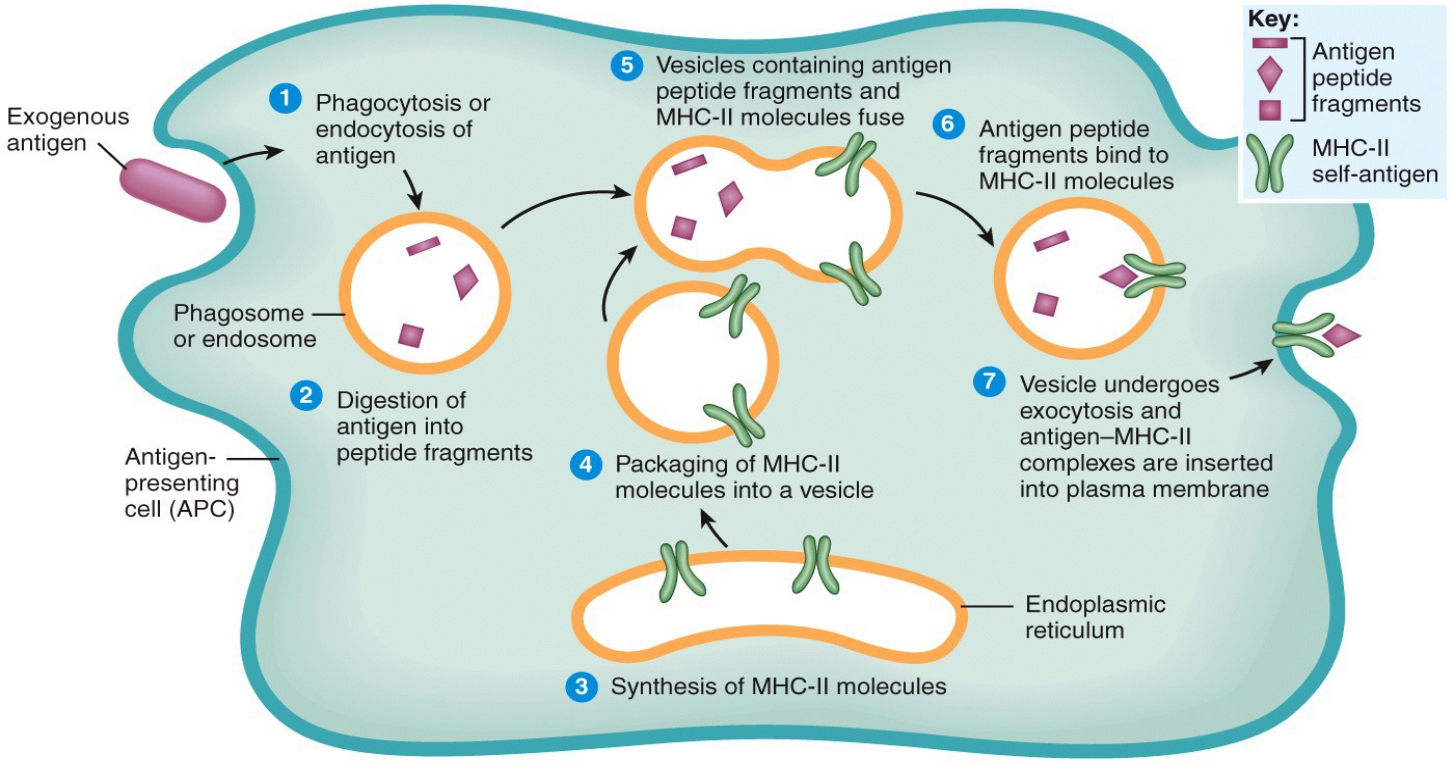
Dendritic Cells



MHCP-II Antigen Processed Cells

Macrophage and dendritic cells are antigen processing cells using MHCP-II. The APCs engulf exogenous antigen and present this epitope-MHC-II complex in the plasma membrane.

Naïve immunocompetent helperTcells (CD4) have Tc receptors able to bind with MHCP-II from either macrophage or dendritic cells. Both APC may activate the helper Tcell.

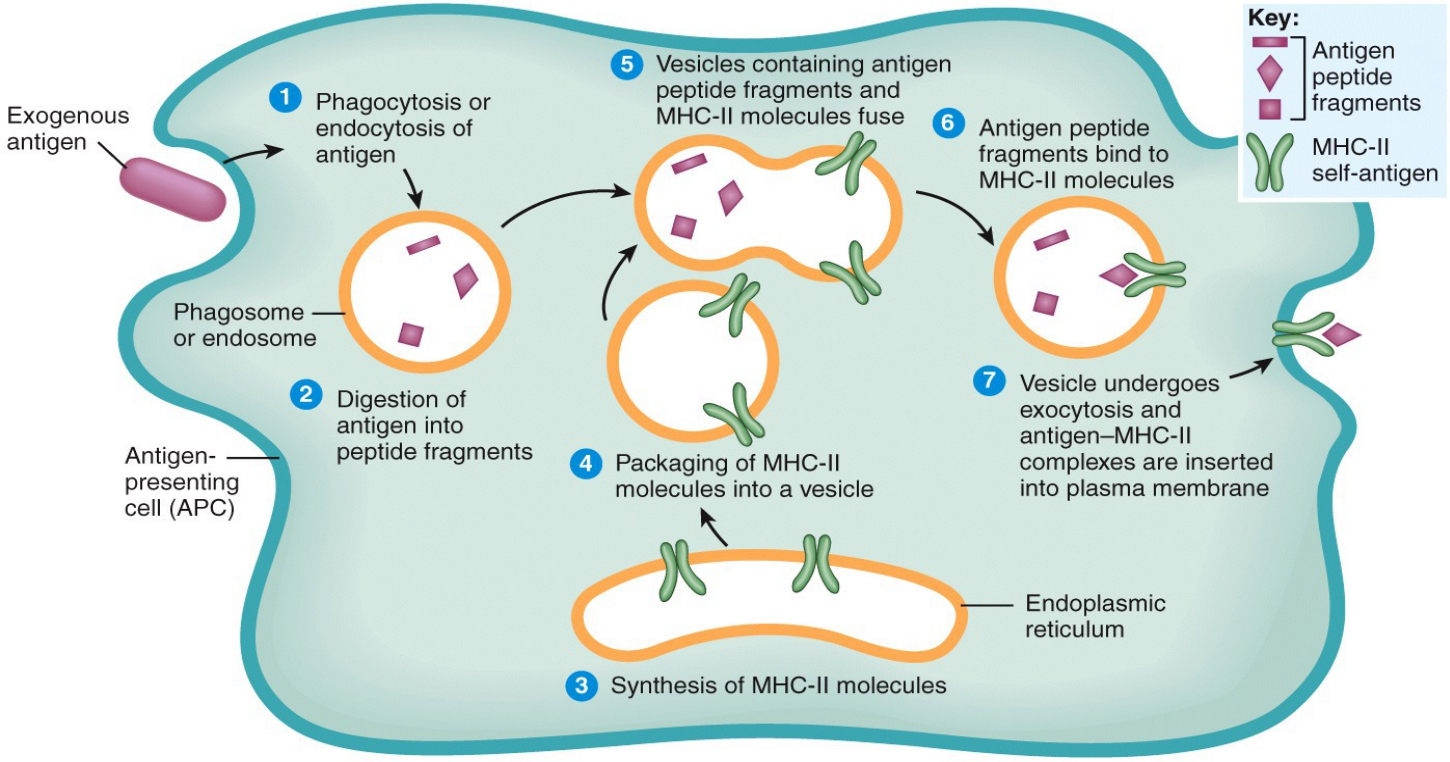


APCs present exogenous antigens in association with MHC-II molecules

Antigen Processing Cells With Both MHCP-I and MHCP-II

Cytotoxic T cells (cTc) receptors only bind to MHCP-I APC for activation.

Dendritic cells are antigen processing cells that have both MHCP-I and MHCP-II proteins. This means dendritic cells may activate naive cytotoxicTc (with receptors matched to MHCP-I) and naive helper Tcells (with receptors matched to MHCP-II).



APCs present exogenous antigens in association with MHC-II molecules

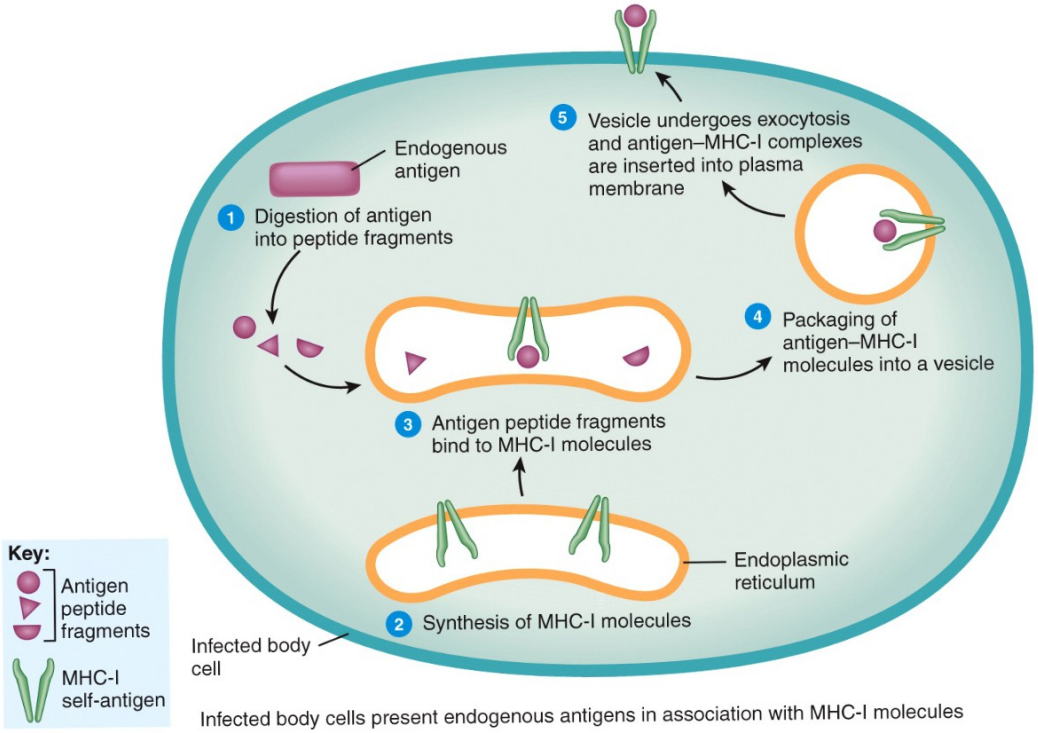
How Host Cells Process and Display Foreign Antigen Using MHC-I

Placing epitope into the host cell's plasma membrane will allow activated cytotoxic T cell's receptors to dock to infected cell's MHCP 1 complex.

If the cell displays bacterial epitope in MHC-I complex then cytotoxic T cell will form a c-T-cell-receptor-MHC-1 complex.

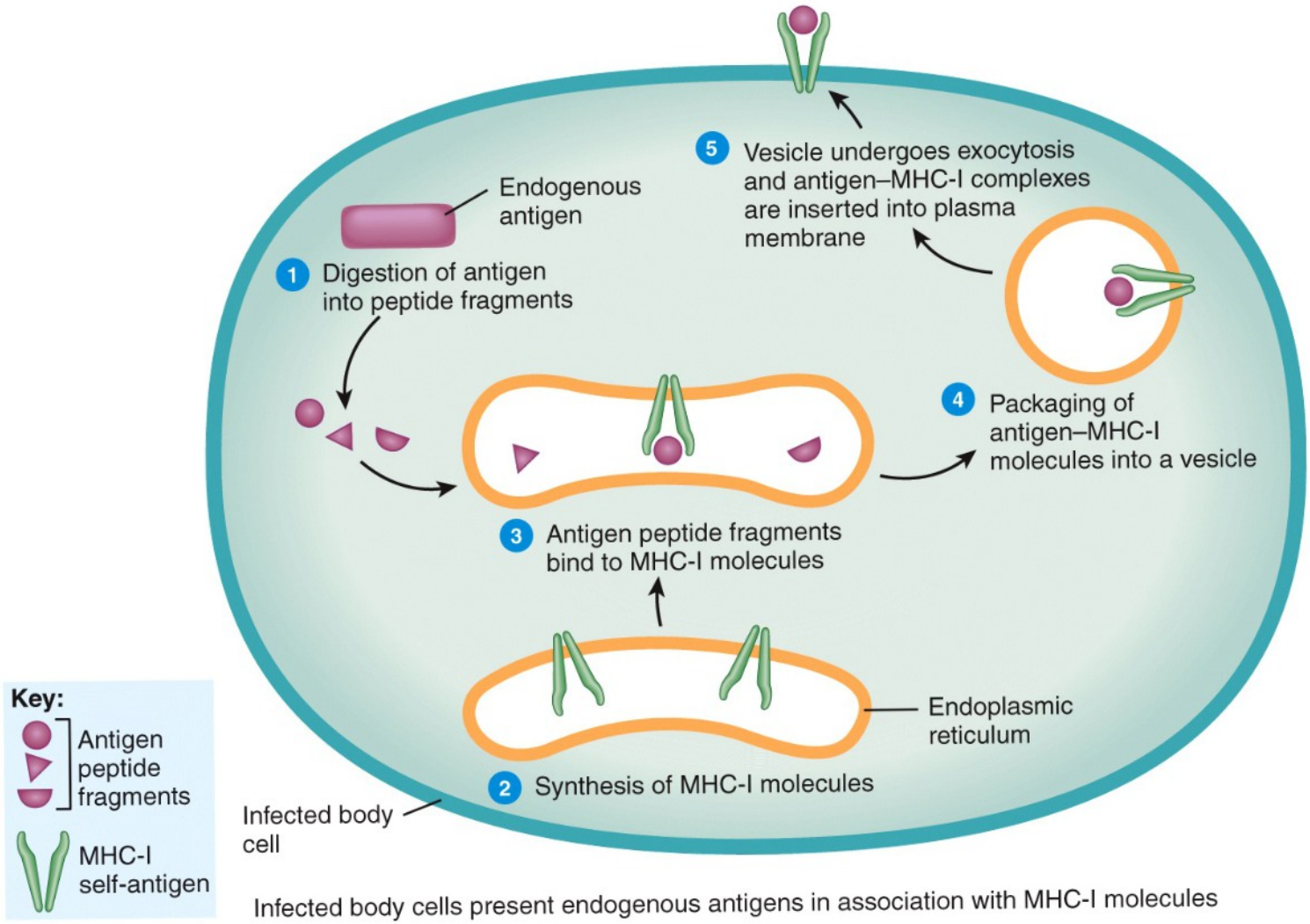
Now the c-T-cell kills the infected cell with the "kiss of death". Endogenous implies that the proteins are from the cell's cytoplasm. // Only cytotoxic T cell receptors recognize host cell's MHC-I type molecules.

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



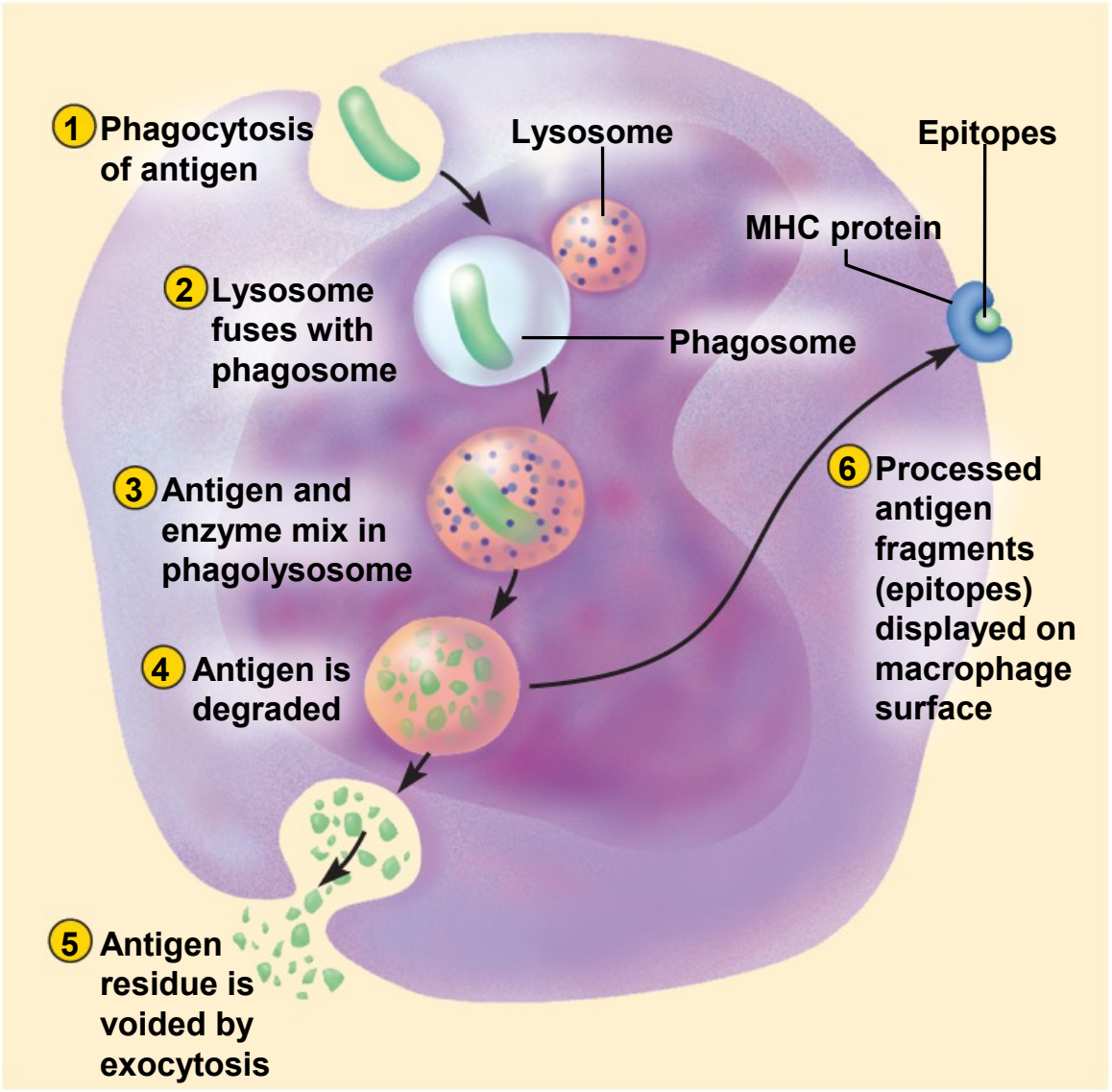
Infected body cells present endogenous antigens in association with MHC-I molecules

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



Infected body cells present endogenous antigens in association with MHC-I molecules

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

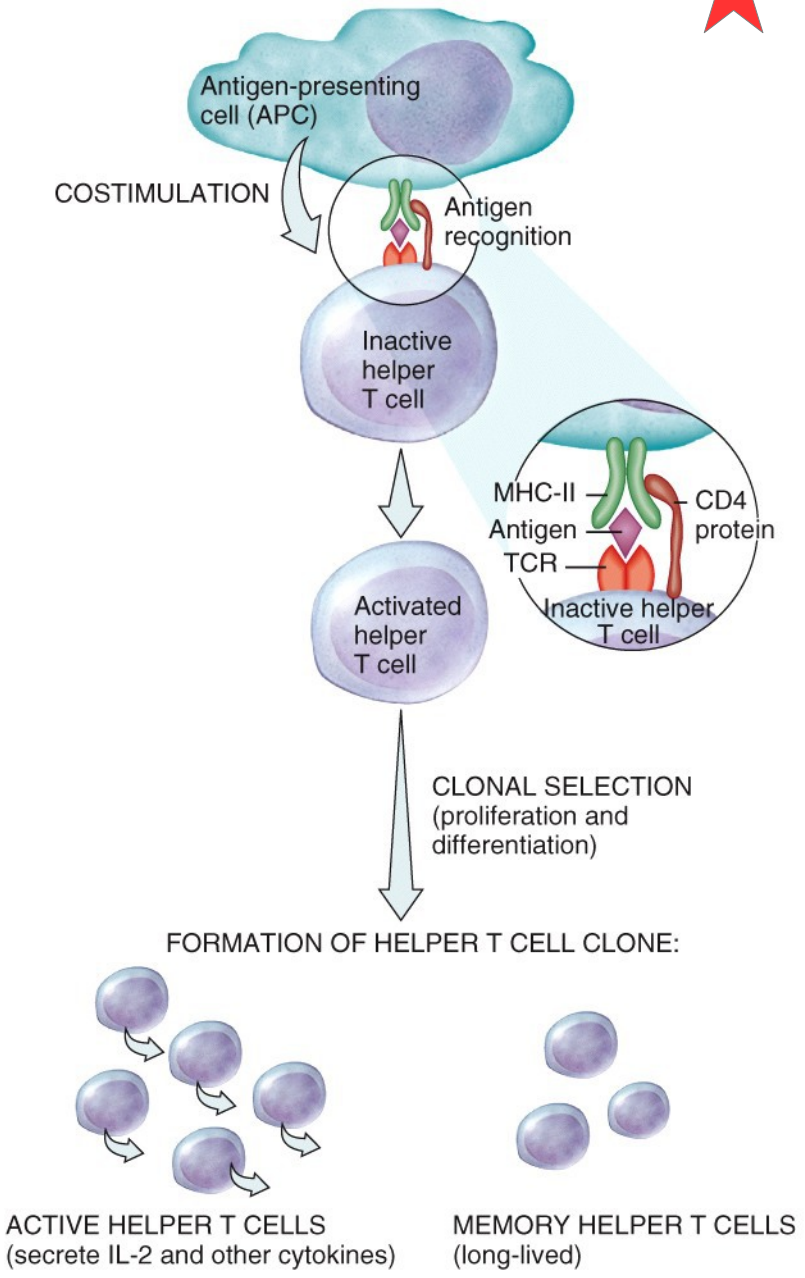
How Are hTc Activated?

