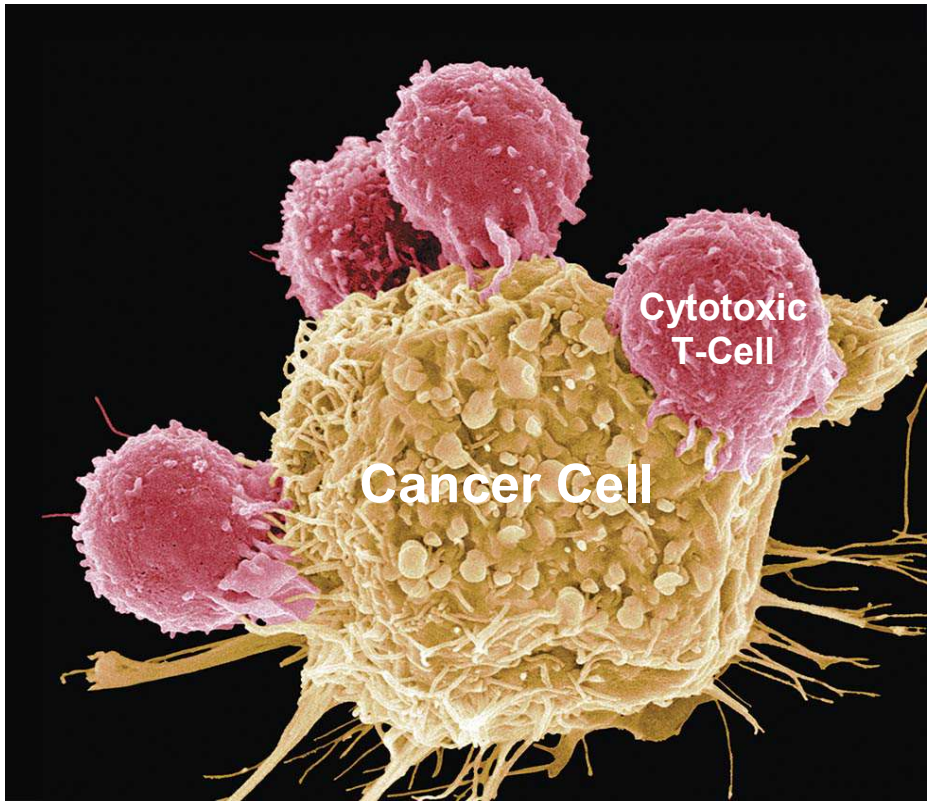
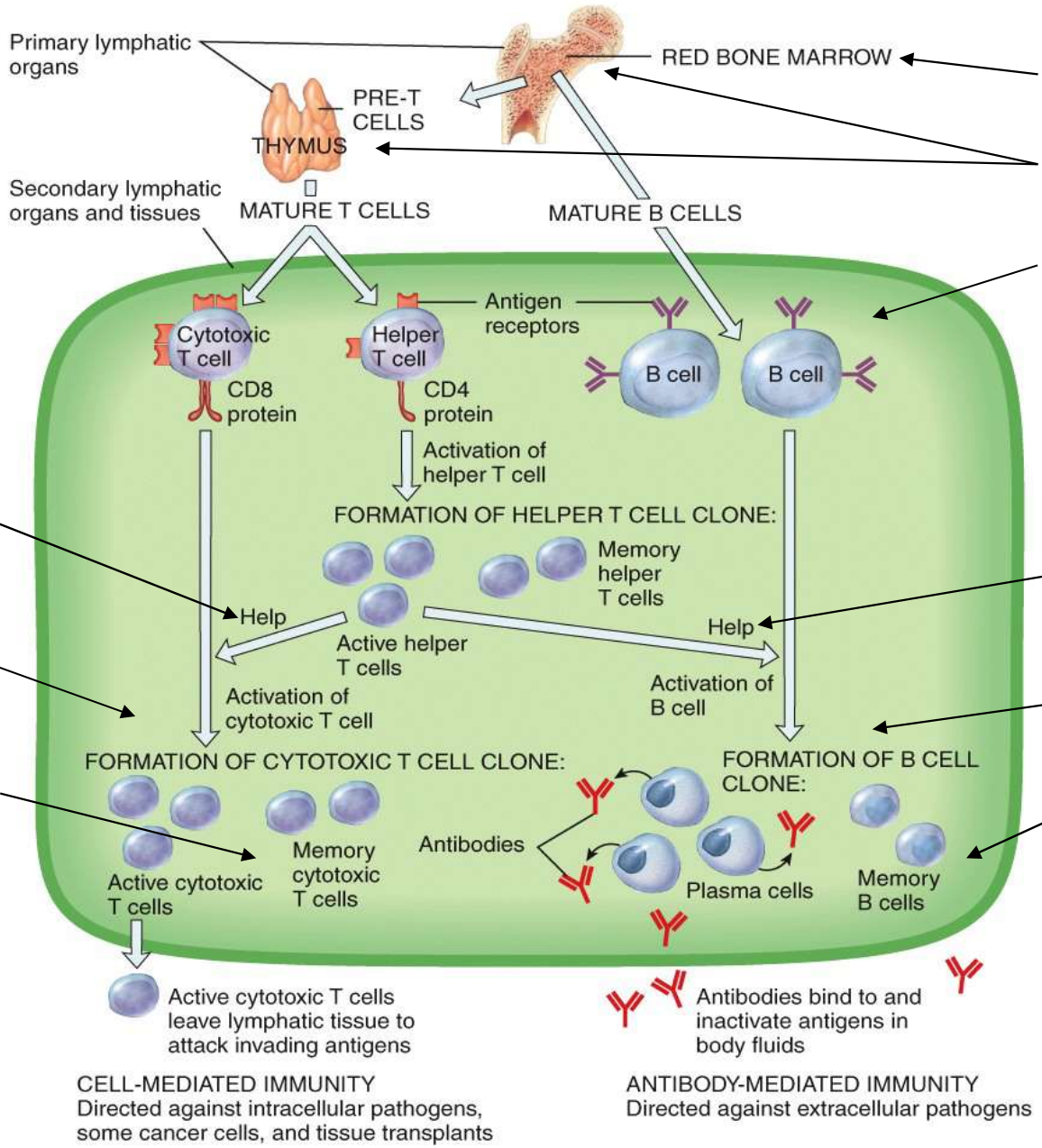
The Third Line of Defense