Immune system must activate helper T cells using Antigen Presentation Cells // HTc have only receptors able to dock with APC with 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 cytokines also attract to area of the 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, the macrophage secretes interleukin-1 (this stimulates and activates H-Tc)

- Activated H-Tc responds by secreting interleukin-2 // interleukin-2 stimulates macrophage to secrete more inerleukin-1 /// this creates positive feedback loop /// macrophage continues to secretes more interleukin-1 /// ***this is a key step in the overall activation of acquired immunity***

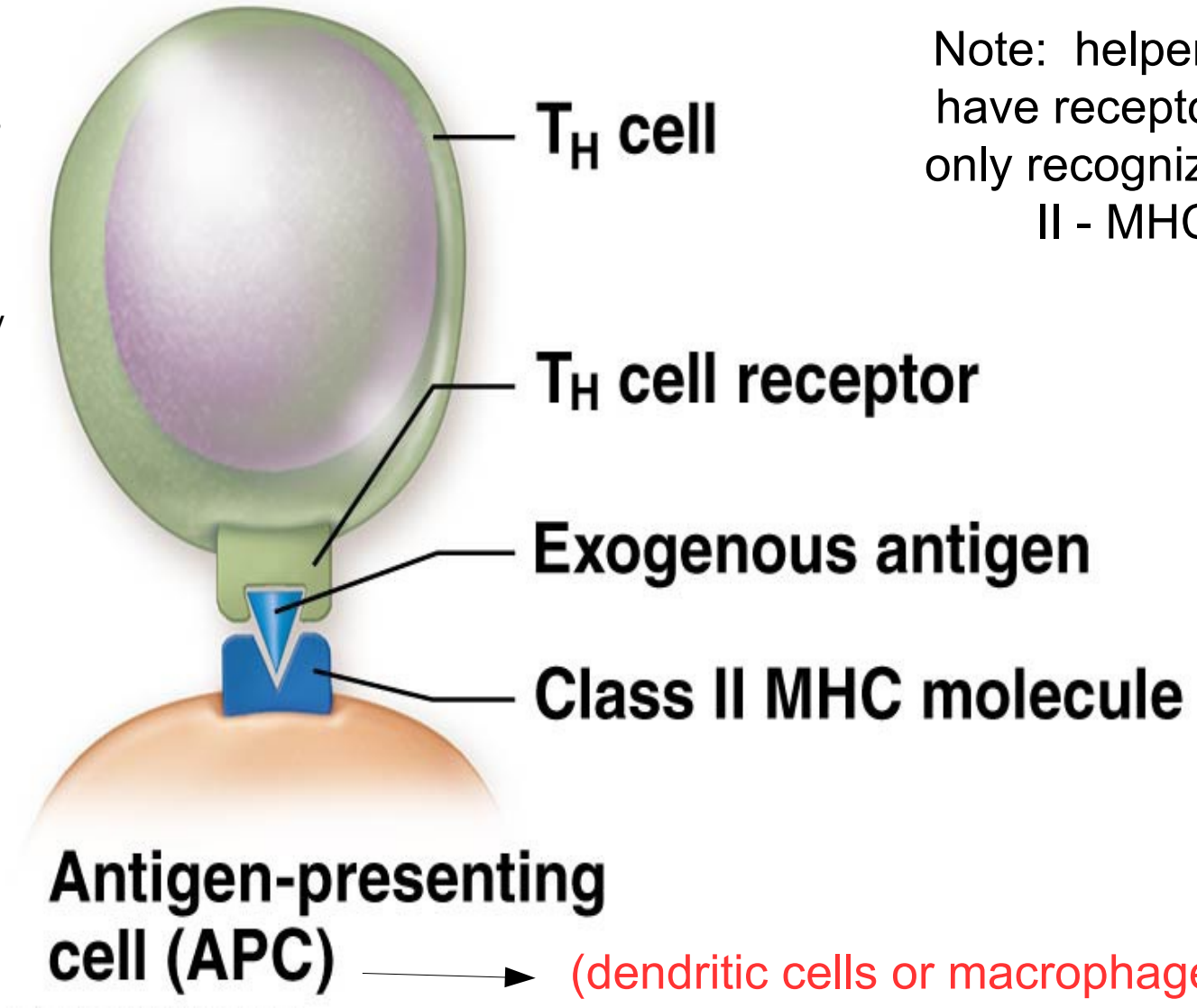
- Activated Helper T Cells now themselves undergoes clonal selection /// H-Tc continues to secrete interleukin-2 with following outcomes.....

  - 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, more 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

(dendritic cells or macrophage display class-II)

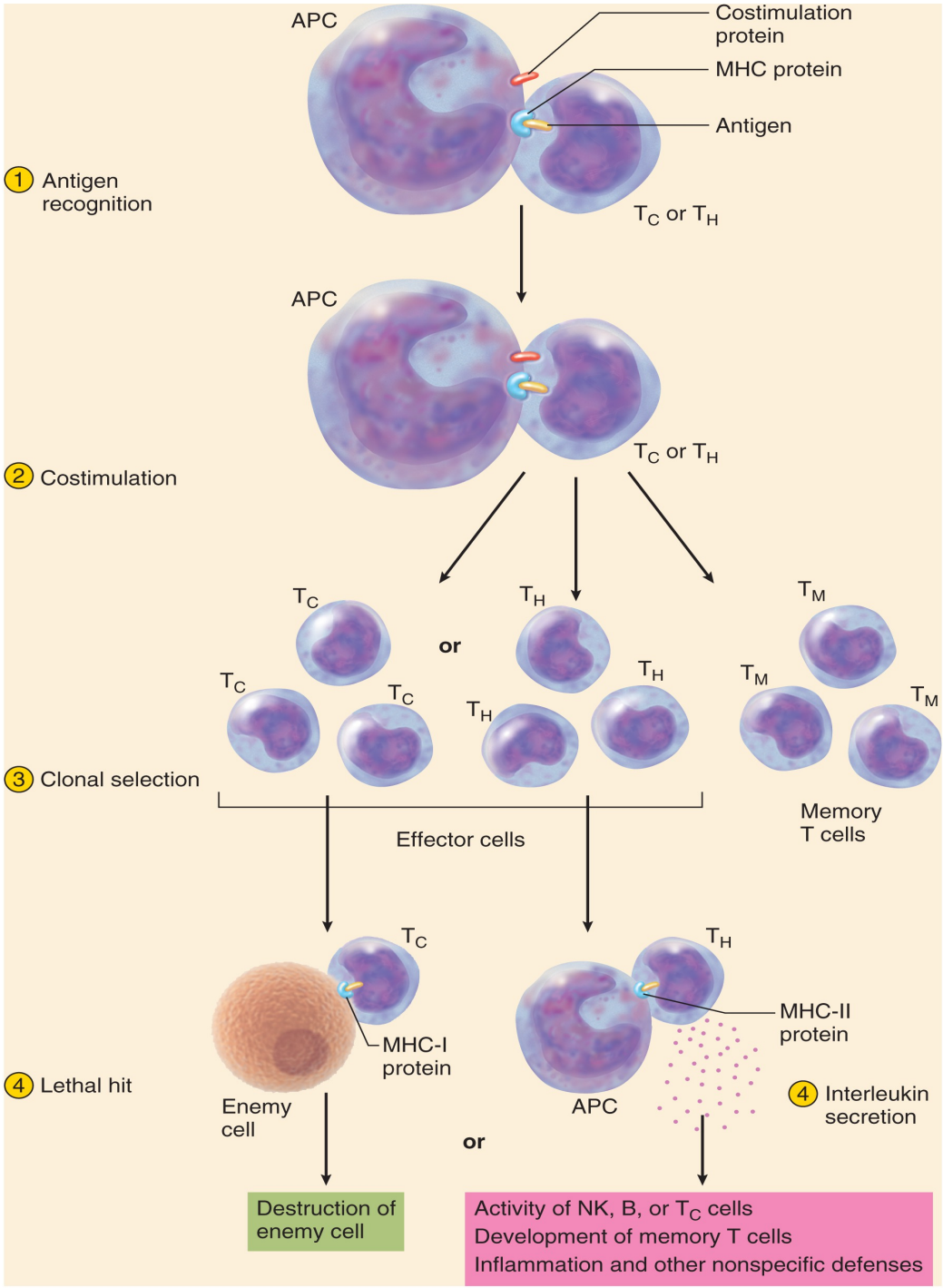
Activation of Cytotoxic T Cells

- 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)

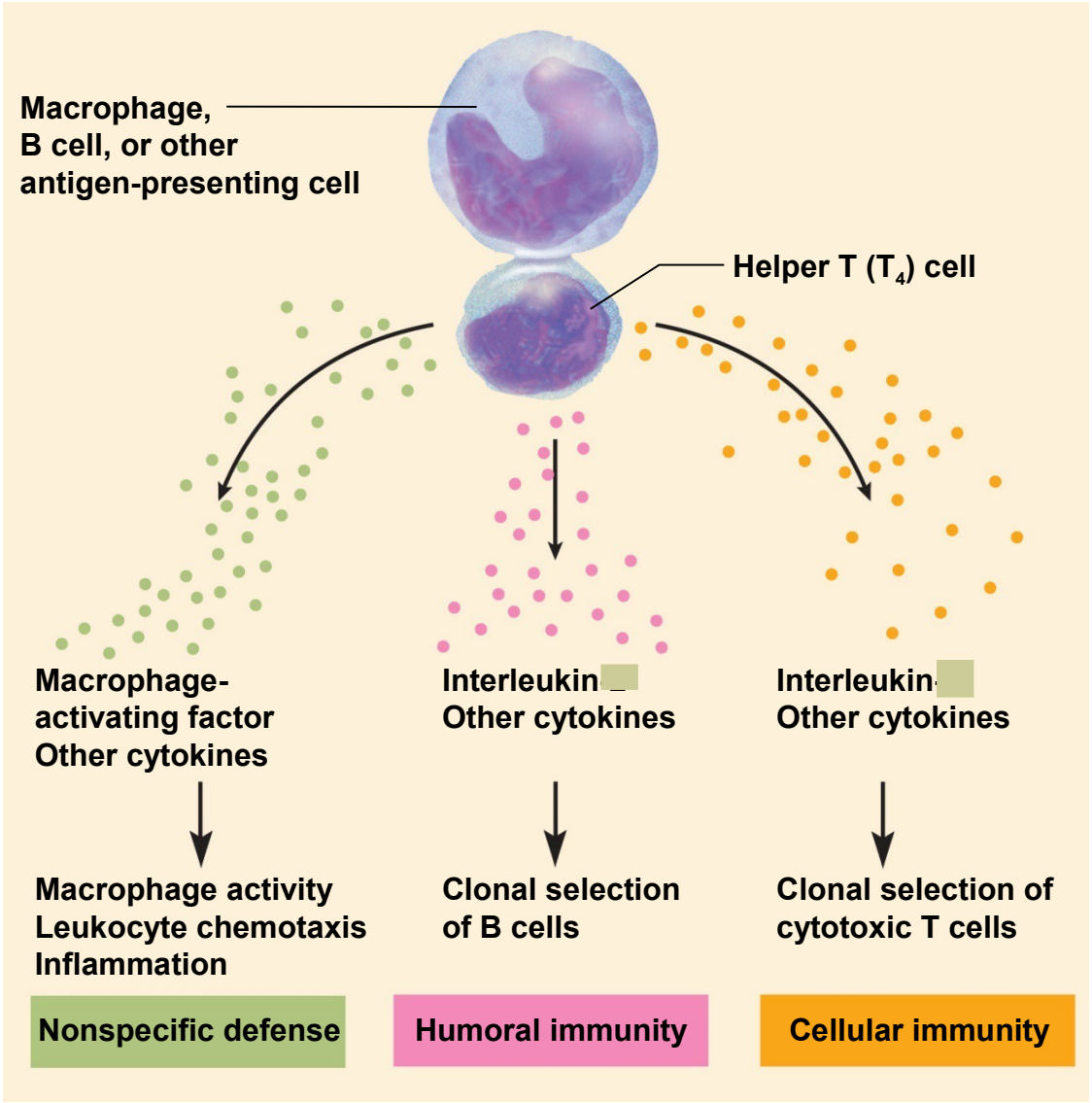
- Note CD8 protein on T cell binds to dendritic cell costimulation protein = "second check" for proper MHC-I receptor complex = costimulation

- Now cytotoxic T cell (Tc) starts clonal selection and at same time makes memory Tc

- Clonal selection make "attack" cytotoxic T cells /// These cytotoxic celsl = 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 Immunity



Helper T Cells are required to activate humoral and cellular immunity

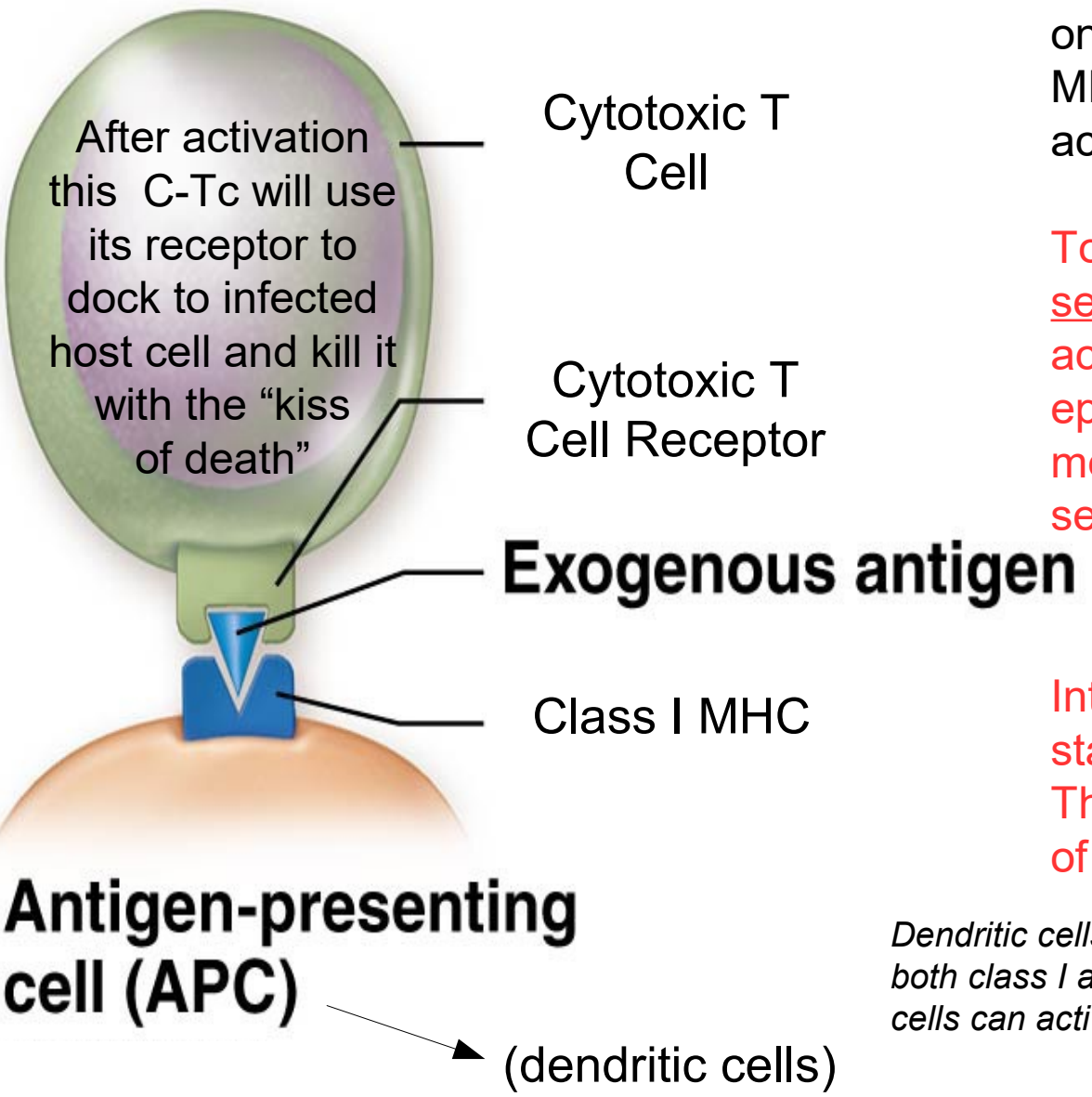
Helper T cells are also required to initiate nonspecific defenses

TH Cells release cytokines that increase the activity of macophage, leukocyte chemotaxis and inflammation.

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

What is left?