"Acquired Immunity"
(Also Called "Adaptive Immunity")



This is a summary of acquired immunity (also called adaptive immunity) .



Born

Educated

Deployed

(Deployed as naive immunocompetent cells)

Recognize

React

Remember

Recognize

React

Remember

What is immunity?

- *Immunity protects us against internal and external threats.*
- *Immunity maybe either innate or non-innate (i.e. adaptive)*
- *Innate immunity exists at time of birth // Relies on numerous factors including physical barriers, cellular phagocytes and many different types of molecules // characterized as "non-specific resistance " to pathogens in non-specific ways*
- *Non-innate means it does not exist at birth /// Develops after birth /// This is "acquired immunity" and characterized as having both "specificity and memory"*
- *We fight infections with three lines of defenses:*
  - *#1 - Physical barriers*
  - *#2 - Non-specific resistance*
  - *#3 - Acquired immunity*

(both innate)

(not innate called adaptive immunity)

What makes acquired immunity “special”?

- *Most important characterists = “specificity” and “memory”*
- *Acquired immunity becomes active only after coming in contact with a pathogen /// acquired immunity recognizes the pathogen because it has “non-self antigen”*
- *Acquired immunity requires a group of widely distributed “wandering” cells” /// many different types of WBC*
- *Different WBC must work together (work “collectively”)*
- *WBC use cytokines and chemokines to talk to each other (i.e. to communicate and coordinate activities between the different WBCs)*
- *There is also cooperation between innate and non-innate immunity which is also mediated by cytokines*

What Are the Two Forms of Acquired Immunity?

- *WBCs called T cells provide cellular adaptive immunity // Cytotoxic T cells - kill host's cells infected with virus or cancer (bad stuff inside our cells!)*

- *WBCs called B cells (when activated they change into plasma cells) provide humoral adaptive immunity*

  - *B cells morph into plasma cells which then produce antibodies /// antibodies do not kill pathogens /// antibodies render pathogens* harmless and tag them for destruction.

- *Clonal selection occurs when T and B cells come in contact with a pathogen /// results in rapid mitosis of T and B cell // each cell type will have similar receptors matched to a specific foreign antigen*

- *Cytotoxic -Tcell, helper-Tcell, and B cells wil all have similar receptors that react to the same foreign antigen from a common pathogen /// during clonal selection memory cells to this antigen are made and rest in lymph nodes*

- *Memory cells do not react to "current" infection but will respond immediately after a second exposure to a similar pathogen. /// first exposure vs second exposure*

Why do we need both cellular and humoral immunity?

Because a pathogen can be either outside or inside our cells!

Humoral Adaptive Immunity: Action of B cell after activated morph into plasma cells // 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 with 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

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 and T cell pairs" that share a unique but common foreign antigen receptor.

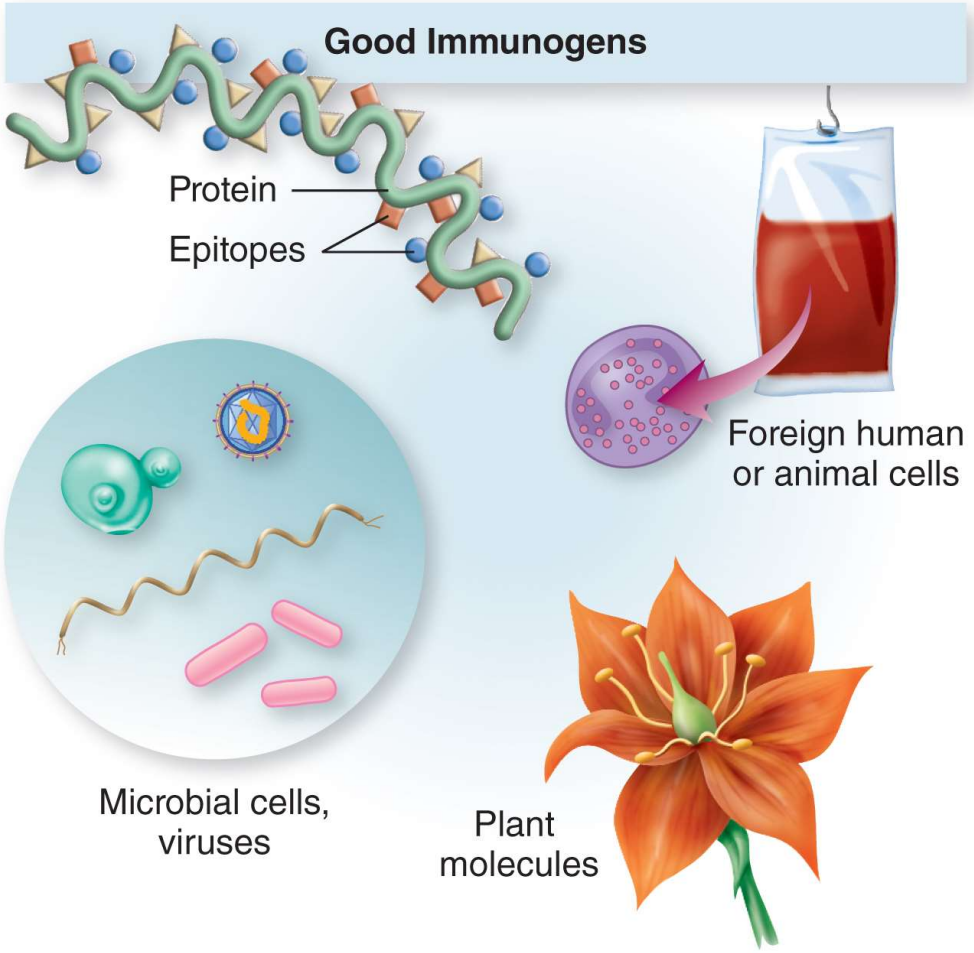
What is the difference between self and non-self antigen?

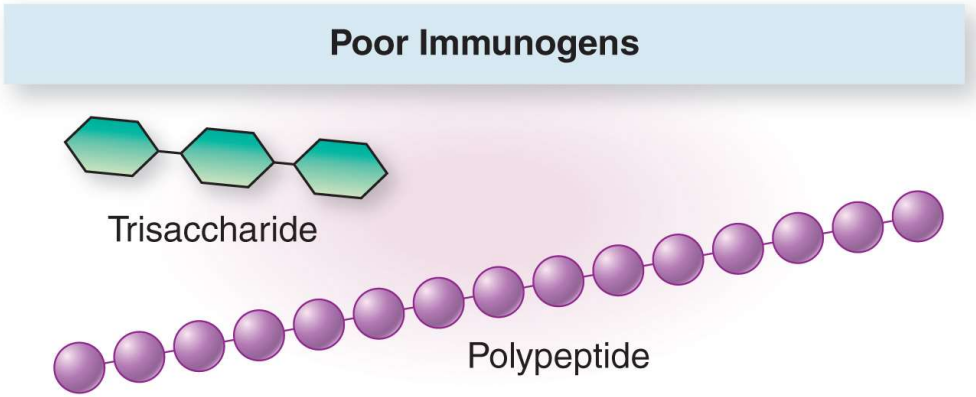
- An antigen is a molecule // proteins, polysaccharides, glycoproteins, glycolipids
- Antigens are embedded into the plasma membrane /// Normally large molecular weight - over 10,000 amu
- An antigens may be defined as being either self-antigen or non-self-antigen
- A non-self antigen is any molecule that triggers an immune response
- Pathogen's have non-self antigen /// bacteria, virus, toxins
- Transplanted tissue is also recognized as being foreign because it too has non-self antigen
- One bacteria may display several foreign antigens on it surface /// each foreign molecule then starts a unique immune response /// E.g. - The flagella and the glycocalyx may each activate separate T and B pairs // each immune response activated by different antigens from the same bacteria

What is the difference between self and non-self antigen?

We have antigens embedded in our plasma membranes that are unique to us /// These antigens are "self-antigen"

- Our immune system can tell the difference between our cell's self-antigen and a foreign cell's non-self antigen
- Our self antigen is unique to only us // only exception is if you have an identical twin – in this case your identical twin would have same antigen as you have
- Two Key Idea:
  - immune system can differentiate between self and non-self antigens
  - our immune system function is to either destroy or render harmless foreign antigen





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

What is the difference between an epitope and an antigen?