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



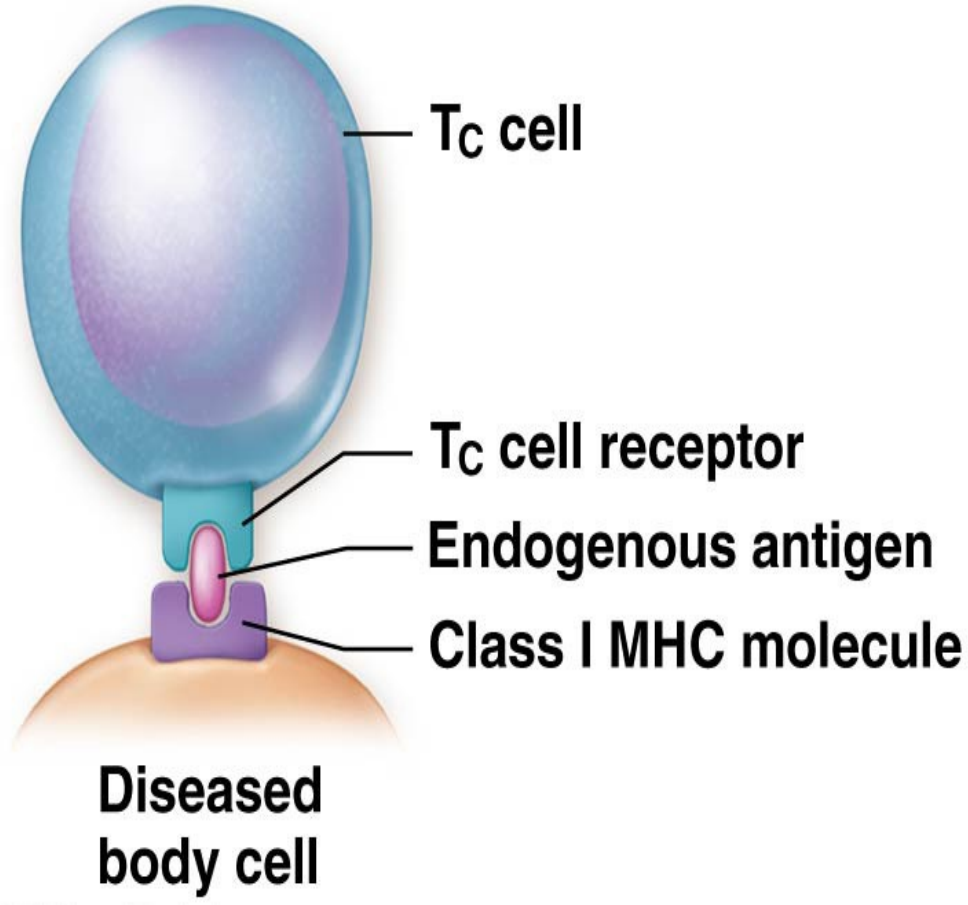
Naive C-Tcells receptors only recognize class I-MHCP // must be activated by dendritic cell

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 // This 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

Activated cytotoxic T cell may now dock to infected host cells that display Pathogen's epitope in class 1 MHCP



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

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

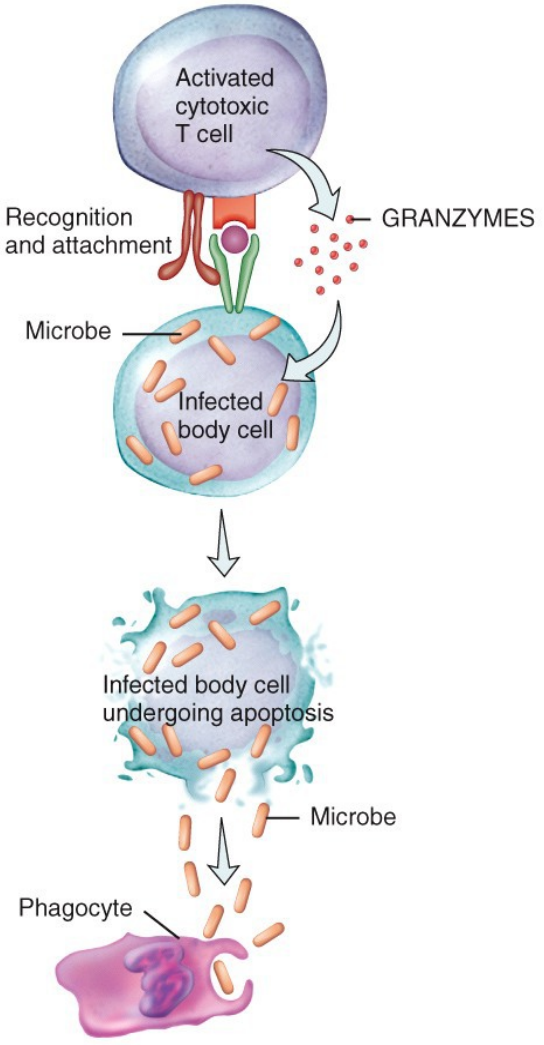
Endogenous means these proteins are from the host cells' cytoplasm

The Kiss of Death Delivered by the Cytotoxic T Cells

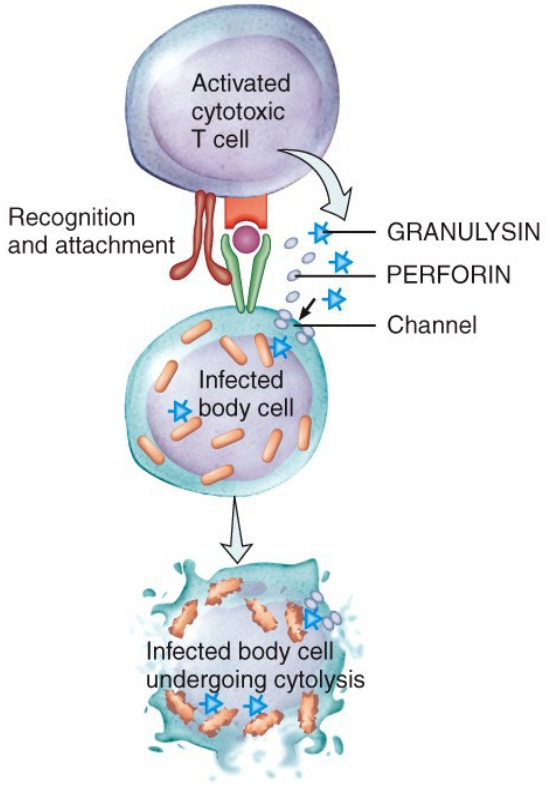
This is the react stage of the “three R”

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

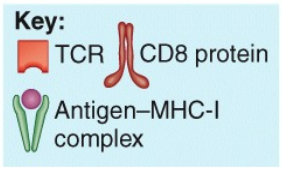
There is also a third way for C-Tc to kill host cells /// releasing massive amounts of cytokines (e.g. cytokine storm)



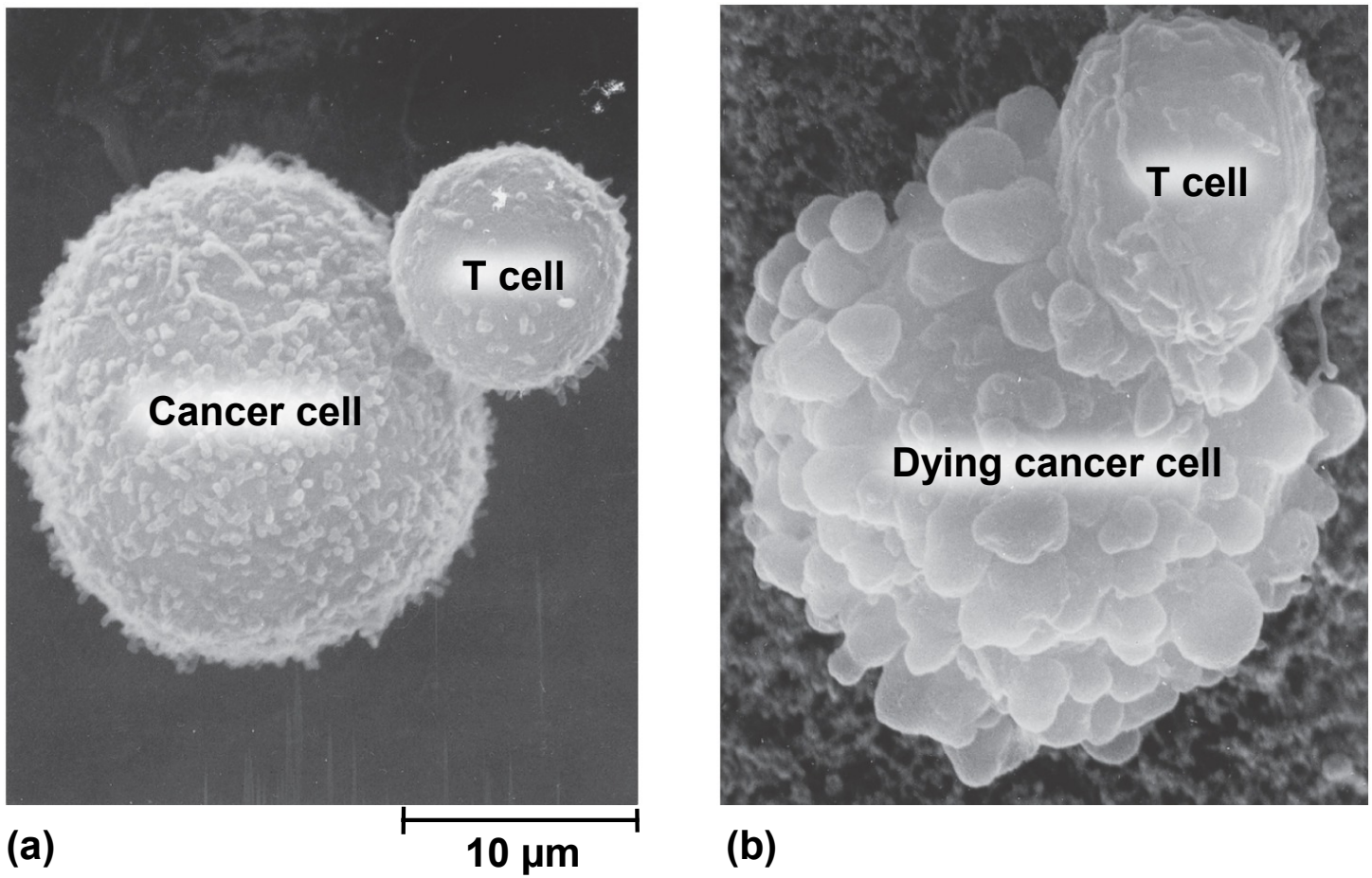
(a) Cytotoxic T cell destruction of infected cell by release of granzymes that cause apoptosis; released microbes are destroyed by phagocyte



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



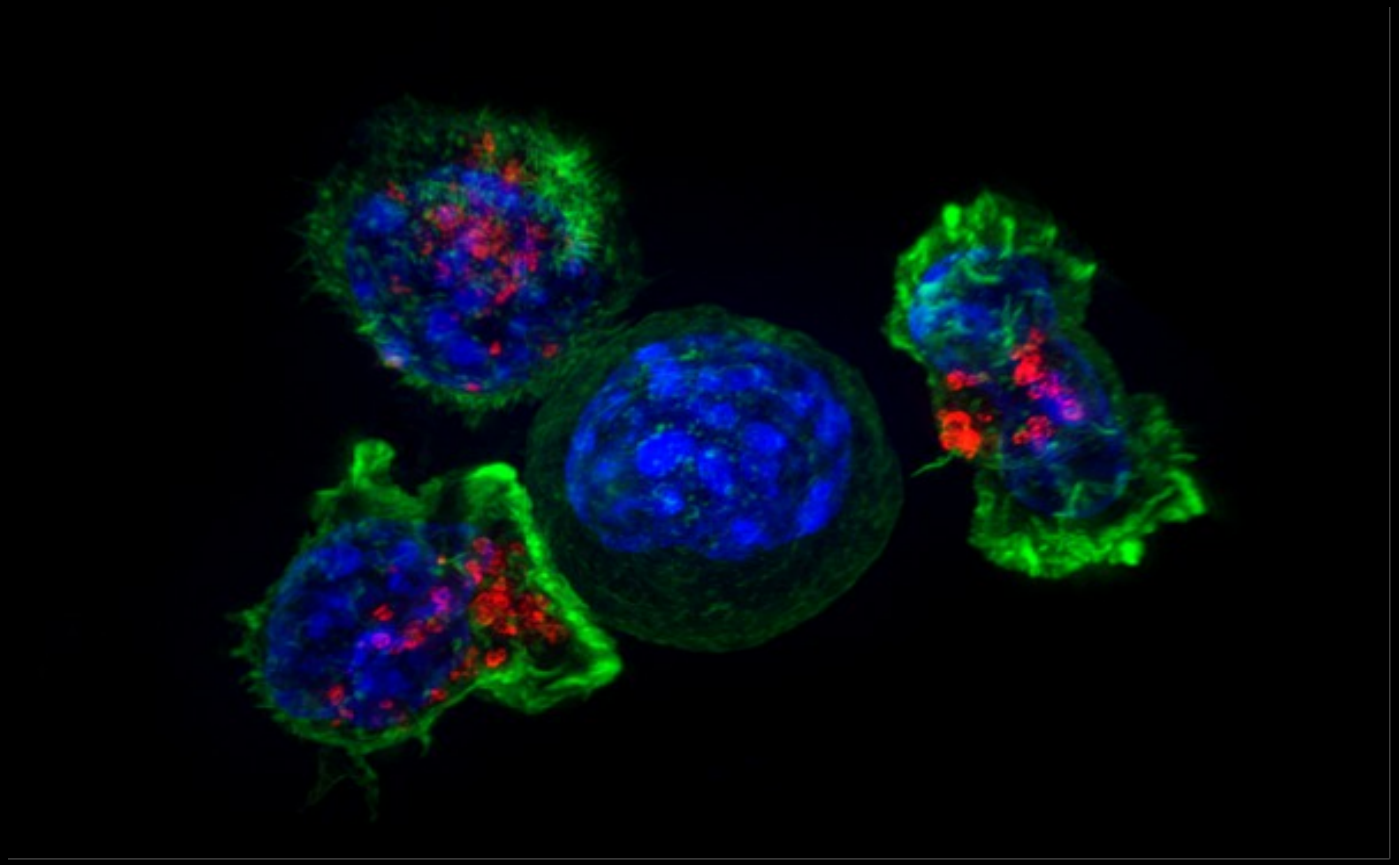
Cytotoxic T Cell Function



Dr. Andrejs Liepins

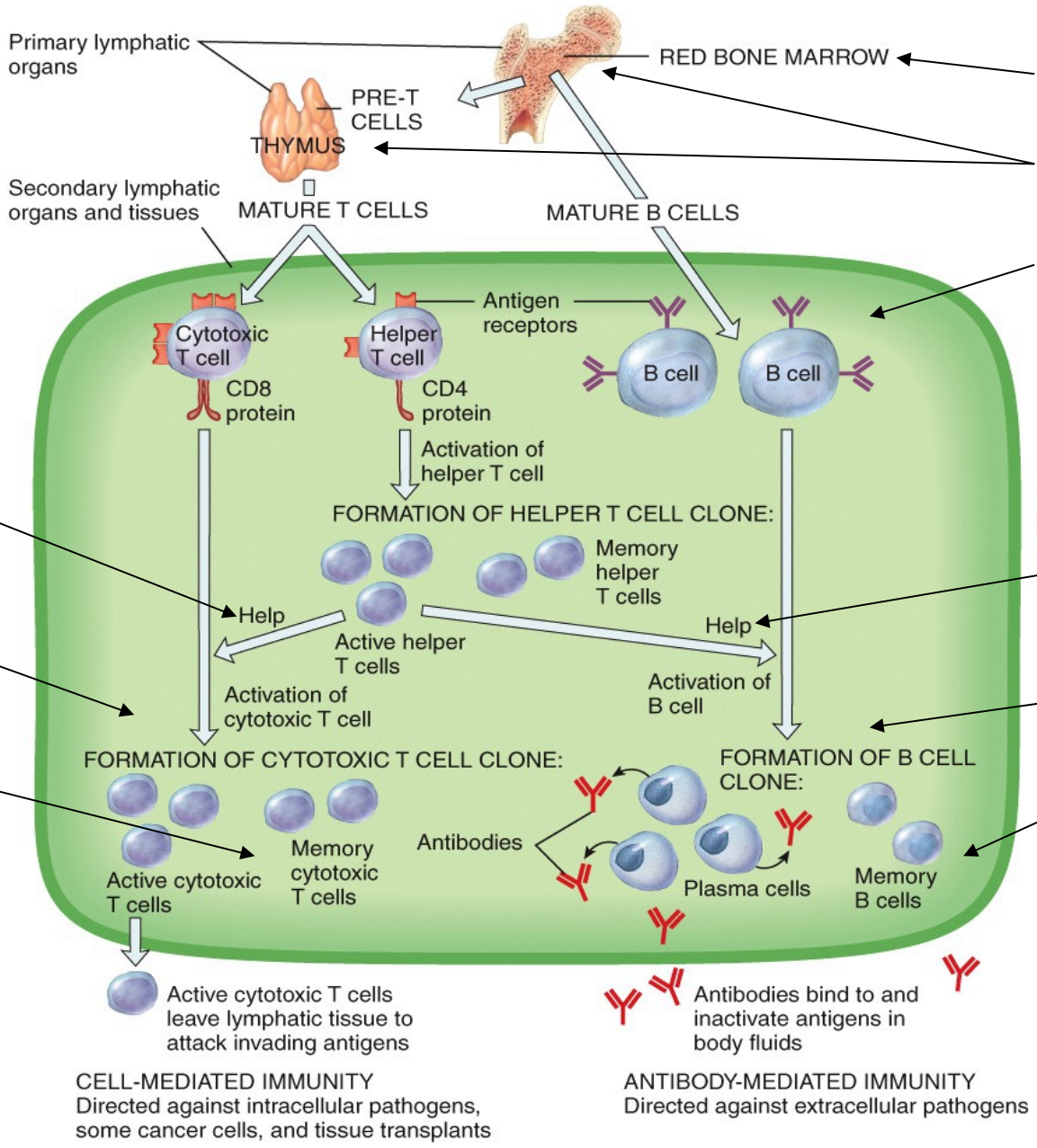
- cytotoxic T cell binding to cancer cell

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.



Born

Educated

Deployed

(Deployed as naive immunocompetent cells)

ACTIVATE To

Recognize

React

Remember

Recognize

React

Remember

How are B cells activated?

Humoral immunity requires the action of B cells

There are different classes of B cells (plasma cells, memory B cells, regulatory B cells)

Each class has a special function

*B cells change into plasma cells /// P**lasma cells that make antibodies** (not B cells) // 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

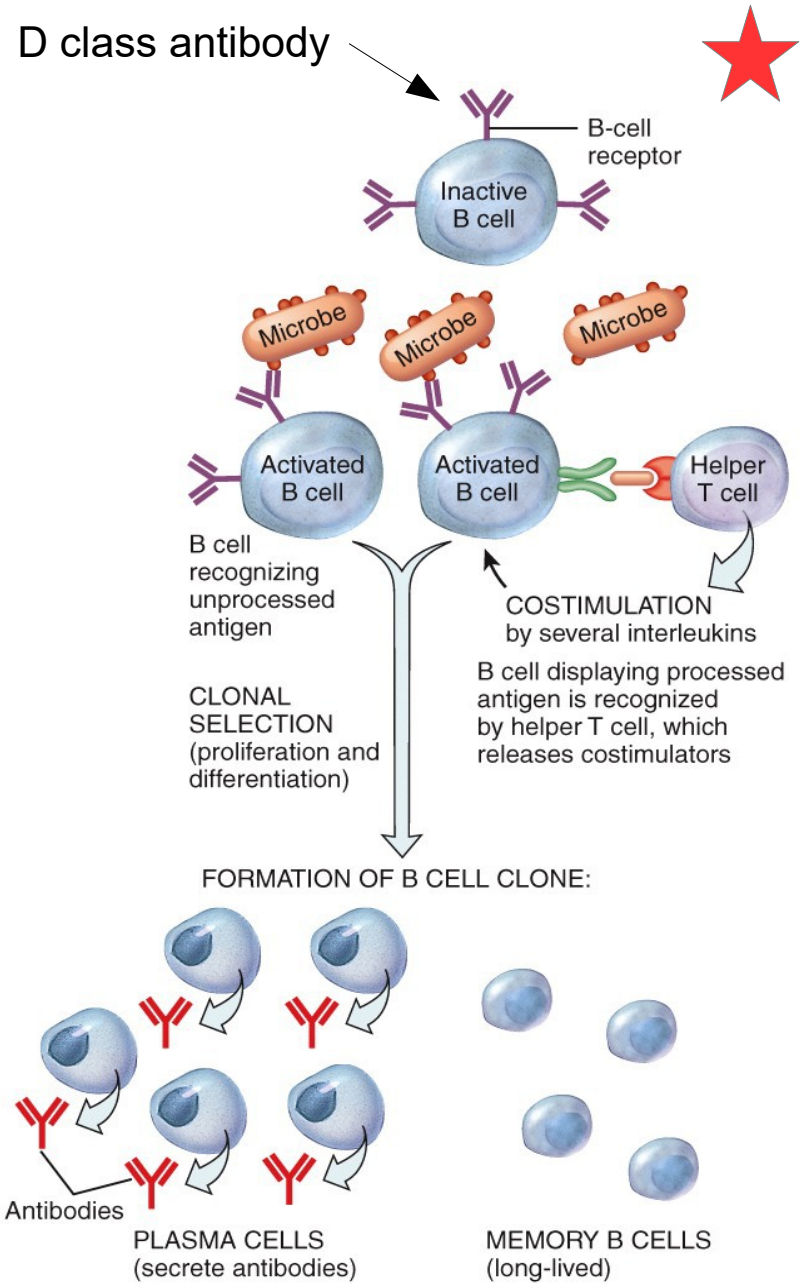
Activation of B Cells

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 selecton 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

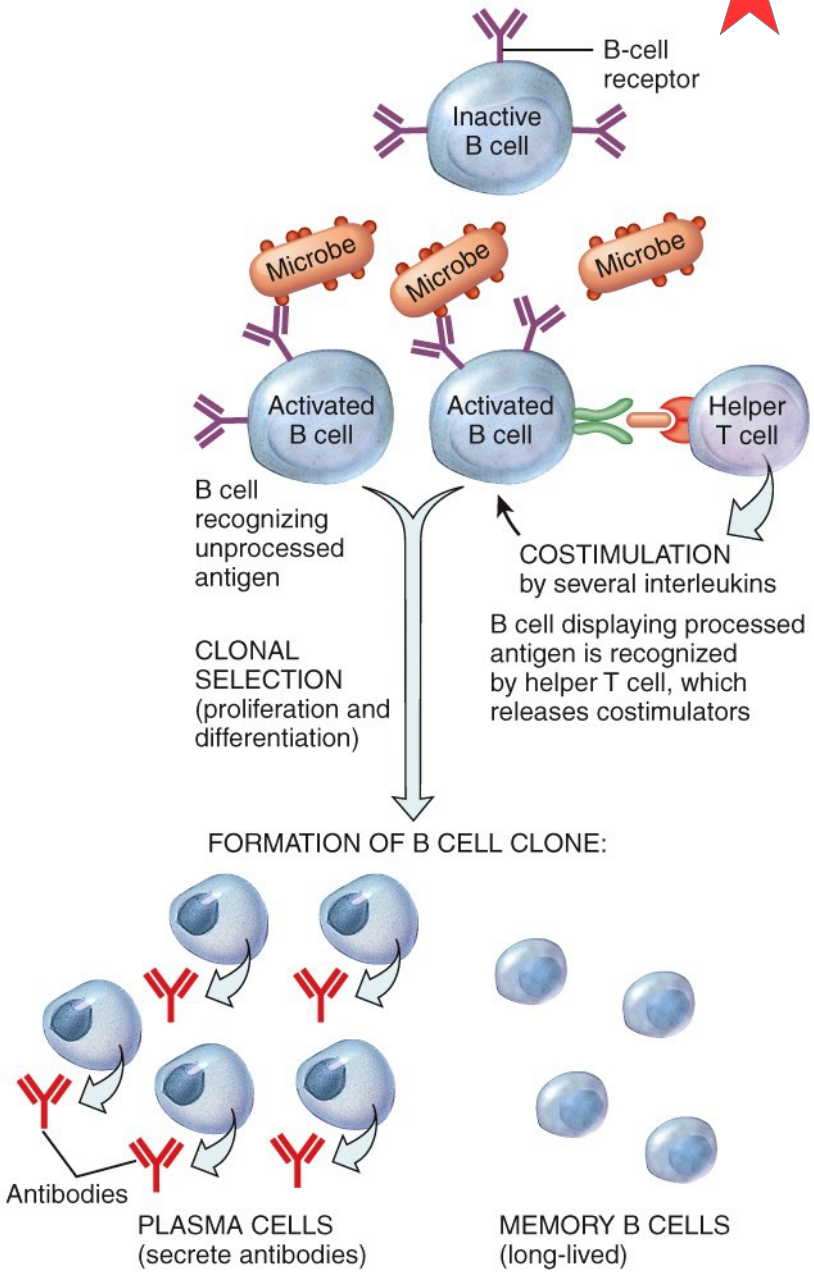
First step in “recognition” (activation) is pathogen binds to a B cell receptor.

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 ithen B celll 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? (see next slide)

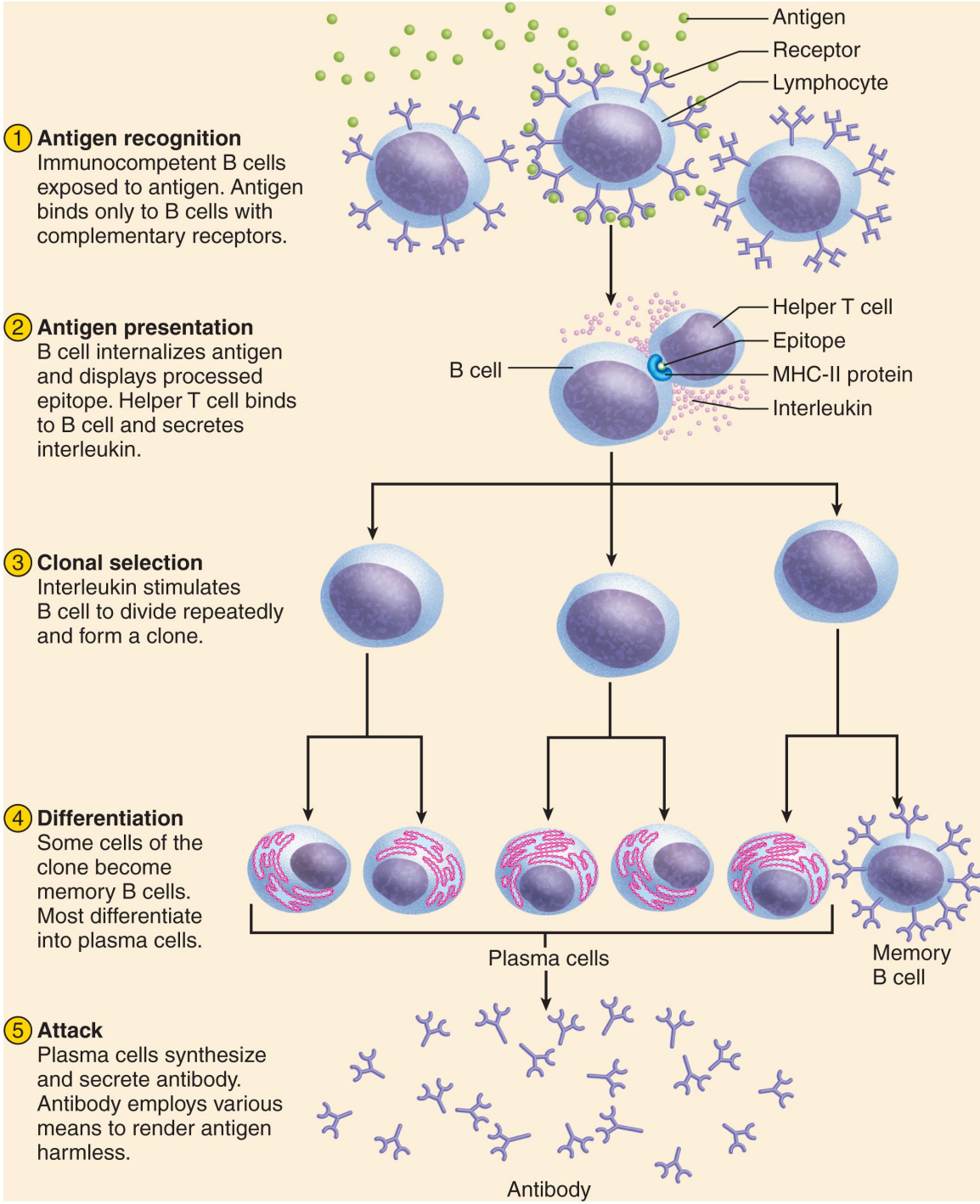
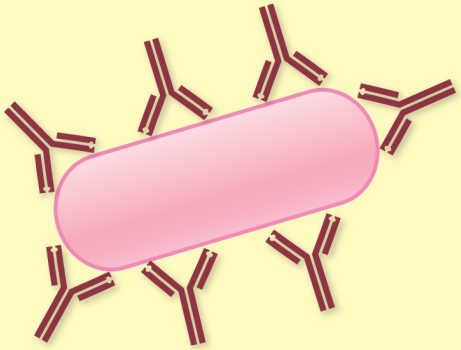
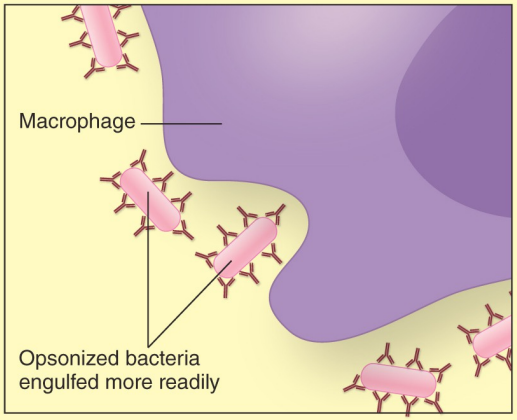


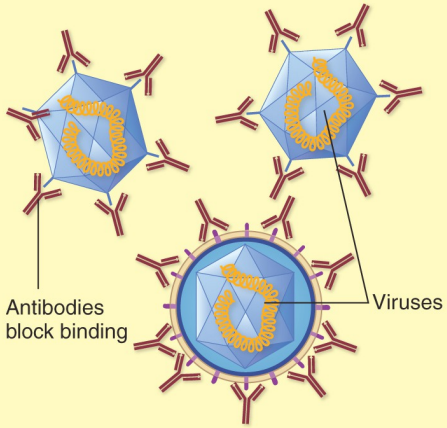
Table 13.7 Summary of Antibody Functions



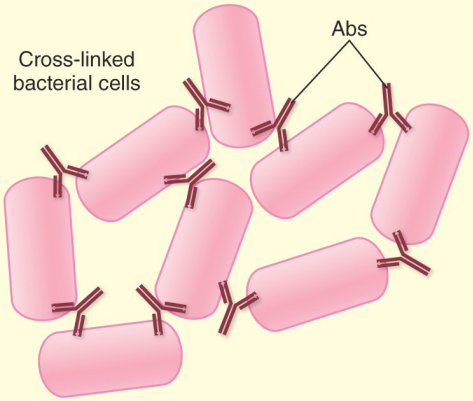
Antibodies coat the surface of a bacterium, preventing its normal function and reproduction in various ways.



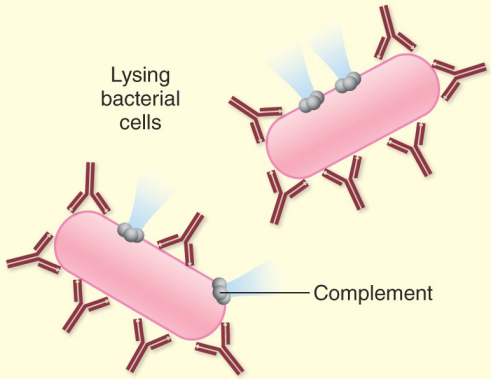
Antibodies called opsonins stimulate **opsonization** (ahp″-son-uh-zaz′-shun), a process that makes microbes more readily recognized by phagocytes, which dispose of them. Opsonization has been likened to putting handles on a slippery object to provide phagocytes a better grip.



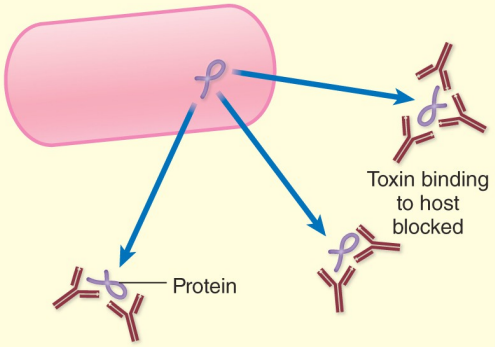
In **neutralization** reactions, antibodies fill the surface receptors on a virus or the active site on a microbial enzyme to prevent it from attaching normally.



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.

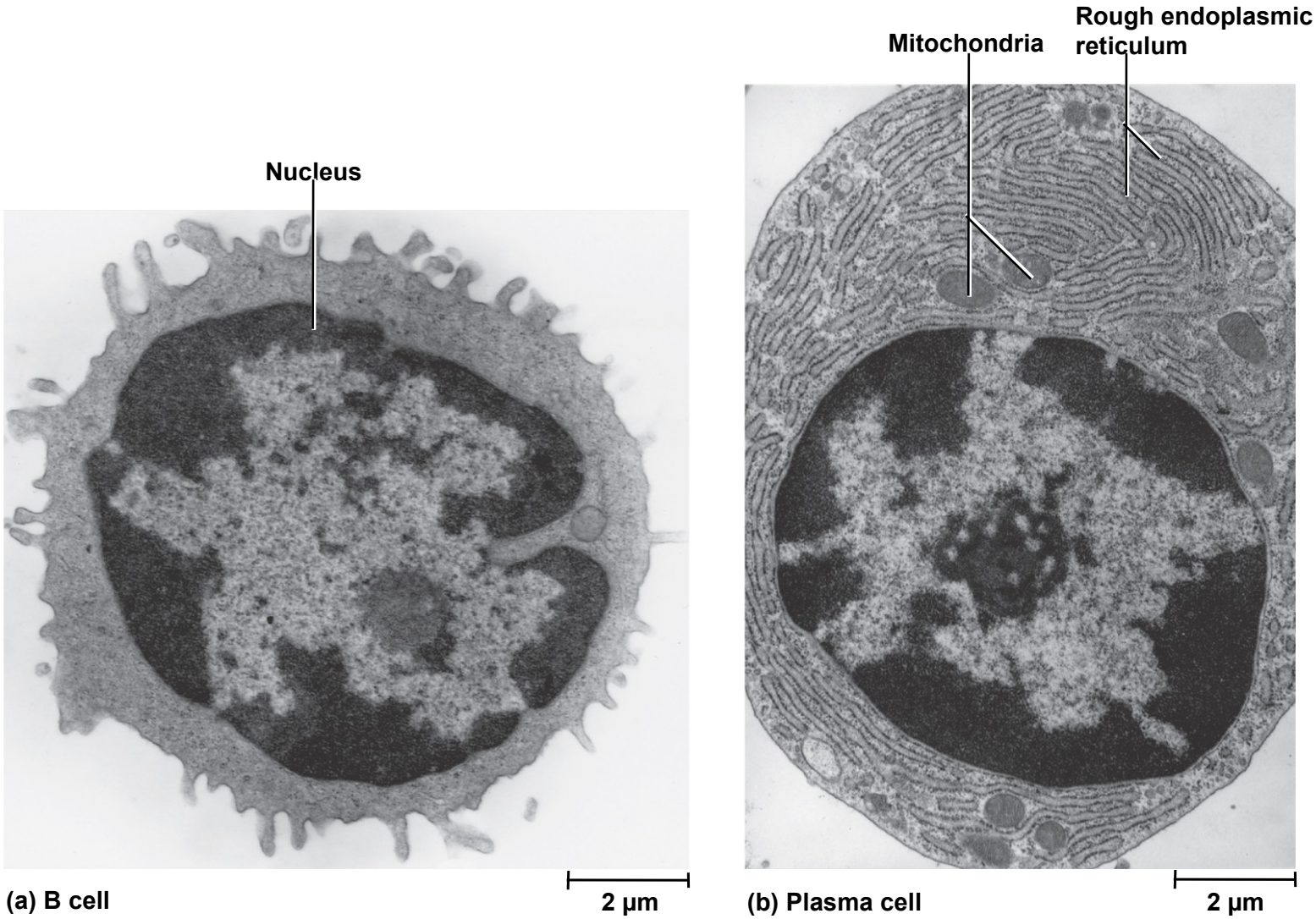


The interaction of an antibody with complement can result in the specific rupturing of cells and some viruses.



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

B cells to Plasma cells



Can you explain the structure and function relationship?

M Cells of the GI Tract

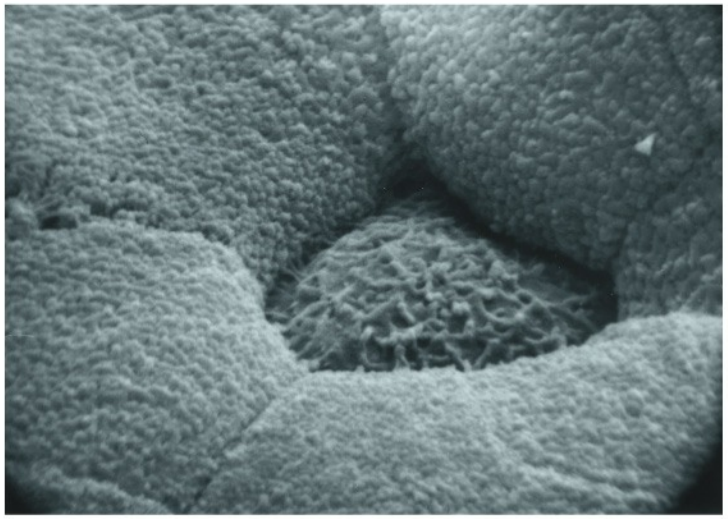
This is how immune cells try to find out (i.e. recognize) what type of pathogens may “break into” the sterile compartments of your body.

Immune system recognize bacteria before they are in our bodies

Prepare memory cell defense against bacteria.

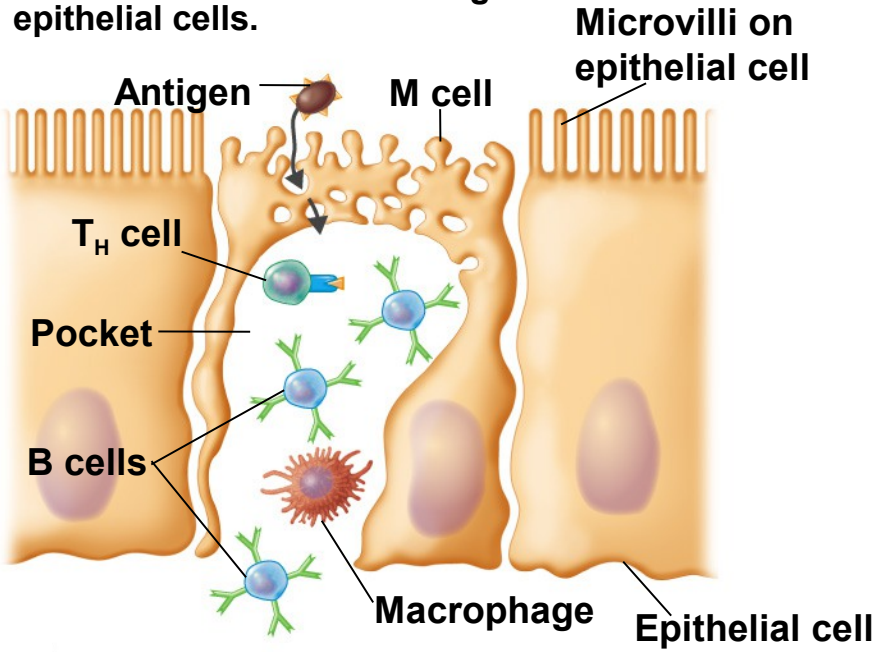
Tonsils have a similar function in bucal cavity!

SigA = secretory immunoglobin A

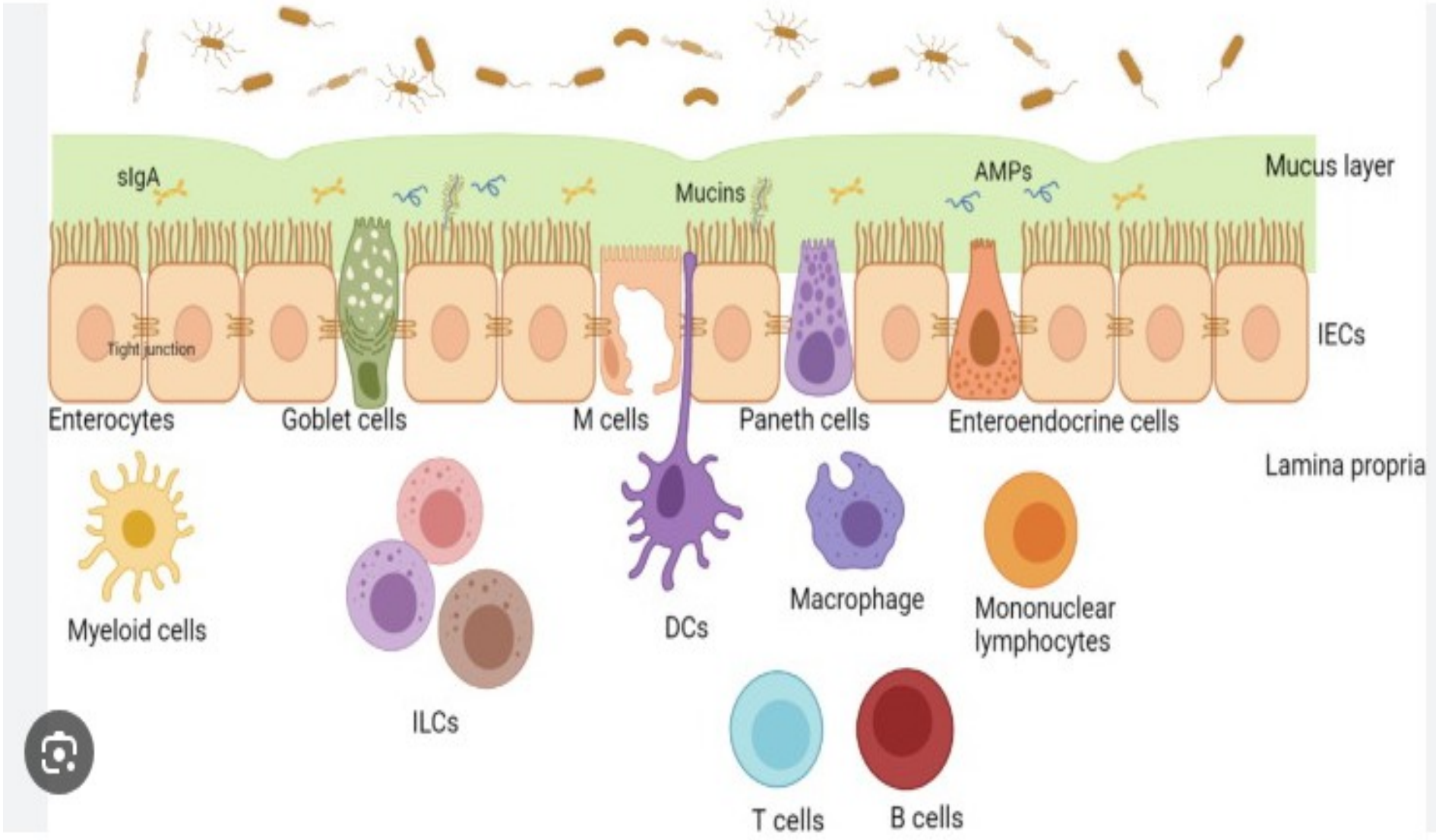


(a) M cell on Peyer’s patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells.