Epitopes = the antigenic determinant

proteosomes digest antigen into peptides // one of the peptides becomes the epitope

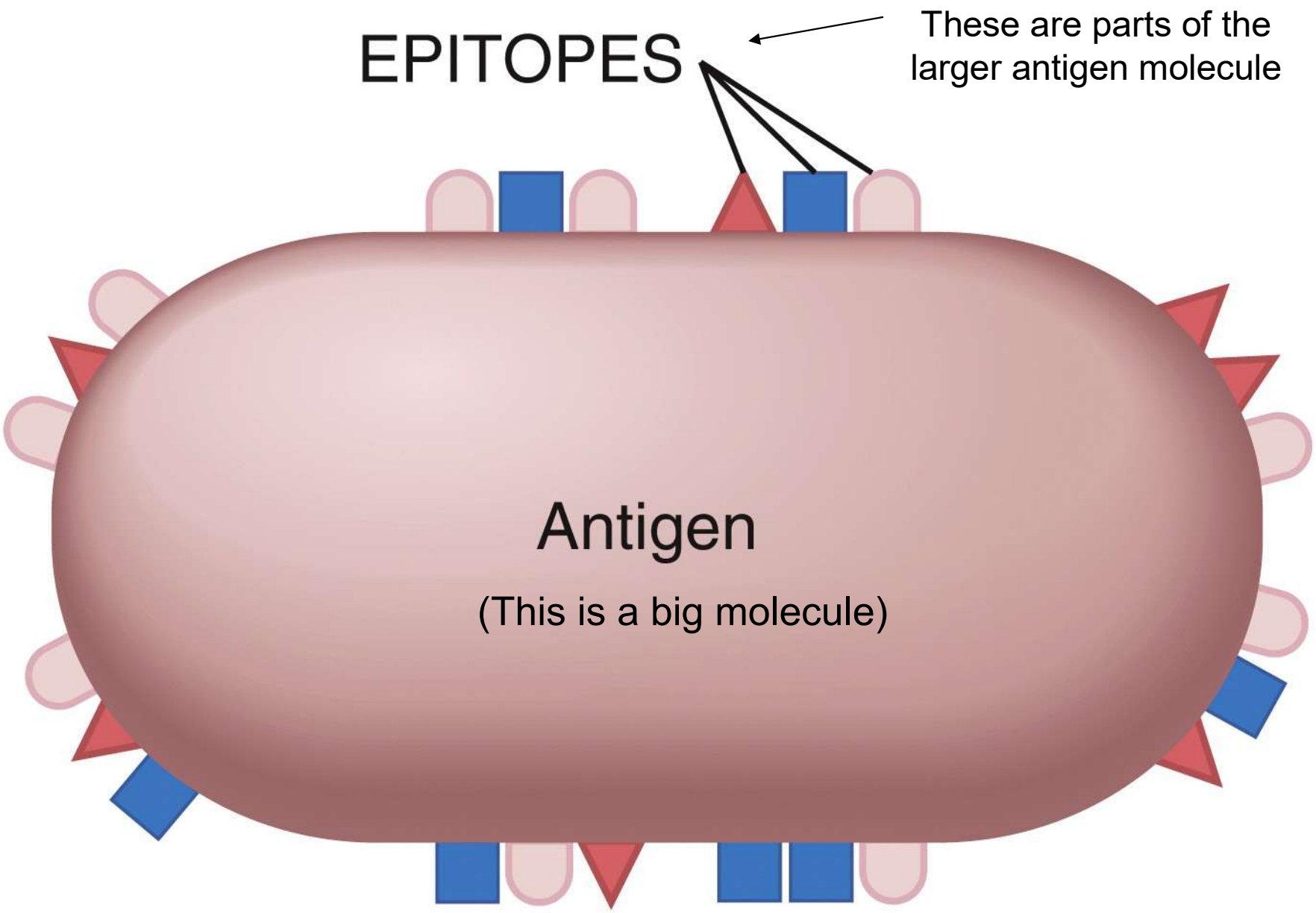
only the epitope is required to stimulate the immune response for T cells

epitope placed in MHC protein will display epitope on surface of antigen presenting cell membranes

this process is know as "antigen presentation"