SEM 1 μm



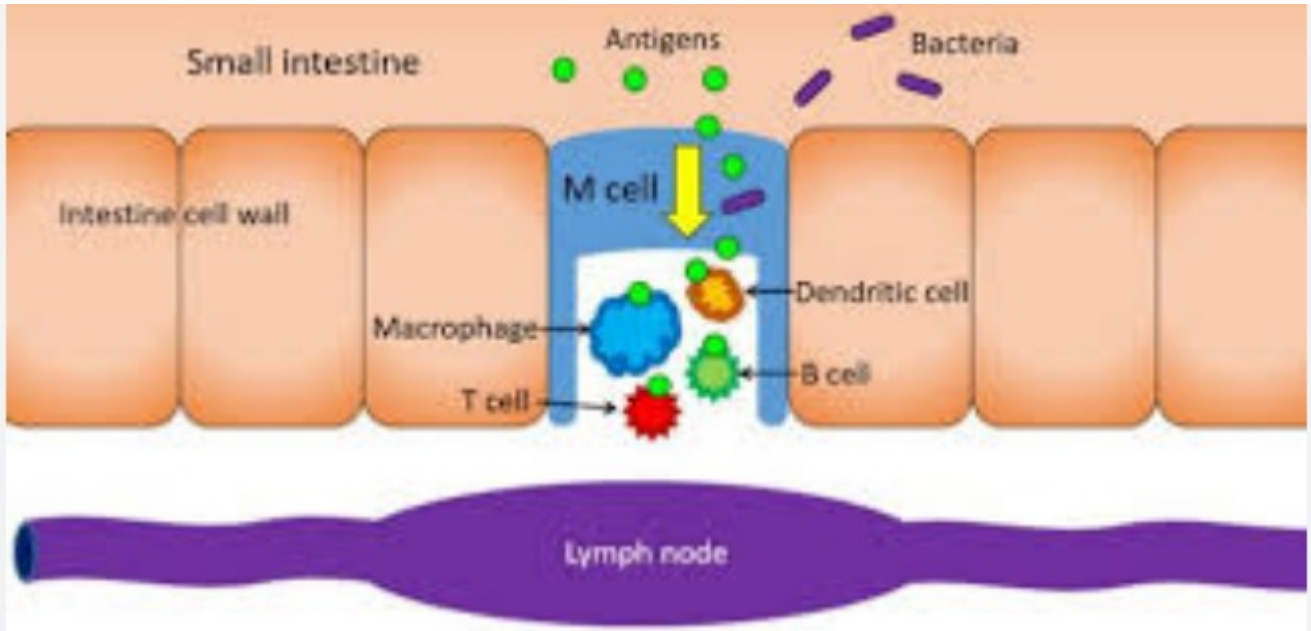
(b) M cells facilitate contact between the antigens passing through the intestinal tract and cells of the body’s immune system.

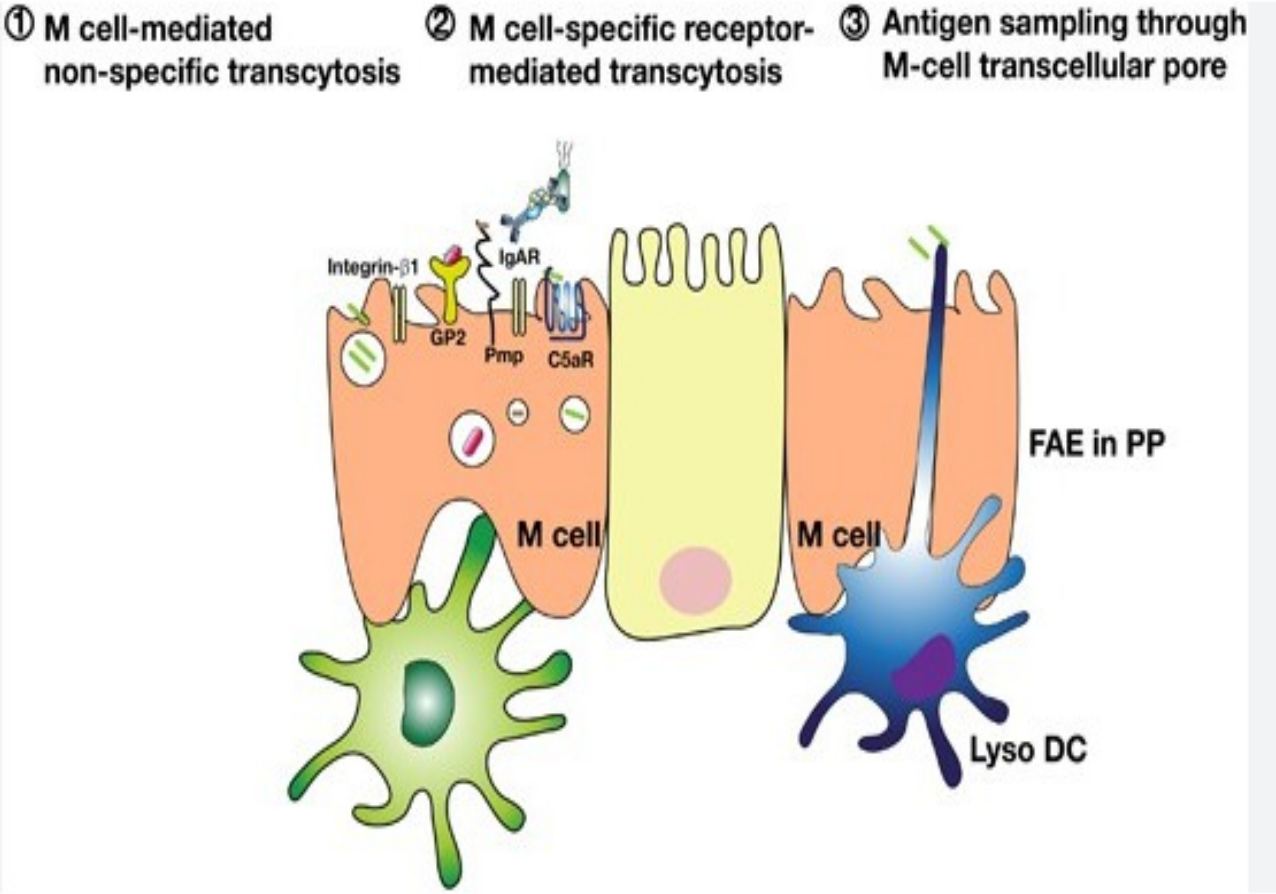


Intestinal Lumen - an overview | ScienceDirect Topics

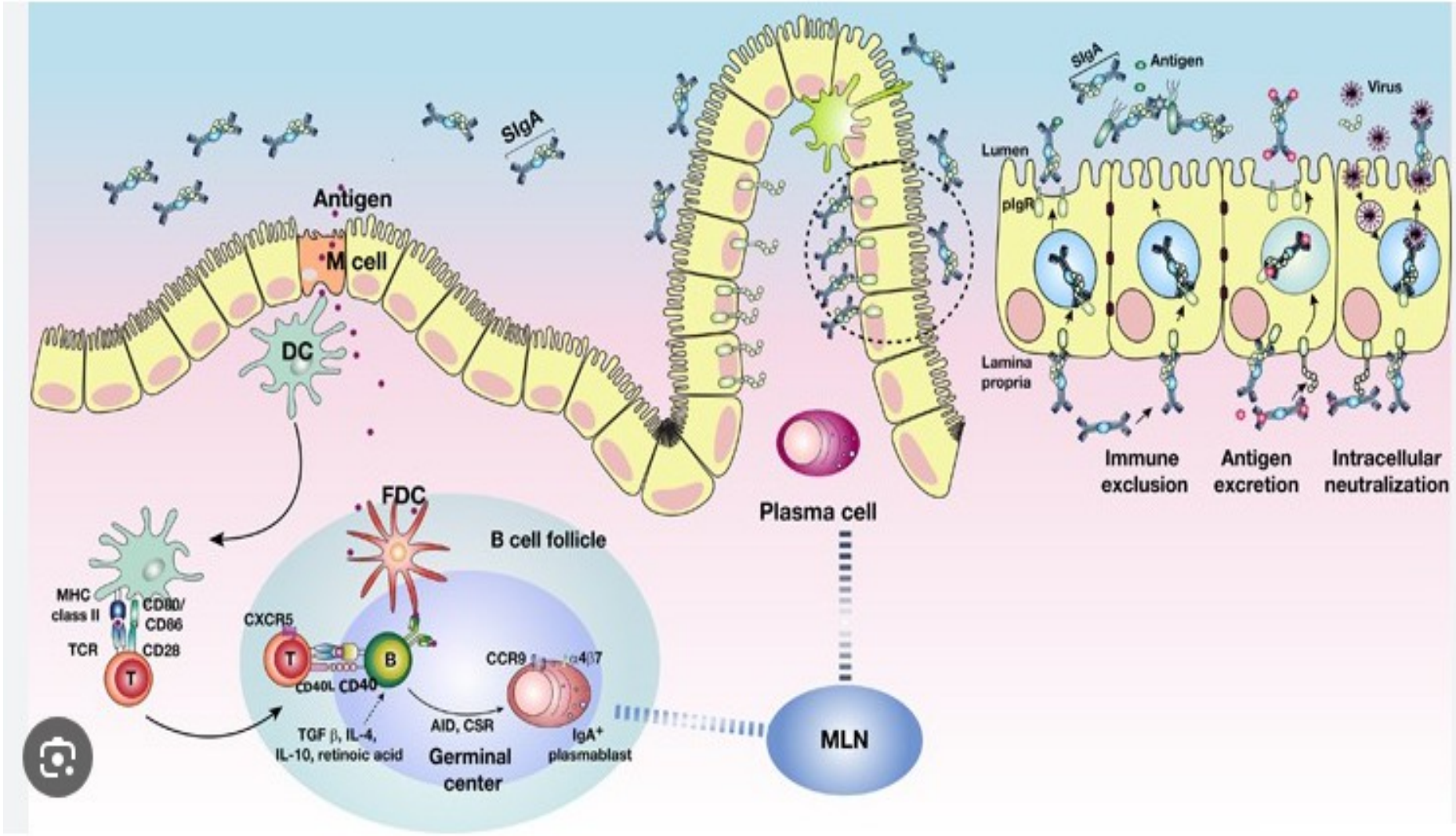
Visit ›

Note: tight junctions between epithelial cells. Function?

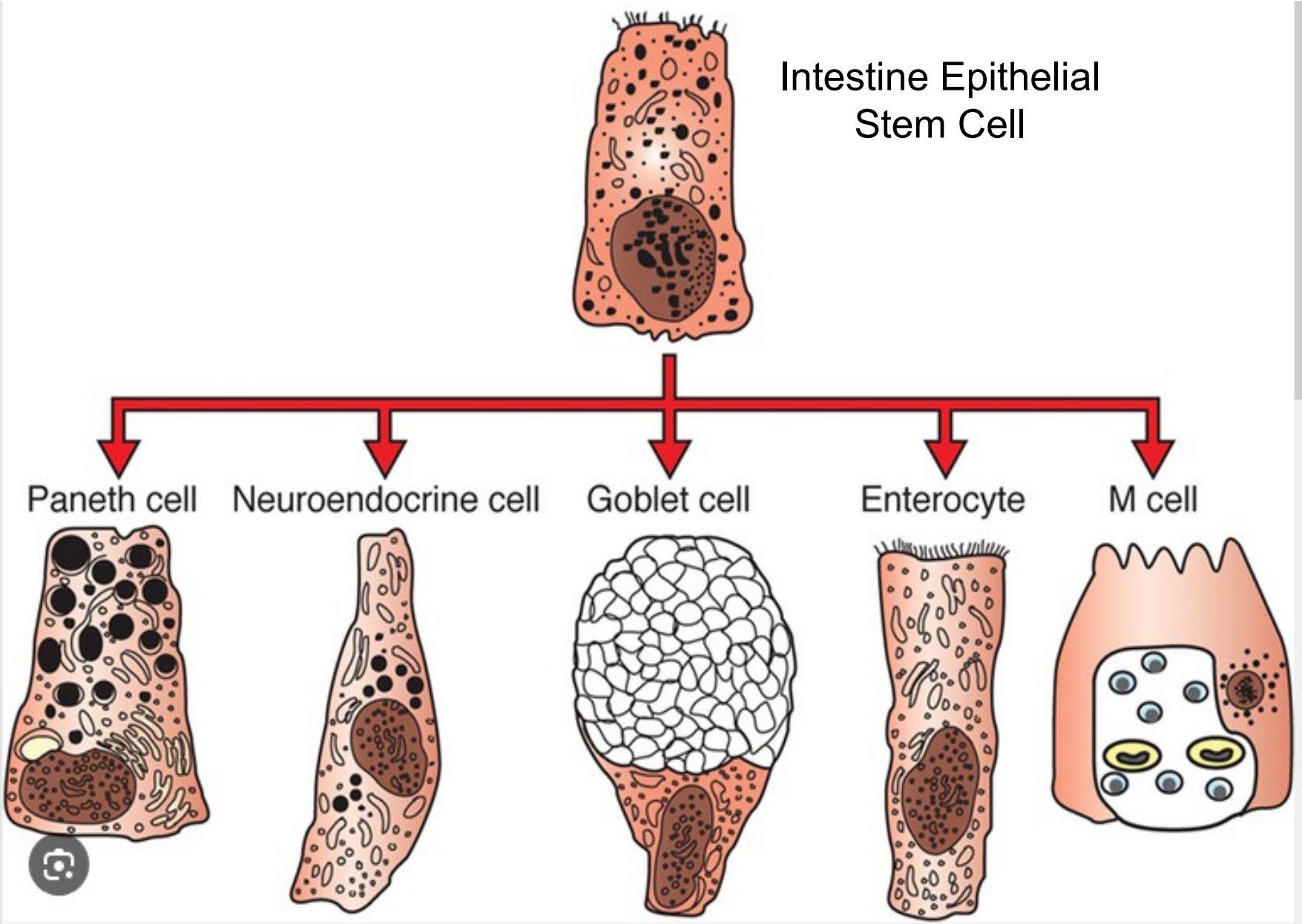

Small intestine
Antigens
Bacteria
Intestine cell wall
M cell
Dendritic cell
Macrophage
B cell
T cell
Lymph node



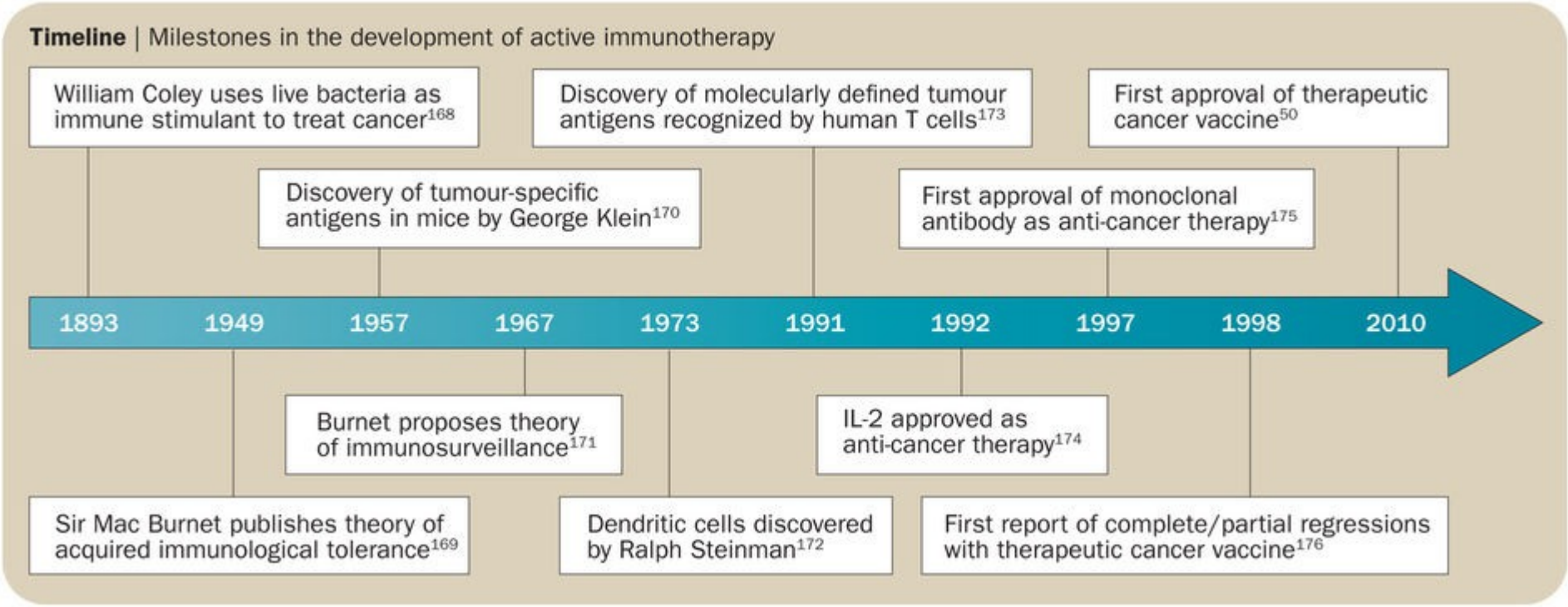
Antigen targeting to M cells for enhancing the efficacy of mucosal vaccines | Experimental & Molecular Medicine



Antigen targeting to M cells for enhancing the efficacy of mucosal vaccines | Experimental & Molecular Medicine


Intestine Epithelial Stem Cell
Paneth cell
Neuroendocrine cell
Goblet cell
Enterocyte
M cell

The History of Immune Therapy



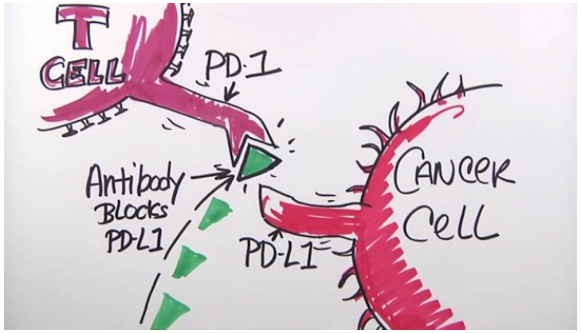
Three Immune Strategies

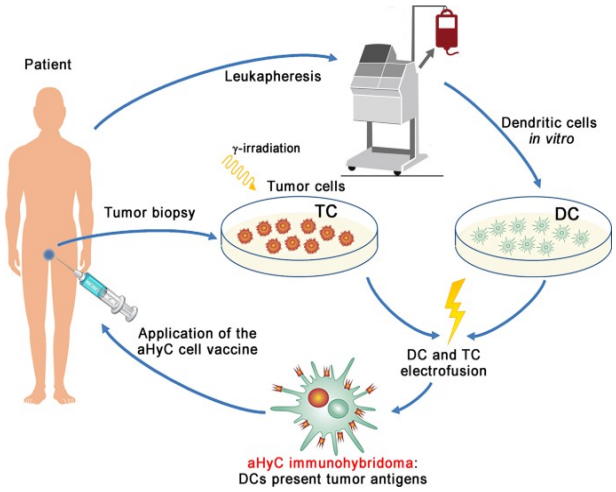
The Old Strategy was surgery, radiation or chemo-therapy // (This was never a cure. Some cancer cells always survived and eventually came back to form a new cancerous mass.)

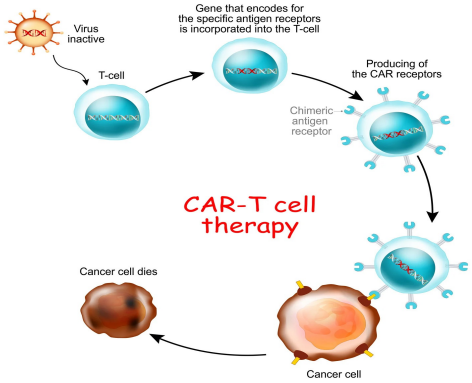
Today's New Strategy = Three Immune therapies

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

- Checkpoint Inhibitors
- Dendritic Cell Vaccine
- CAR-T Cells







How Can We Use Our Knowledge of the Immune System 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 eliminate all the cancer cells. It never provided a lasting cure.

- Today we are on the threshold of understanding how to use our cytotoxic T cells and antibodies to cure many forms of cancer.