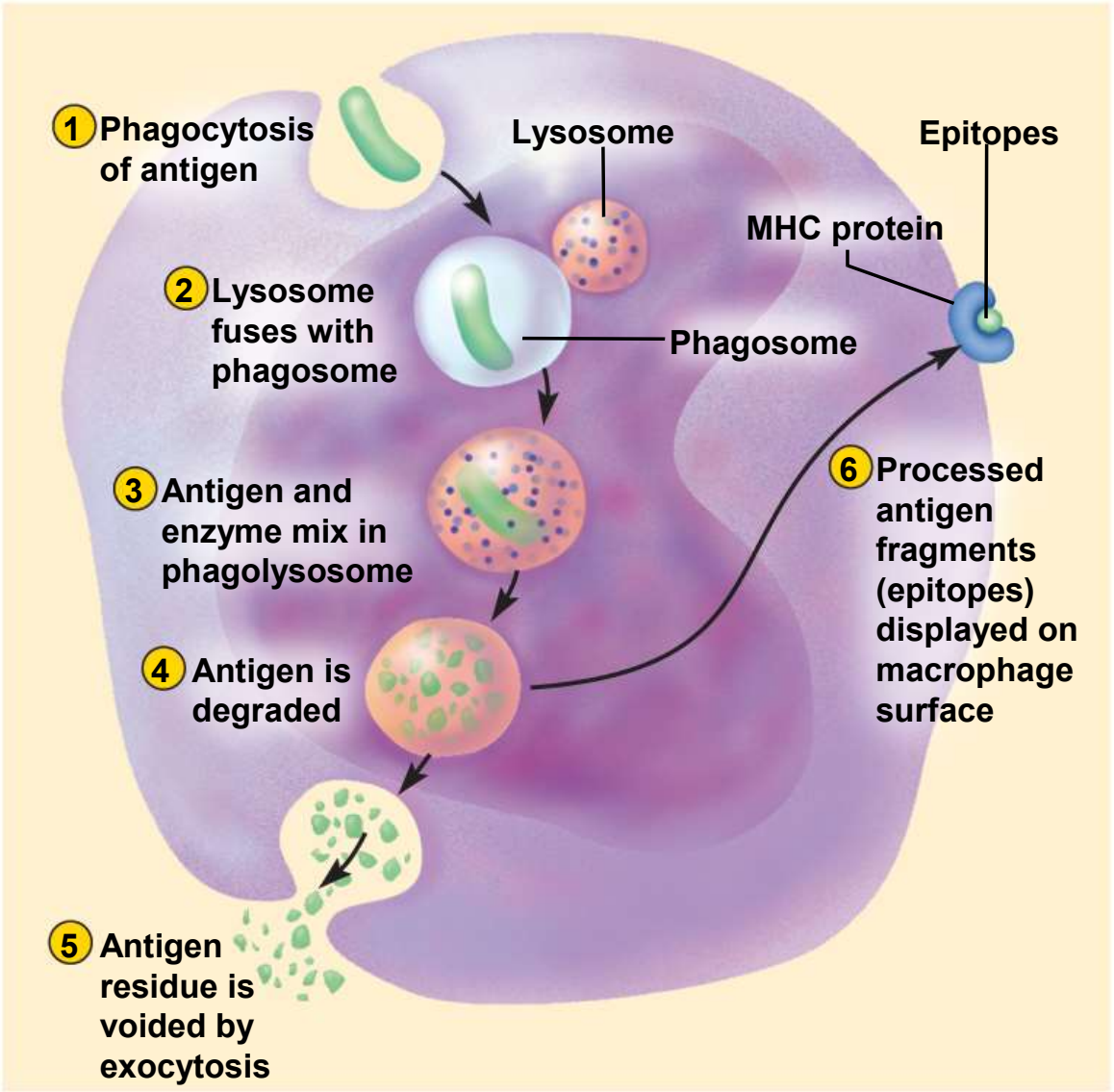
cells which carry out this process are called antigen processing cells = macrophage, dendritic cells, B cells

APC play key step in the function of acquired immunity // more to come on this topic later


EPITOPES
These are parts of the larger antigen molecule
Antigen
(This is a big molecule)

How APC Processes Antigens into an Epitope

Epitope is inserted into the outer face of the plasma membrane.

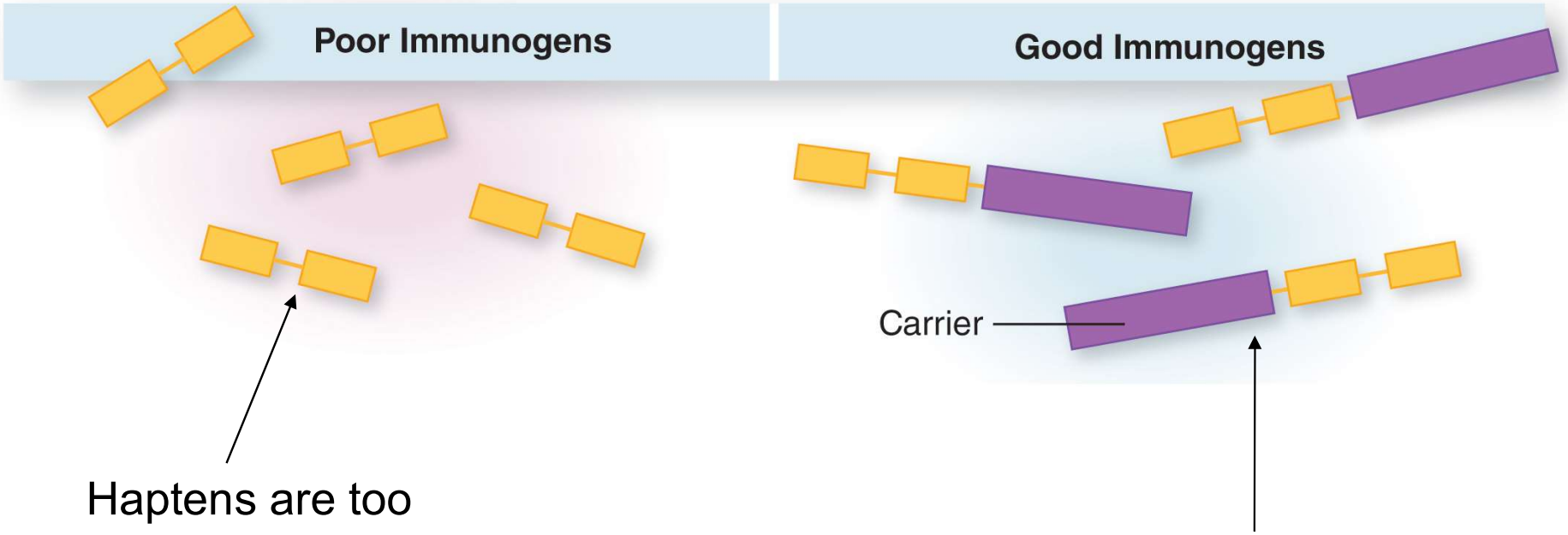


Why do some people exhibit an immune response to a small molecules like penicillin?

Haptens = term describes a molecule that is to small to be antigenic /// e.g. penicillin is a hapten

- haptens able to combine with a host macromolecule (e.g. albumin)
- this then creates a unique complex that the body recognizes as foreign
- cosmetics, detergents, industrial chemicals, poison ivy, and animal dander may all be haptens for some people
- if penicillin binds to host proteins then it will result in an allergic response // degranulate mast cells systemically

Haptens



Haptens are too small to act as an antigen.

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

What Immune Cells Are Antigen-Presenting Cells (APCs)?

Only these three cells are APCs

- Dendritic cells (Class-I and Class-II MHC)
- Macrophages (only Class II-MHC)
- B cells (only Class-II MHC)

- These three cell are able to “capture” foreign antigen and “display” the bacteria's epitope on the APC's plasma membranes using major histocompatibility proteins (type MHCP-II and/or MHCP-I)

- All the other nucleated host cells only display antigen (i.e. both self and non-self) using MHC-I (Class-1 MHC) */// note - mature RBC are not cells so they don't display any MHCP*

What is the Significance of Major Histocompatibility Complex Proteins (MHCP)?

- MHCP allow APC and host cells to display the types of cytoplasmic protein that they have in their cytoplasm (host proteins or foreign proteins from bacteria, virus, and cancer)
- Two type of major histocompatibility proteins: MHCP-I and MHCP-II
- New MHCP is constantly being produced by the rough endoplasmic reticulum
- MHCP and cytoplasmic proteins migrate from the cytosol to the plasma membrane where they become embedded into plasma membrane's outer face as a MHC-epitope complex
- MHCP are shaped like a “hot dog bun” // the epitope they carry is referred to as the hot dog /// T cell receptors (on cytotoxic and helper T cells) are matched to these “hot dogs” /// there are billions of possible epitopes with host having billions of T cell receptors matched to these epitopes
- As MHCP move through cytoplasm they “pick up” cytoplasmic proteins /// MHCP with their epitope are embedded into plasma membrane's outer face
- Now WBCs can see the different types of proteins that are inside host cell's cytoplasm /// both normal proteins and abnormal proteins (i.e. cancer, virus, bacterial)

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

MHCP-I is only associated with host's nucleated cells (not RBC)

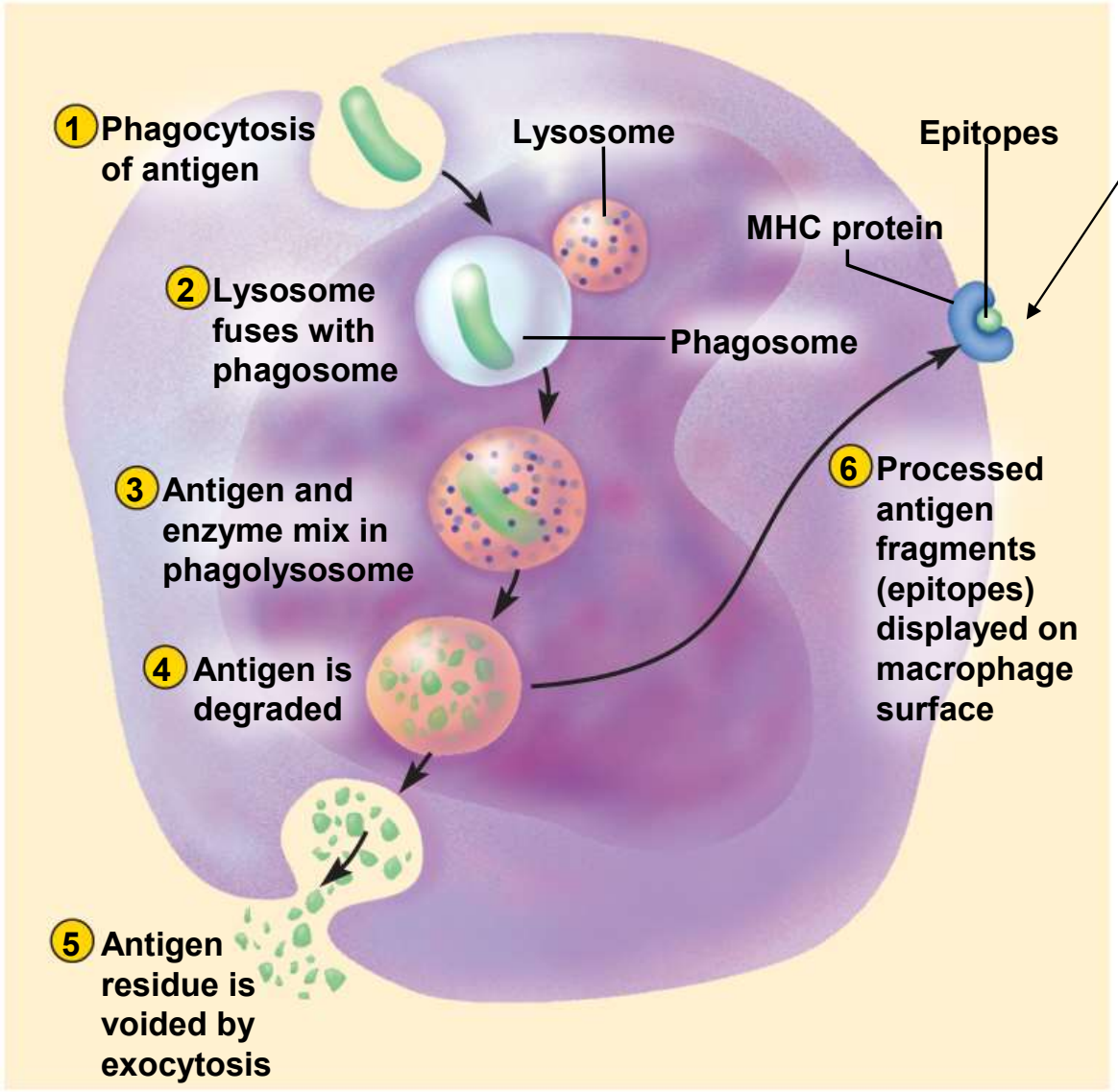
- After cytotoxic-Tc are activated by dendritic cells cytotoxic-T- cells have receptors that are able to bind to the antigen HCP-I on surface of infected host's cells
- Natural killer cells also bind to MHCP-1 (but non-specifically as immune surveillance cells)