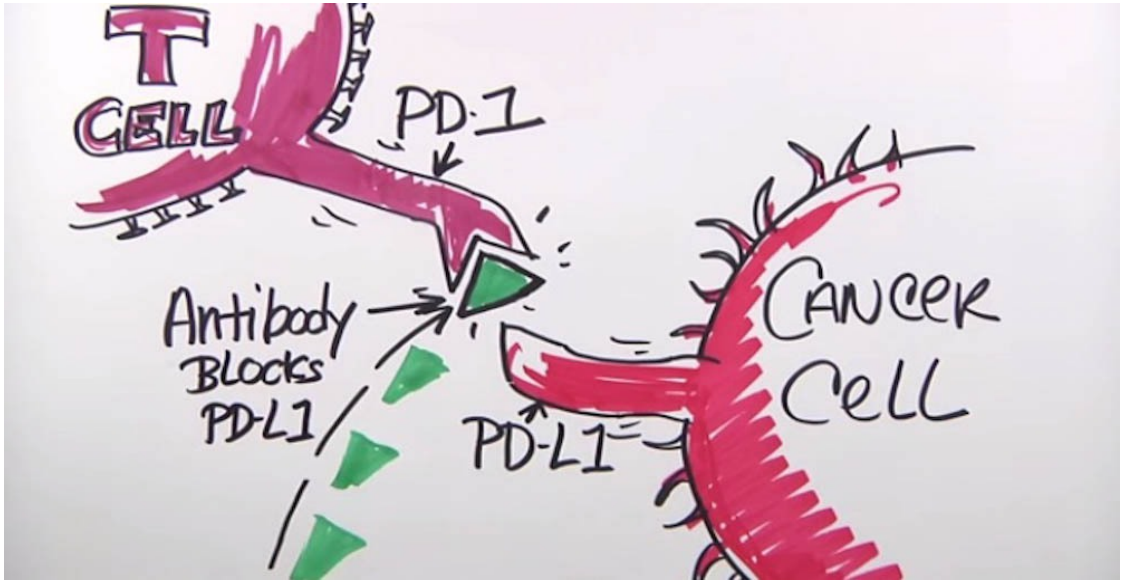
- Cancer immunotherapy is able to leverage our knowledge about the immune system to direct the immune system cells to identify “specific types of molecules only found on cancer cells” and to kill these cells. We are also able to inhibit cancer cells ability to turn off our immune cells from attacking cancerous cells.

- Immunotherapy targets and kill only cancer cells. Not healthy host 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



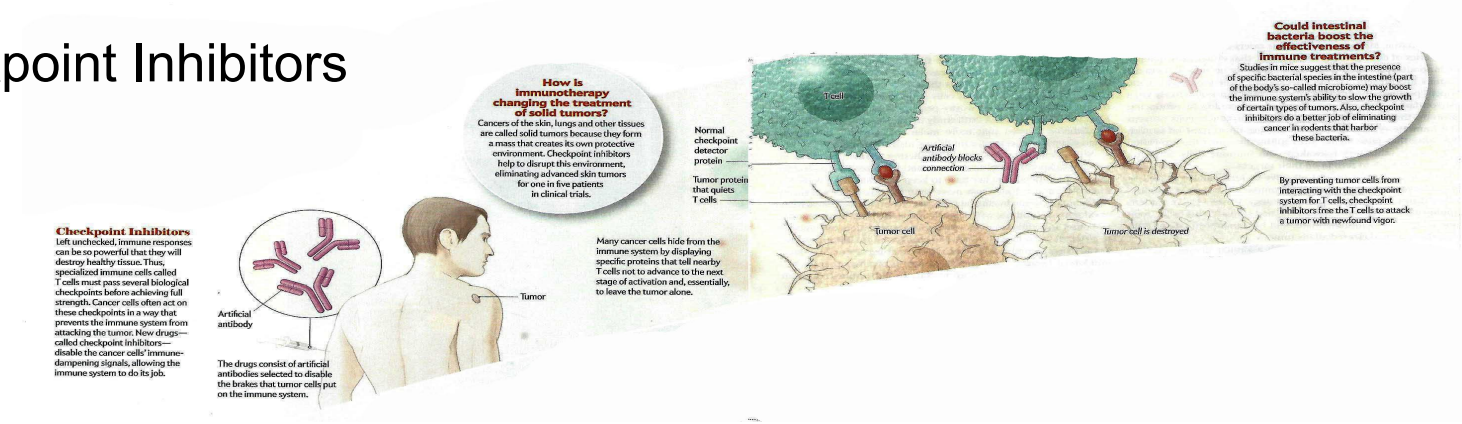
PD1 is a receptor on the T cell to inhibit the cytotoxic-Tc response (it is like a brake that our immune system's regulatory T cells may use to regulate how aggressive the cTcell response will be)

Cancer cells have evolved a ligand PD-L1 to the PD1 that protects the cancer cell from the cTcell attacking the cancer cell.

Checkpoint inhibitors are monoclonal made antibodies used to mask either the PD1 site, PD-L1, or both.

Now the cTcell is able to freely attack the cancer cell.

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.

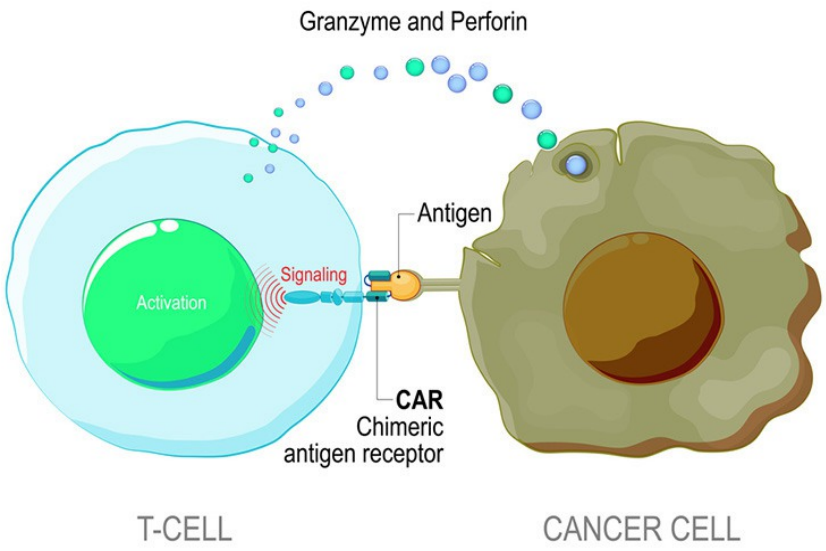
New drugs called checkpoint inhibitors, disable the cancer's immune dampening signals to allow the immune system to do its job. Checkpoint inhibitors are “designed antibodies” made to disable the “T cell checkpoint” that tumor cells use to suppress our immune response to cancer.

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% of early clinical trials. Current therapy outcomes are even higher.

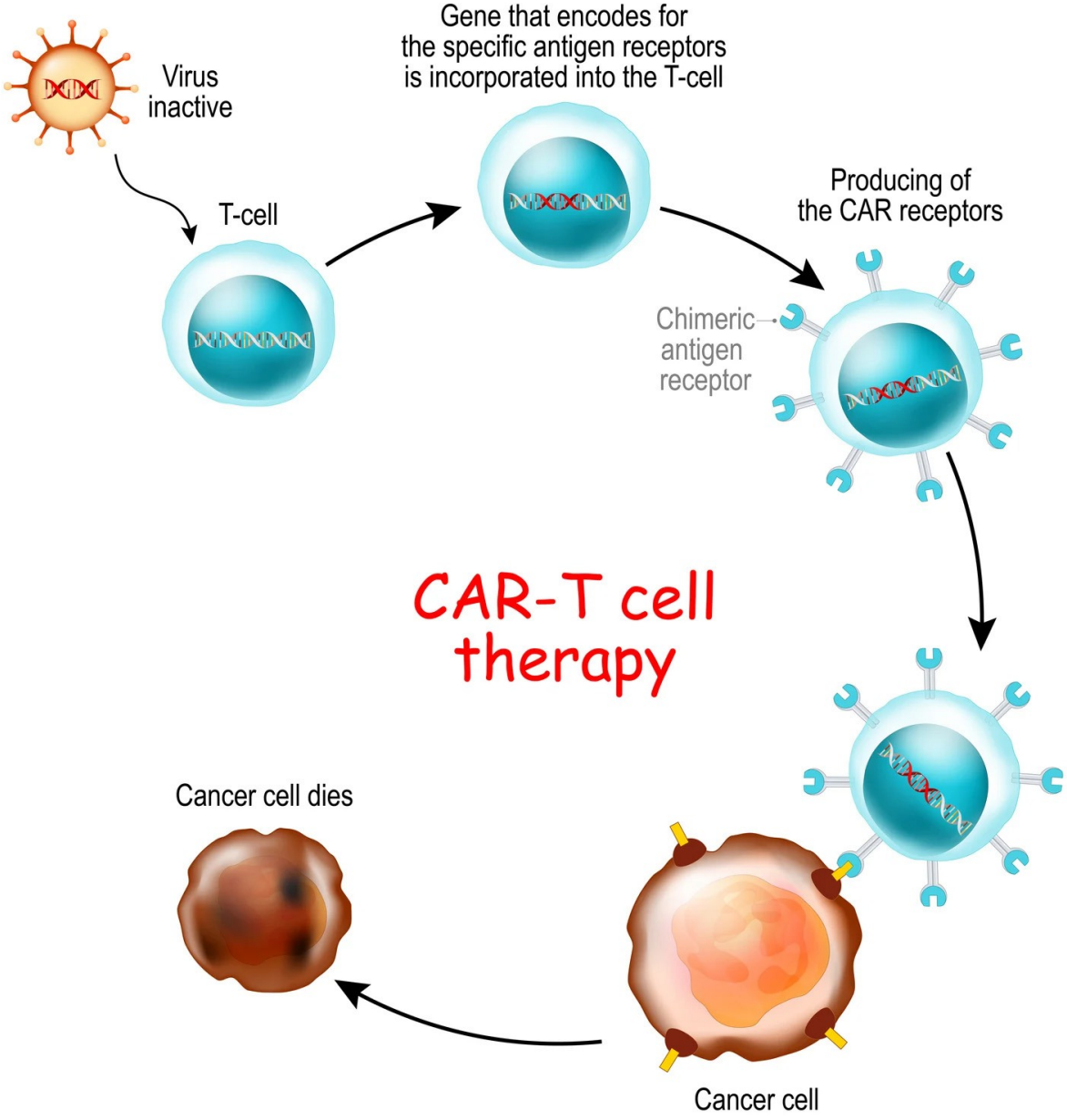
The Second Immunotherapy

CAR T-cell therapy

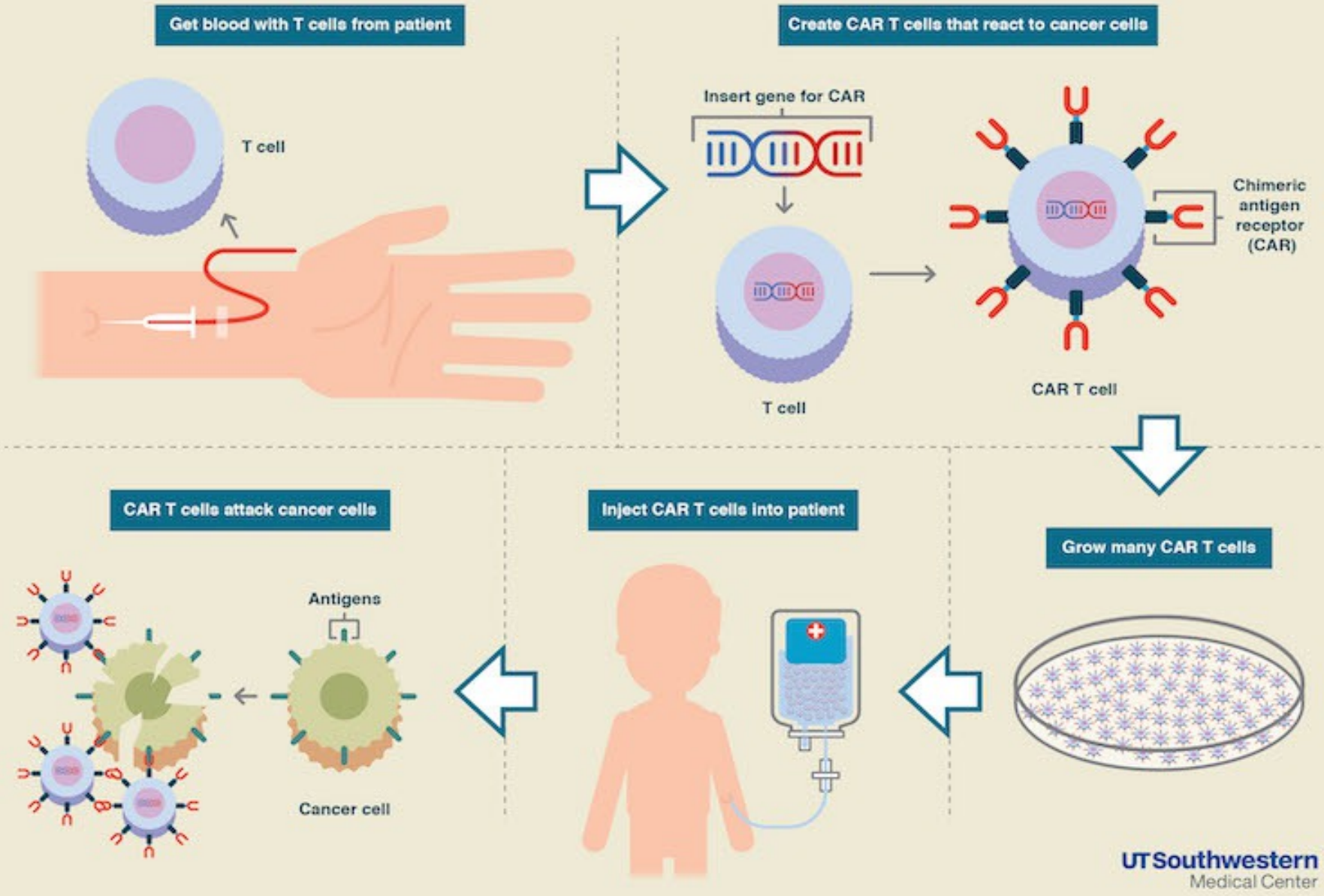


Chimeric antigen receptor cells (CAR-T Cells)

> Identify a unique antigen on the membrane of the cancer cell.
> Design a receptor to bind to the cancer antigen then make a mRNA molecule to build the receptor. This is the “CAR”.
> Remove T cells from patient, insert mRNA CAR into T cells and then induce clonal selection. Make millions of CAR T cells.
> Infuse cTcells with CAR back into patient to kill cancer cells.
> cTcell-CAR will attack non-solid tumors (e.g. cancers of the blood)


Virus
inactive
T-cell
Gene that encodes for
the specific antigen receptors
is incorporated into the T-cell
Producing of
the CAR receptors
Chimeric
antigen
receptor
CAR-T cell
therapy
Cancer cell dies
Cancer cell

CAR T-cell Therapy



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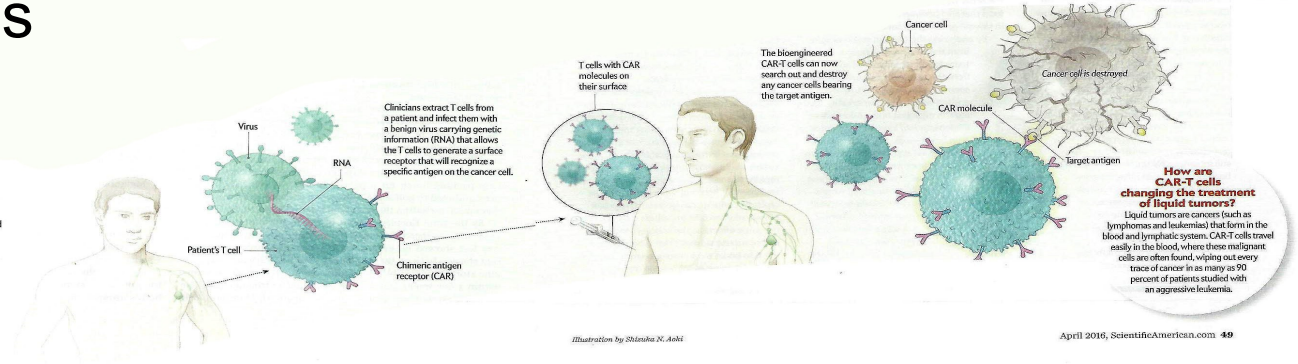
Medical Center

CAR-T Cells



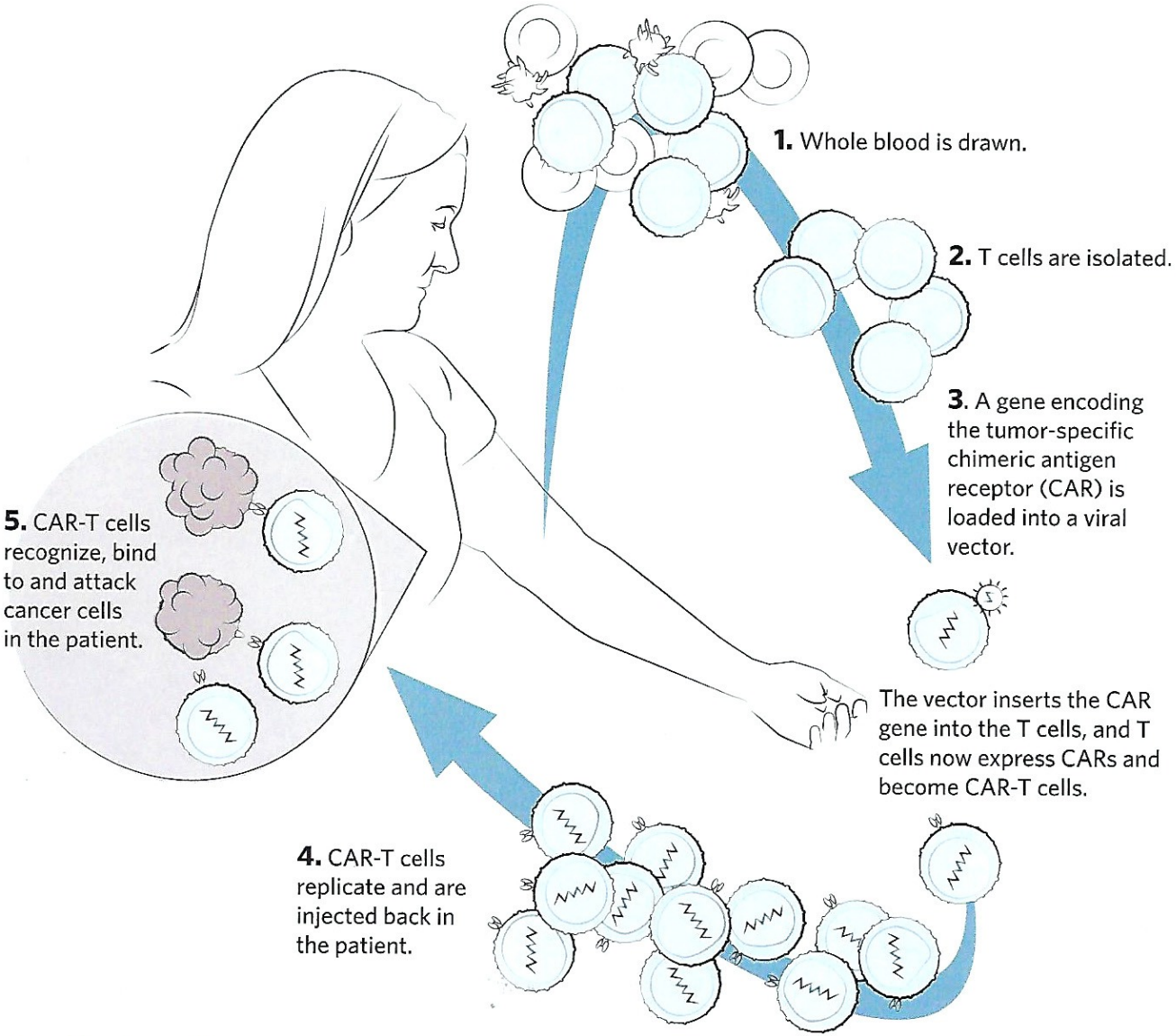
Chimeric antigen receptor cells (CAR-T Cells) combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hydrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens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

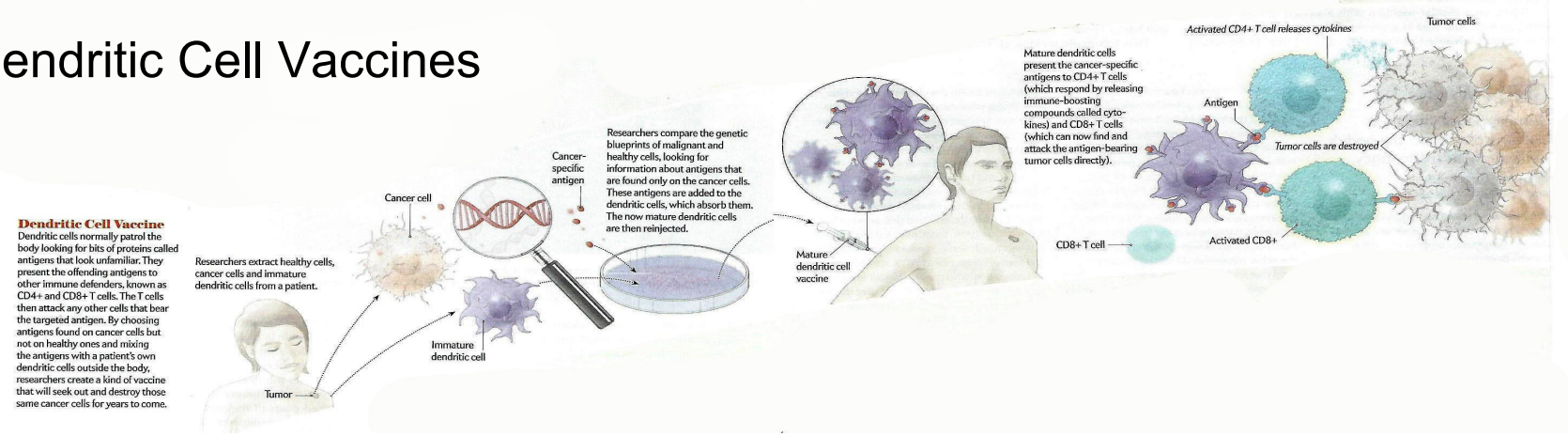
Liquid tumors are cancers (lymphomas and leukemia) that form in the blood and lymphatic system. CAR-T cells travel easily in the blood, where these malignant cells are often found, wiping out every trace of cancer with 90 percent success.