MHCP-II is the foreign antigen holder used by antigen presenting cells

- Macrophage + Dendritic cells (also has MHCP-I) + B cells
- Helper-Tc are able to bind to MHCP-II on macrophage, B cells, and dendritic cells

How APC Processes Antigens into an Epitope

Epitope is inserted into the outer face of the plasma membrane.



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

Macrophage, dendritic cells, and B cells have MHC-II

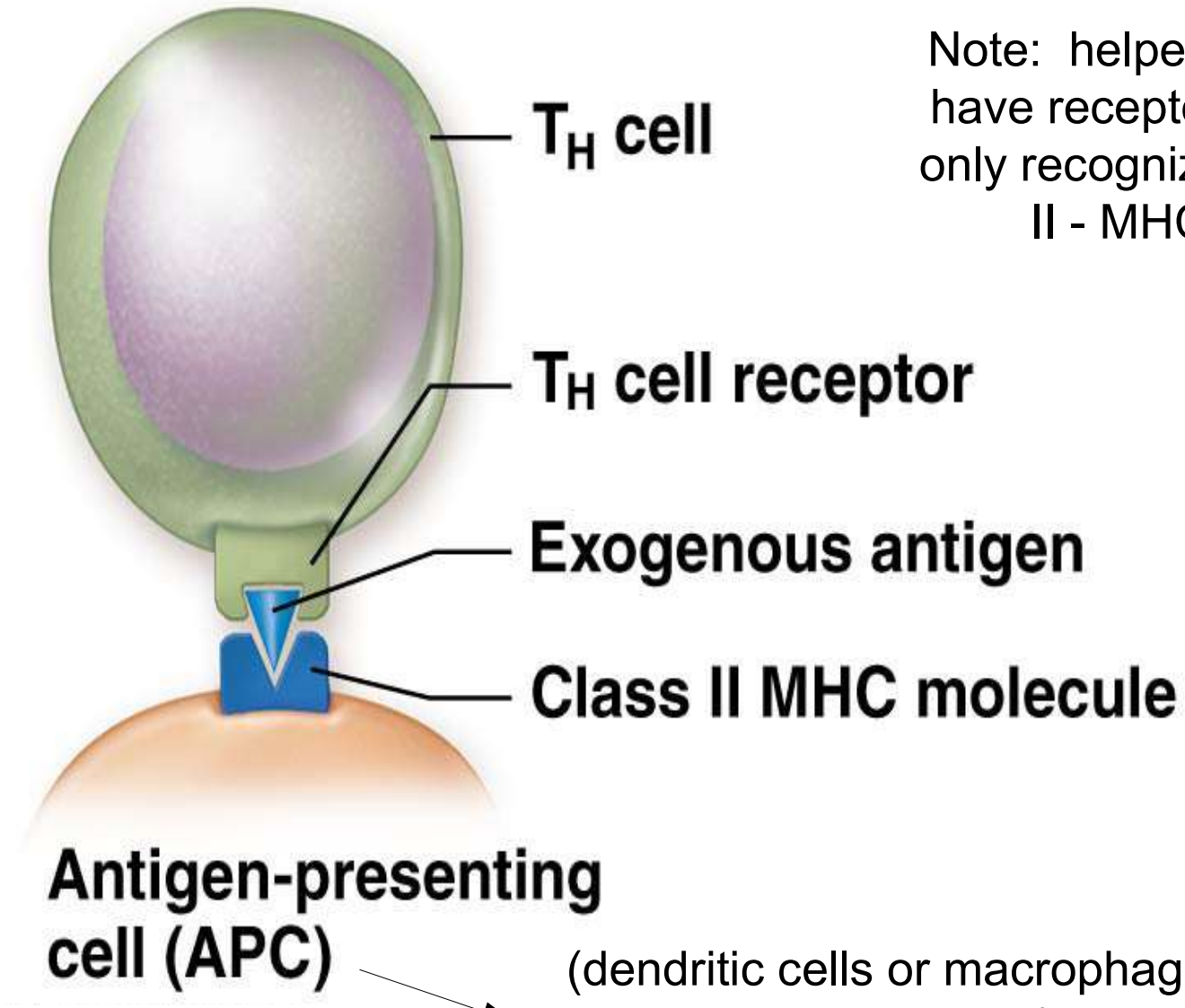
Dendritic cells have both Class-1 and Class II MHCP