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

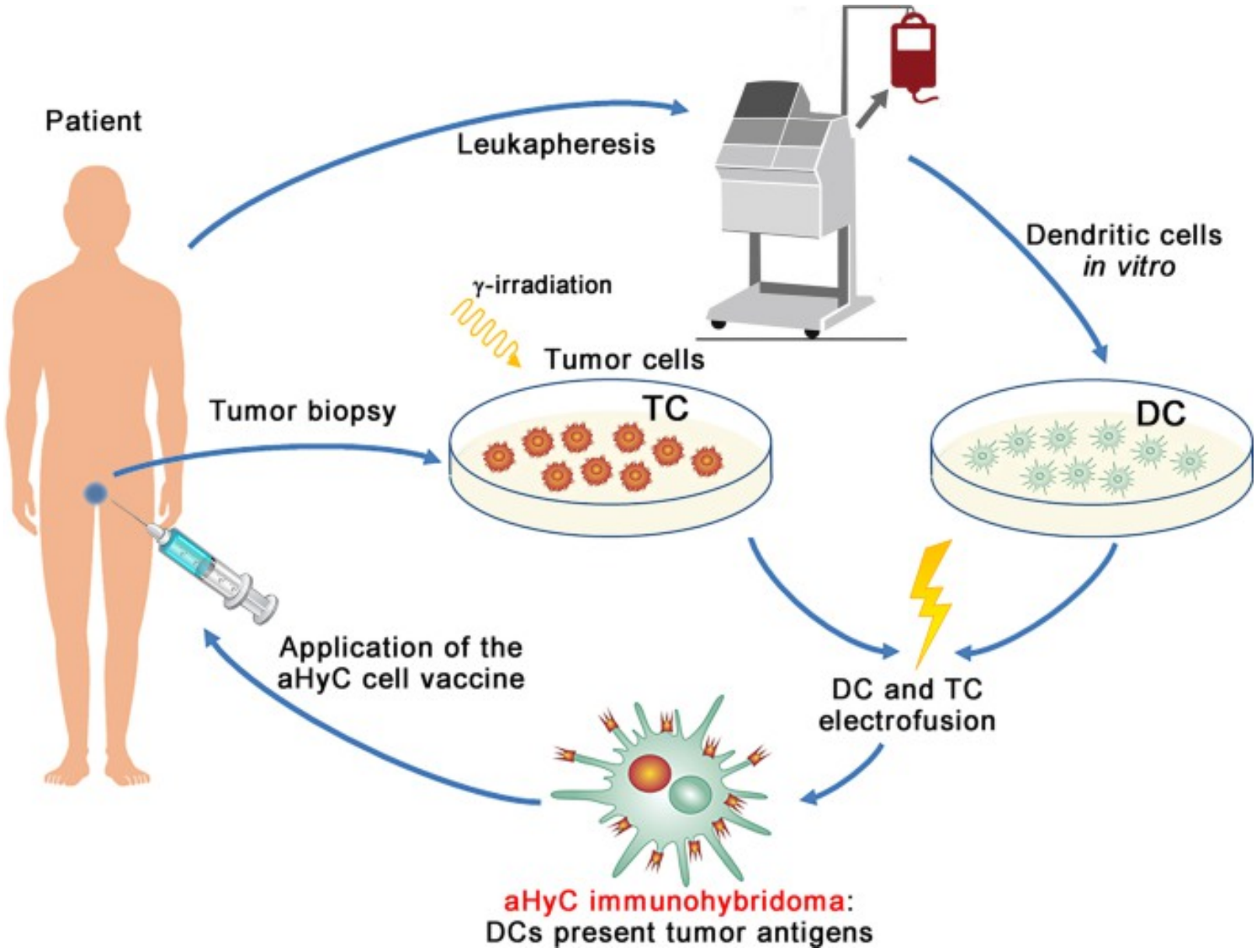


Dendritic cells normally patrol the body looking for bits of protein called antigens that look unfamiliar. They **present the offending antigens to other immune defenders, know as CD4 and CD8 T cells**. The T cells then attack any other cells that bear the targeted antigen.

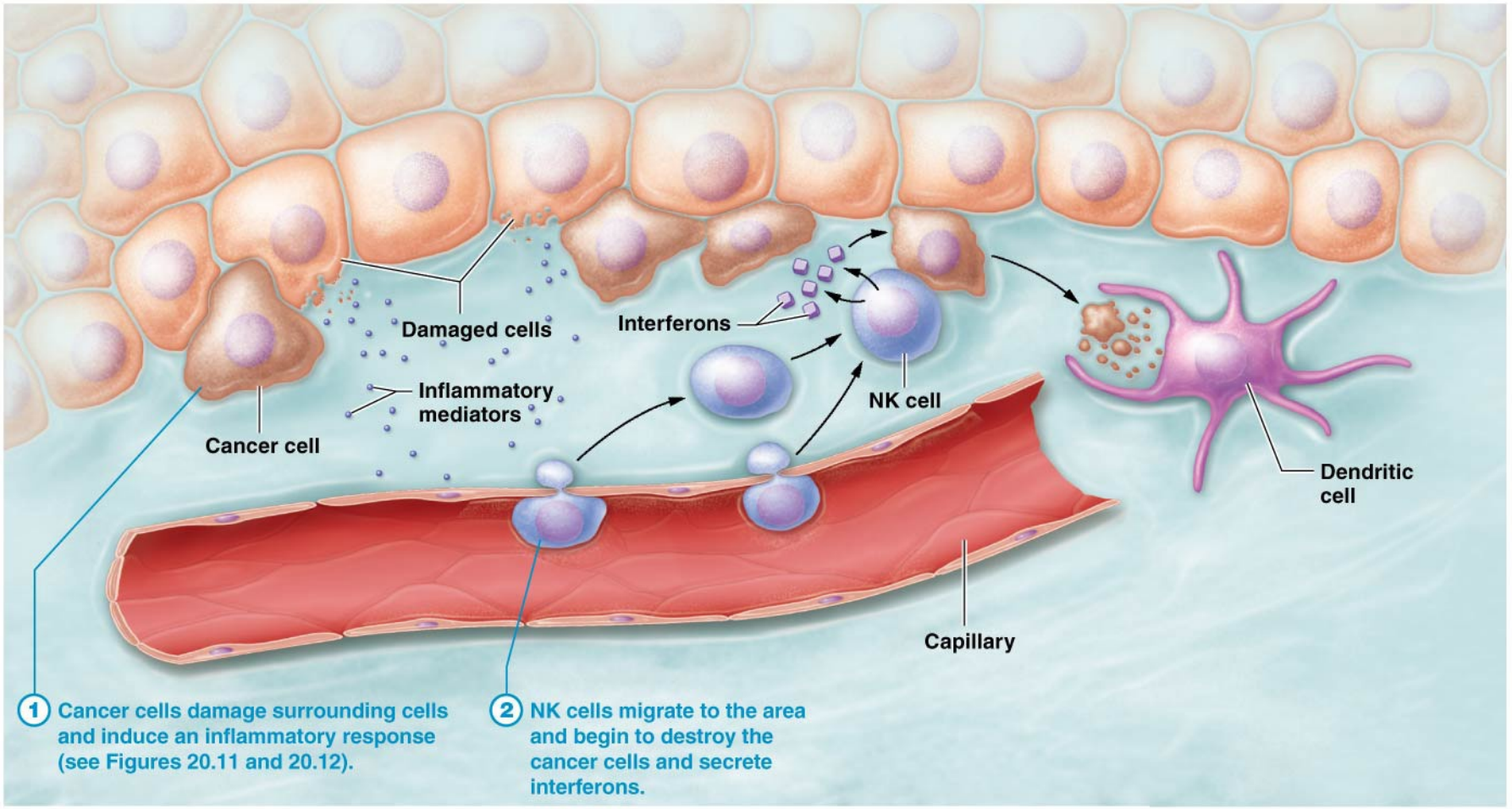
By choosing antigens found on cancer cells but not on healthy ones and mixing the antigens with a patient's own dedritic cells outside the body, researchers create a kind of vaccine that will seek out and destroy those same cancer cells for years to come.

Researchers extract healthy cells, cancer cells and 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.

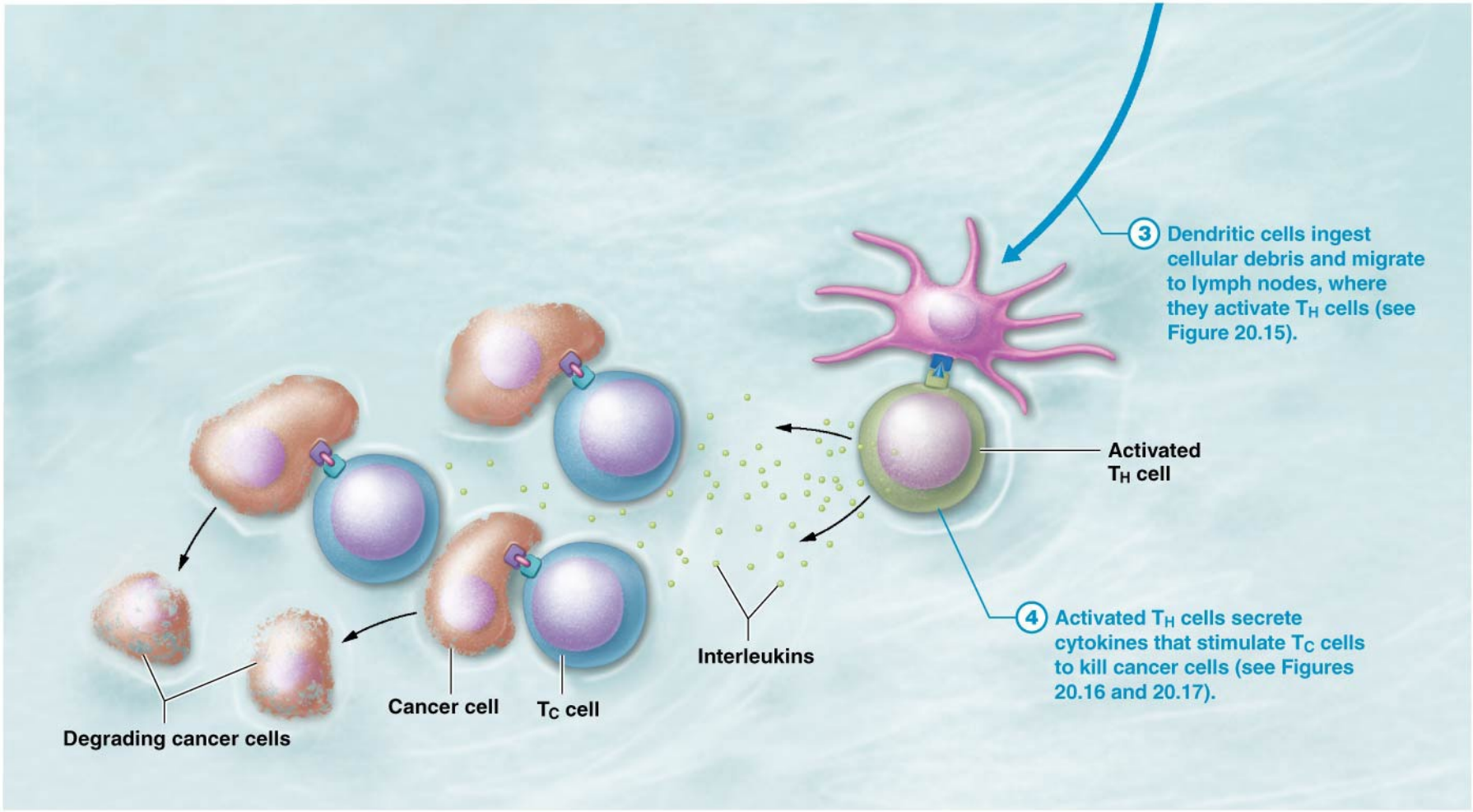
Dendritic Cell Vaccines



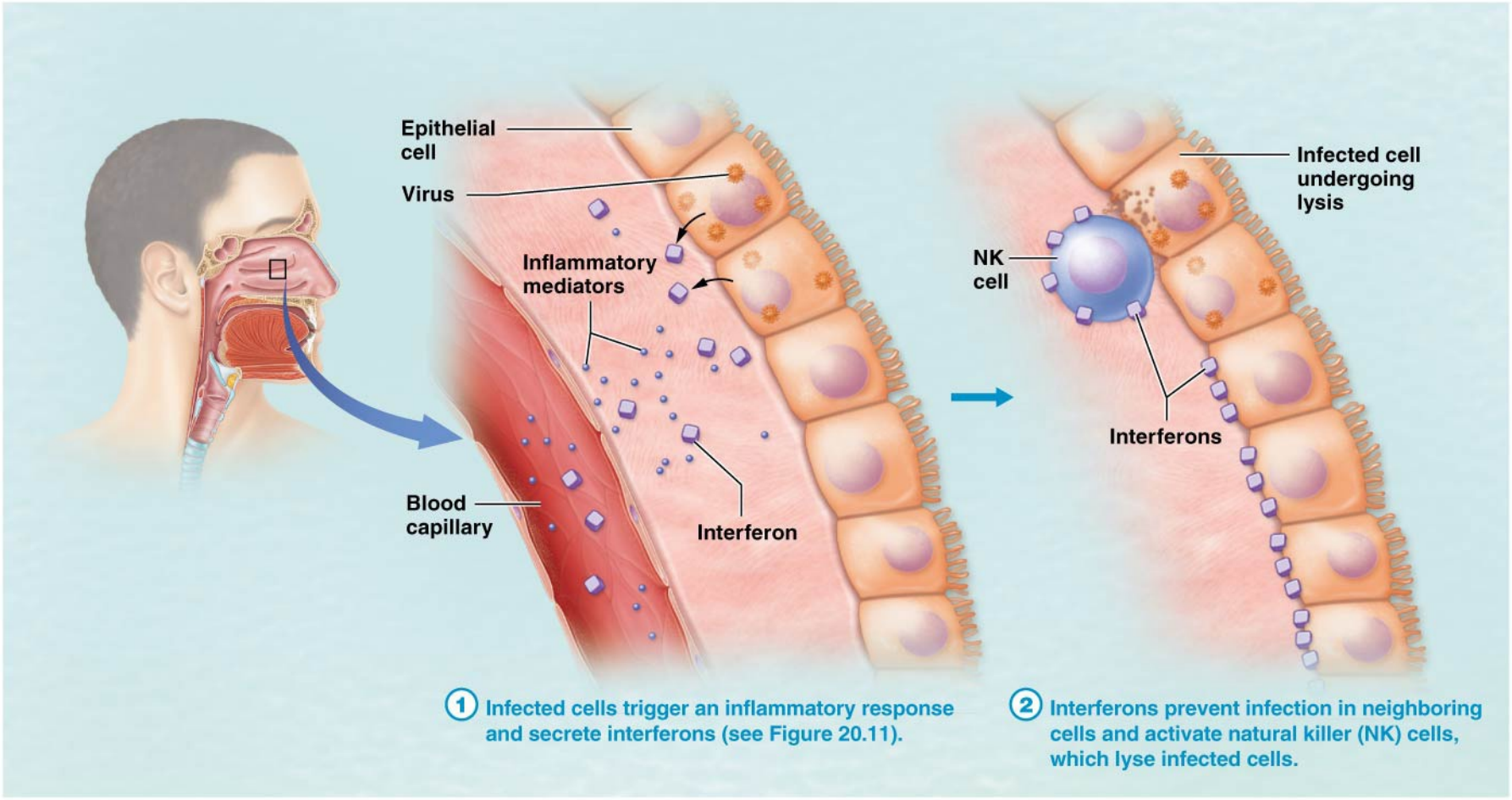
The Big Picture
Using the Immune Response to Cancer Cells. (slide 1 fo 2)



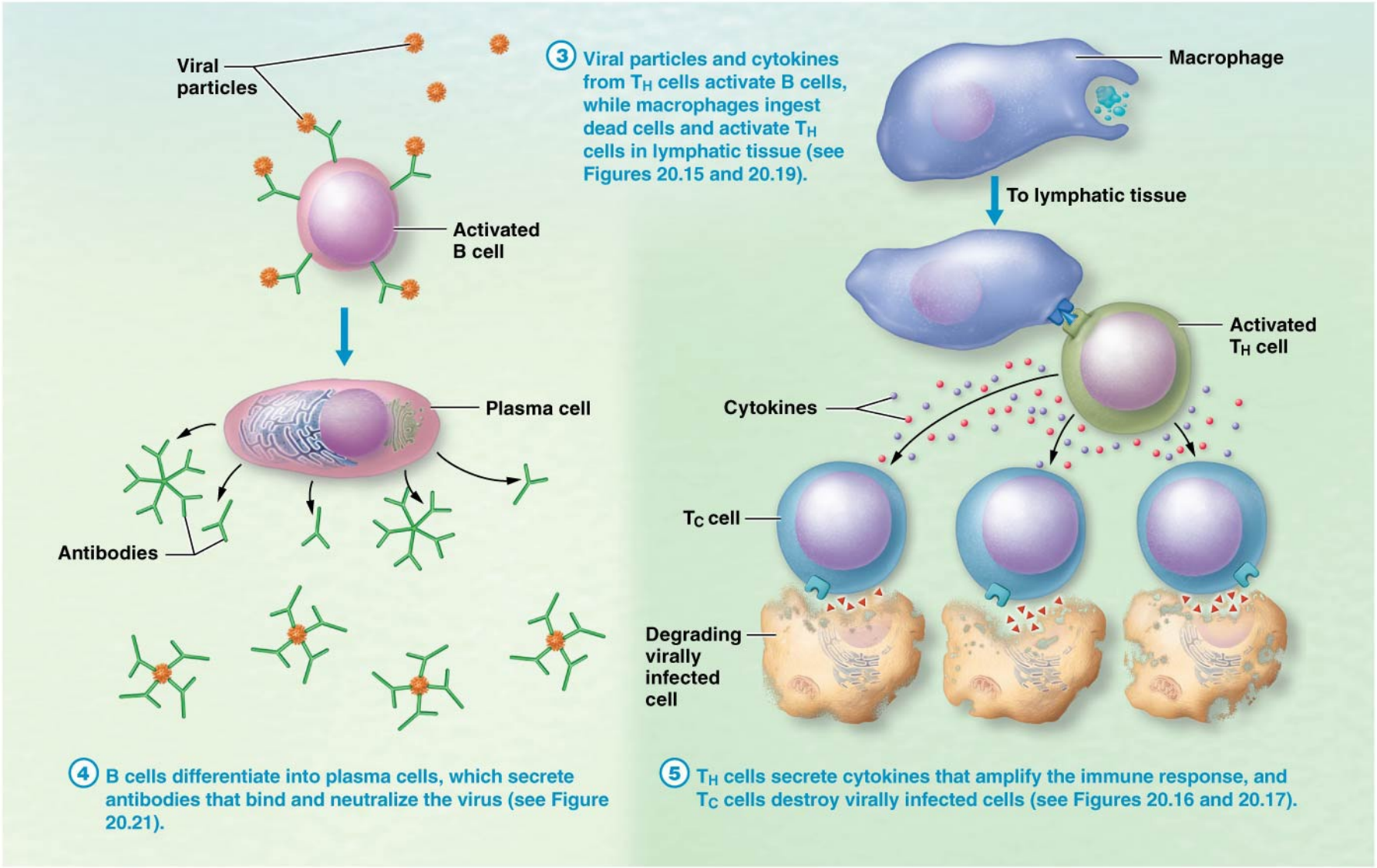
The Big Picture
Using the Immune Response to Cancer Cells. (slide 2 of 2)



The Big Picture
Immune Response to the Common Cold.
This is a viral infection. (slide 1 of 2)

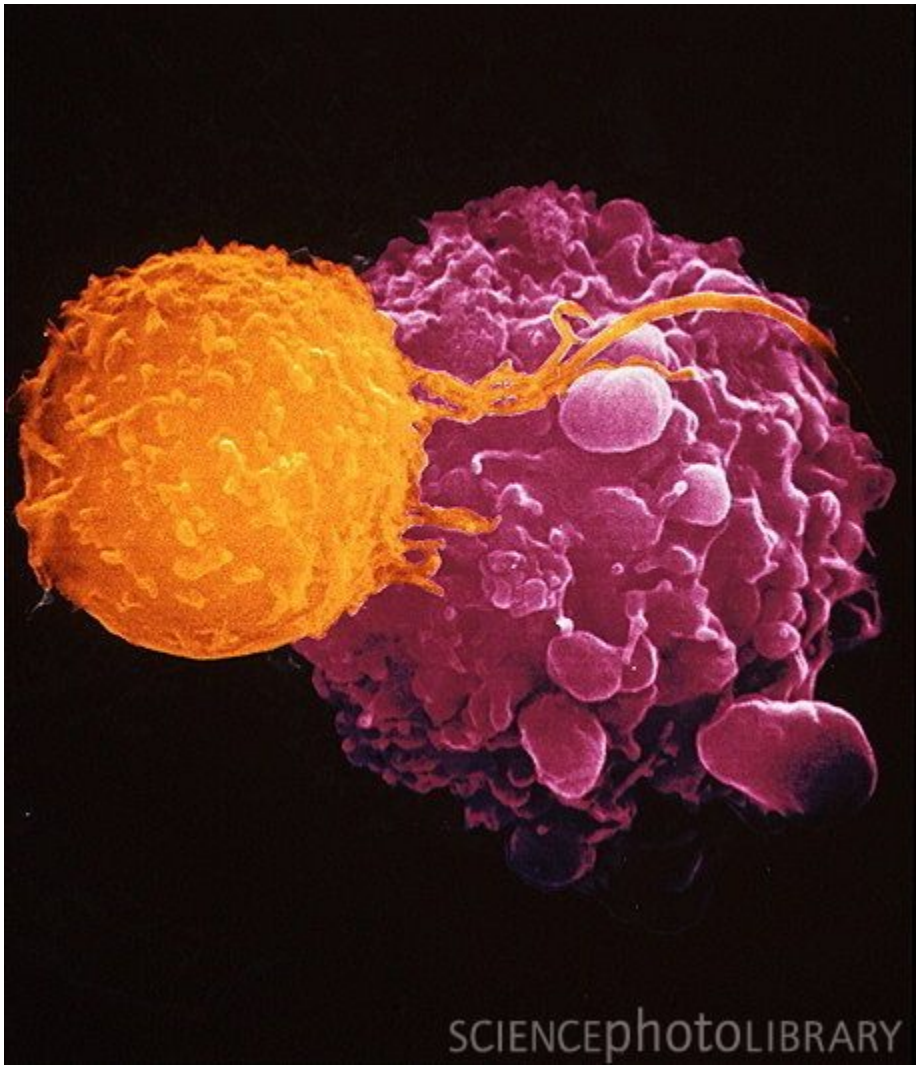


The Big Picture
Using the Immune Response to the Common Cold.
This is a viral infection. (slide 2 of 2)

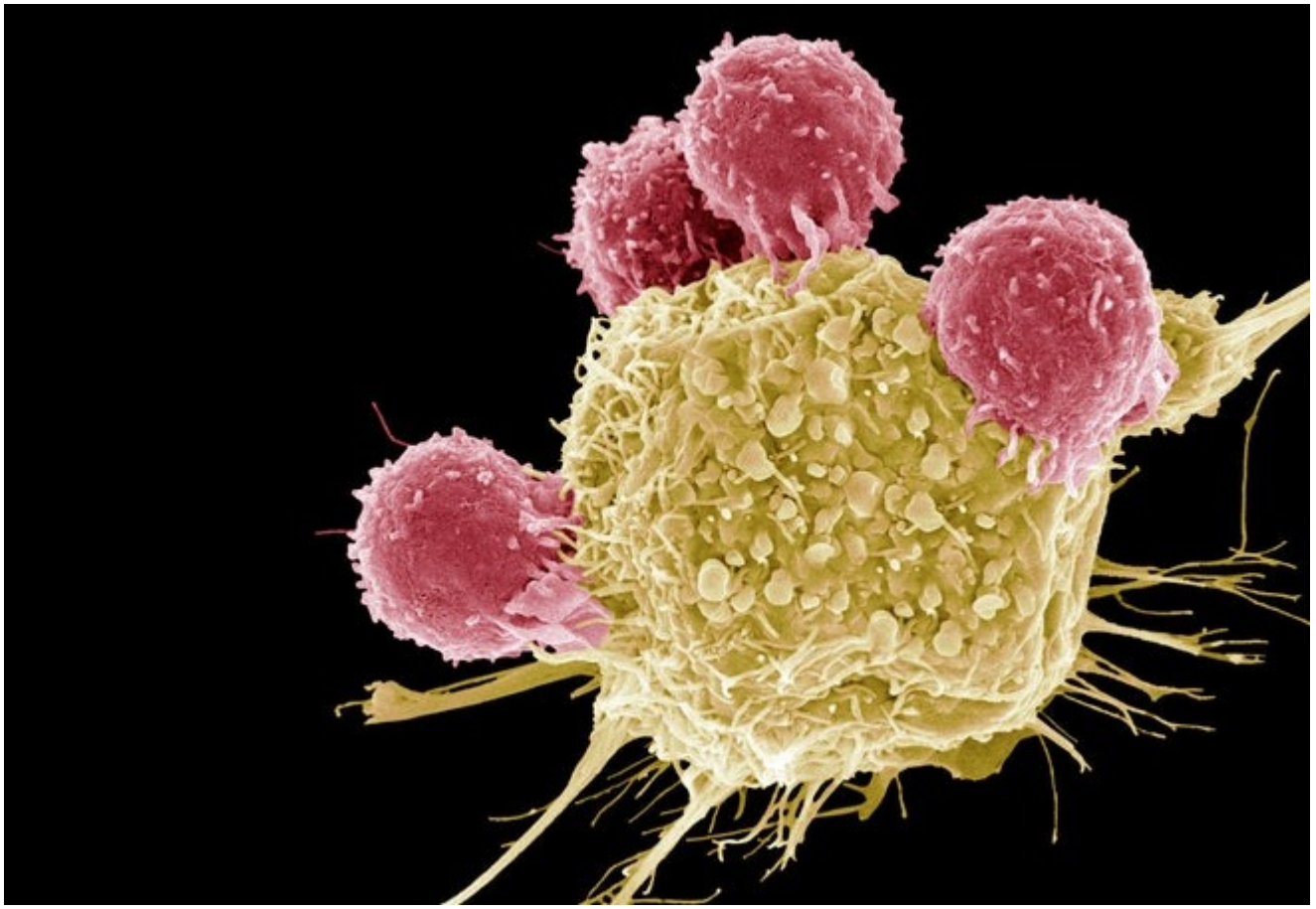


Immune system fighting a cancer cell.

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



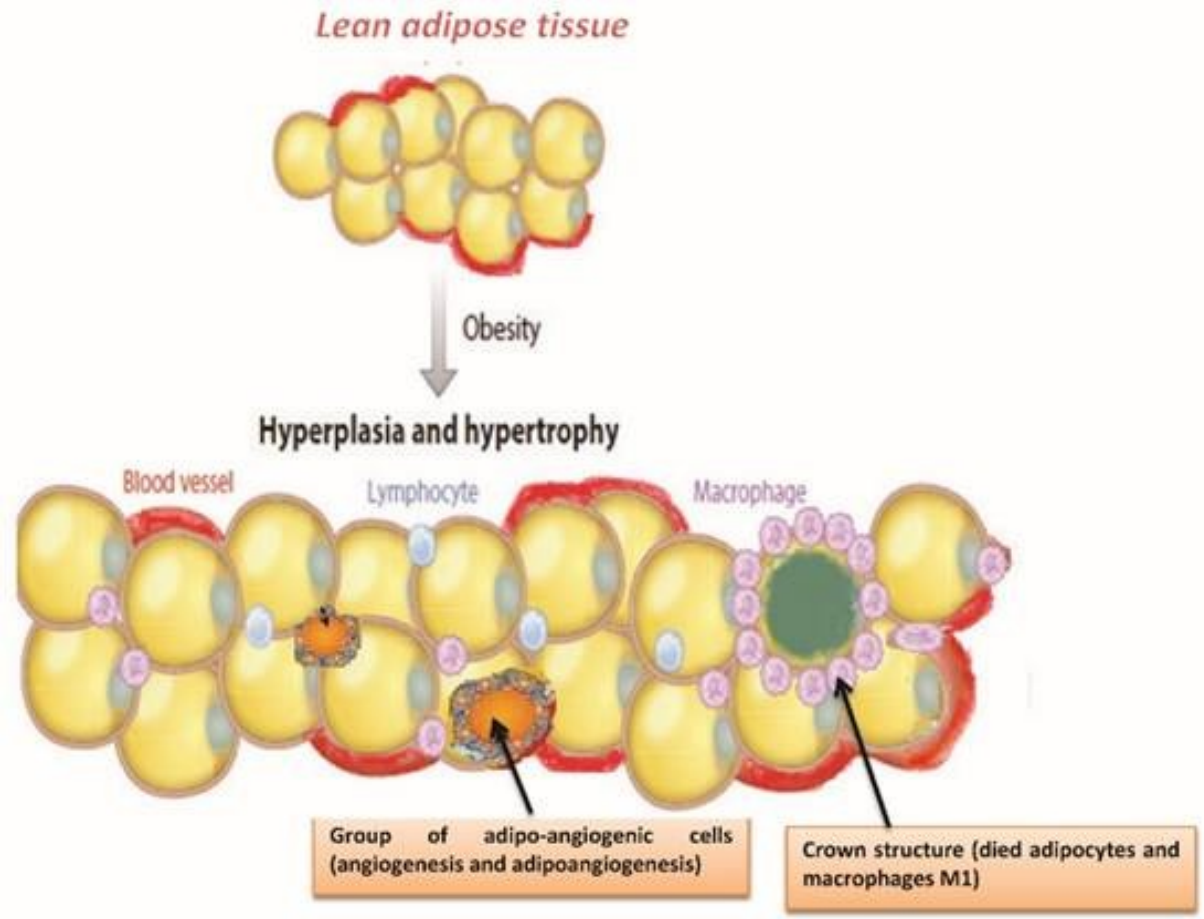
Coloured scanning electron micrograph of T cells (pink) attacking a cancer cell. Editing T cells' genes could soon enhance their cancer-attacking abilities.

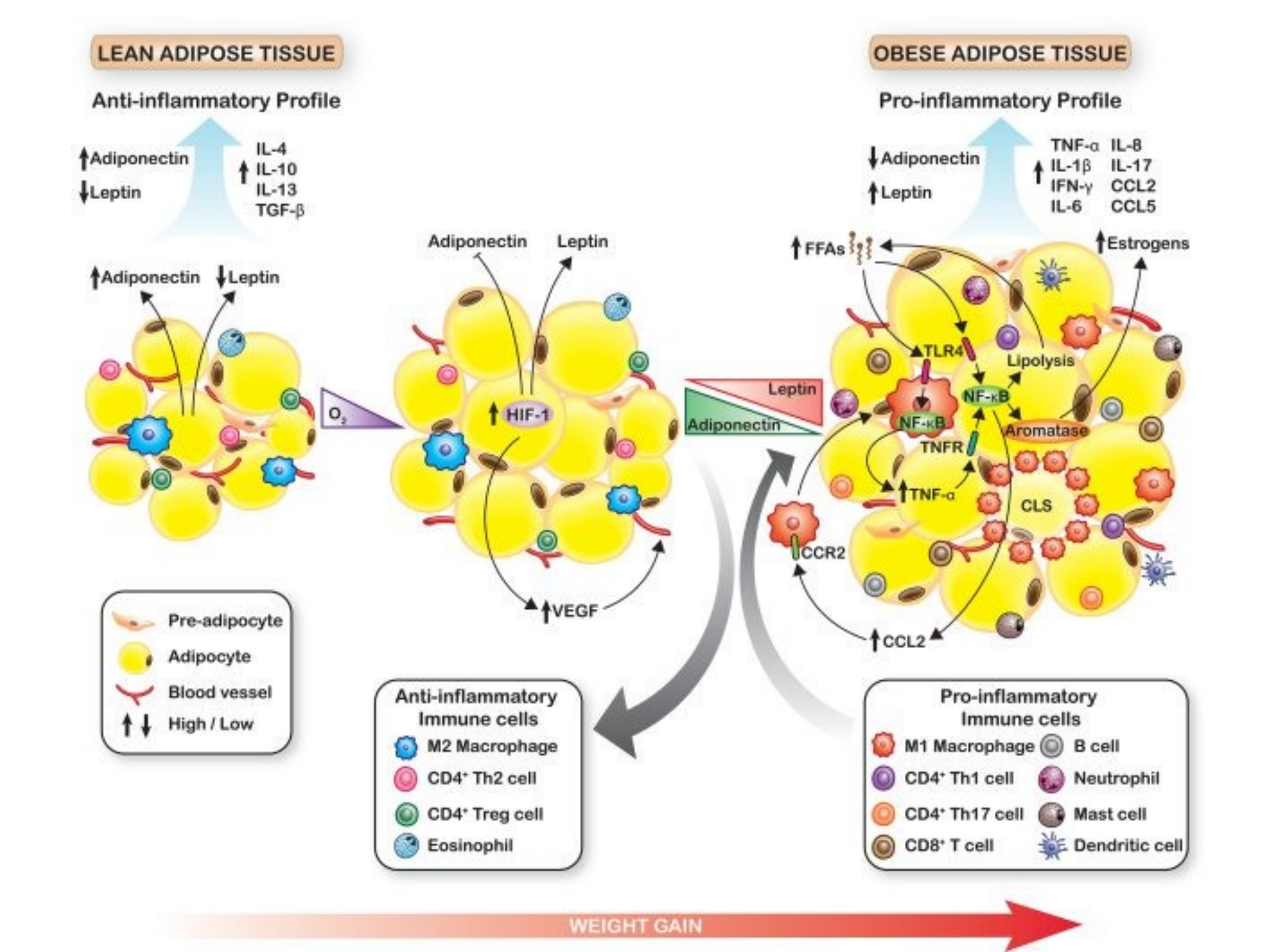


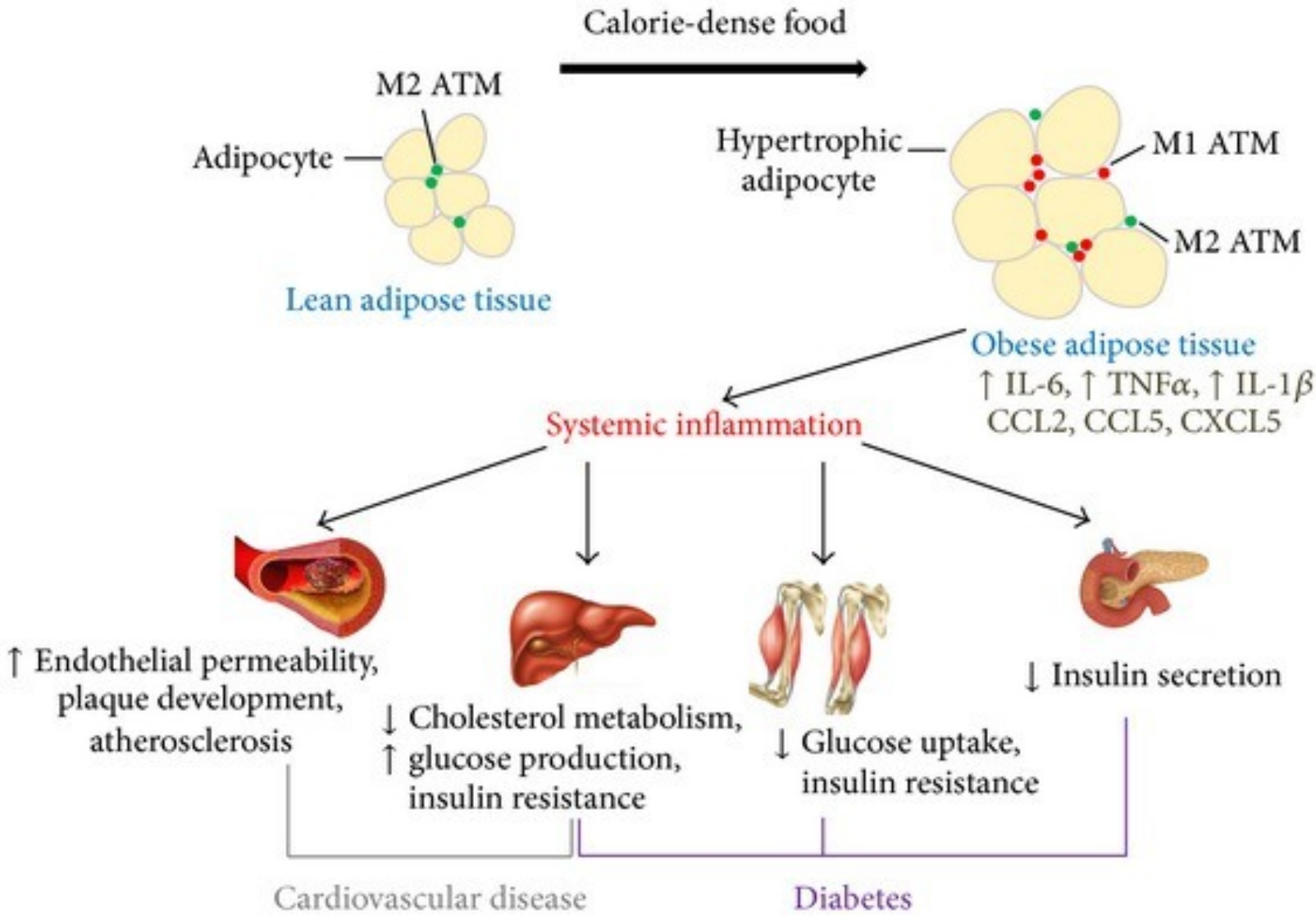
Obesity contributes to development of diabetes and cardiovascular disease. Adipose tissue is composed of two main cell types, adipocytes and stromovascular mononuclear cells (i.e., resident leukocytes).

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, TNFα, and IL-1β) 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
OBESE ADIPOSE TISSUE
Pro-inflammatory Profile
↓Adiponectin
↑Leptin
TNF-α
↑IL-1β
IFN-γ
IL-6
IL-8
IL-17
CCL2
CCL5
↑Adiponectin ↓Leptin
Adiponectin
Leptin
O2
↑HIF-1
↑VEGF
Leptin
Adiponectin
↑FFAs
↑Estrogens
↑TLR4
Lipolysis
NF-κB
NF-κB
Aromatase
TNFR
↑TNF-α
CLS
CCR2
↑CCL2
Pre-adipocyte
Adipocyte
Blood vessel
↑↓ High / Low
Anti-inflammatory Immune cells
M2 Macrophage
CD4+ Th2 cell
CD4+ Treg cell
Eosinophil
Pro-inflammatory Immune cells
M1 Macrophage
B cell
CD4+ Th1 cell
Neutrophil
CD4+ Th17 cell
Mast cell
CD8+ T cell
Dendritic cell
WEIGHT GAIN


Calorie-dense food
M2 ATM
Adipocyte
Lean adipose tissue
Hypertrophic adipocyte
M1 ATM
M2 ATM
Obese adipose tissue
↑ IL-6, ↑ TNFα, ↑ IL-1β
CCL2, CCL5, CXCL5
Systemic inflammation
↑ Endothelial permeability, plaque development, atherosclerosis
↓ Cholesterol metabolism, ↑ glucose production, insulin resistance
↓ Glucose uptake, insulin resistance
↓ Insulin secretion
Cardiovascular disease
Diabetes