Helper T-cells only bind to MHC-II

All other nucleated host cells have MHC-I

Cytotoxic-T-cells and NK cells only bind to MHC-I

This is how a naive helper T cell is activated and starts clonal selection.



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

(dendritic cells or macrophage display class-II)

How Are H-Tc Activated?

- Helper T Cells receptor bind to the epitope-MHC-II-complex of an antigen presenting cell (APC)

- If APC is a macrophage, after binding to the H-Tc the macrophage secretes interleukin-1 /// This activates H-Tc /// H-Tc responds by secreting interleukin-2 // 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 similar active H-Tc
  - H-Tc cytokines required to activate cytotoxic Tc
  - H-Tc cytokines required to activate B-cells
  - Form memory H-T cells – saved for future use
  - Form regulatory T cells – controls intensity of immune response

- Activated T Helper cells will also stimulate non-specific defenses / stimulate macrophage activity, NK cells, and inflammation

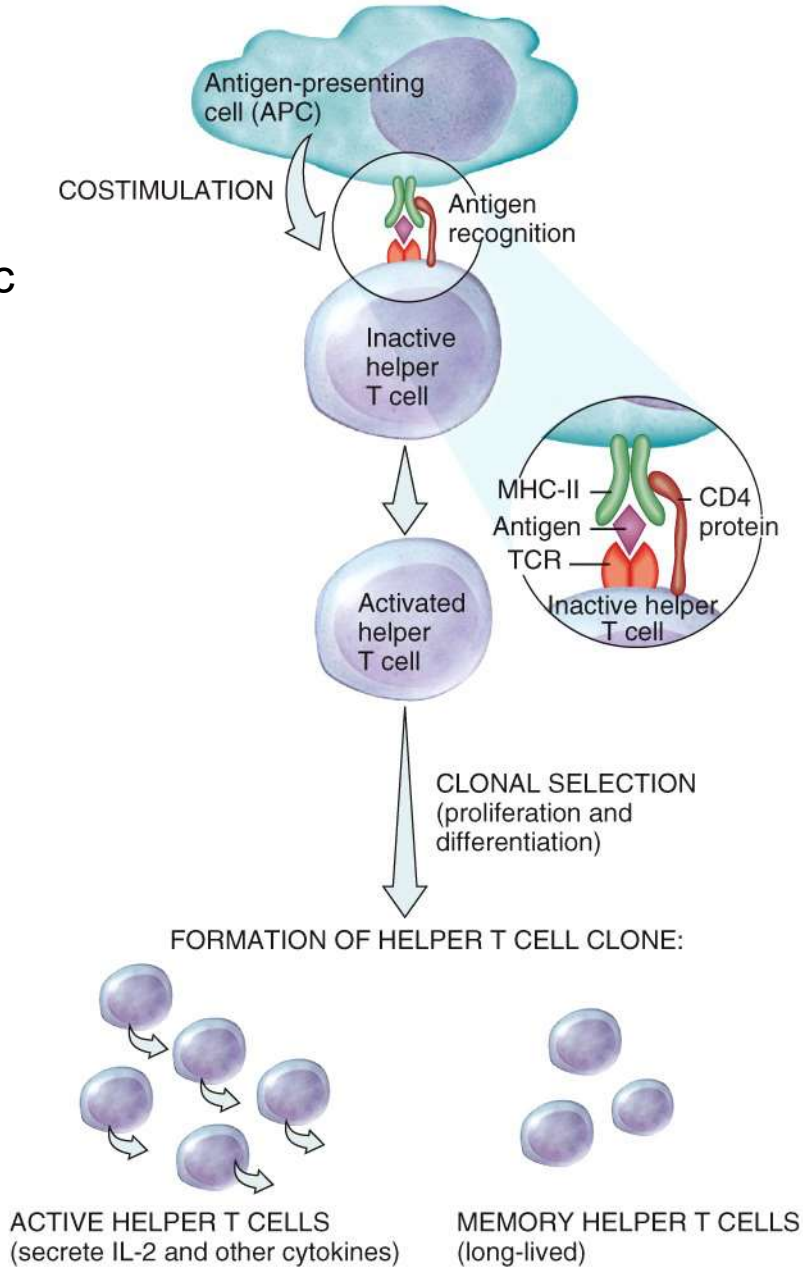
Activation of Helper T Cells

Immune system must activate helper T cells using Antigen Presentation Cells (either Dendritic Cells or Macrophage)

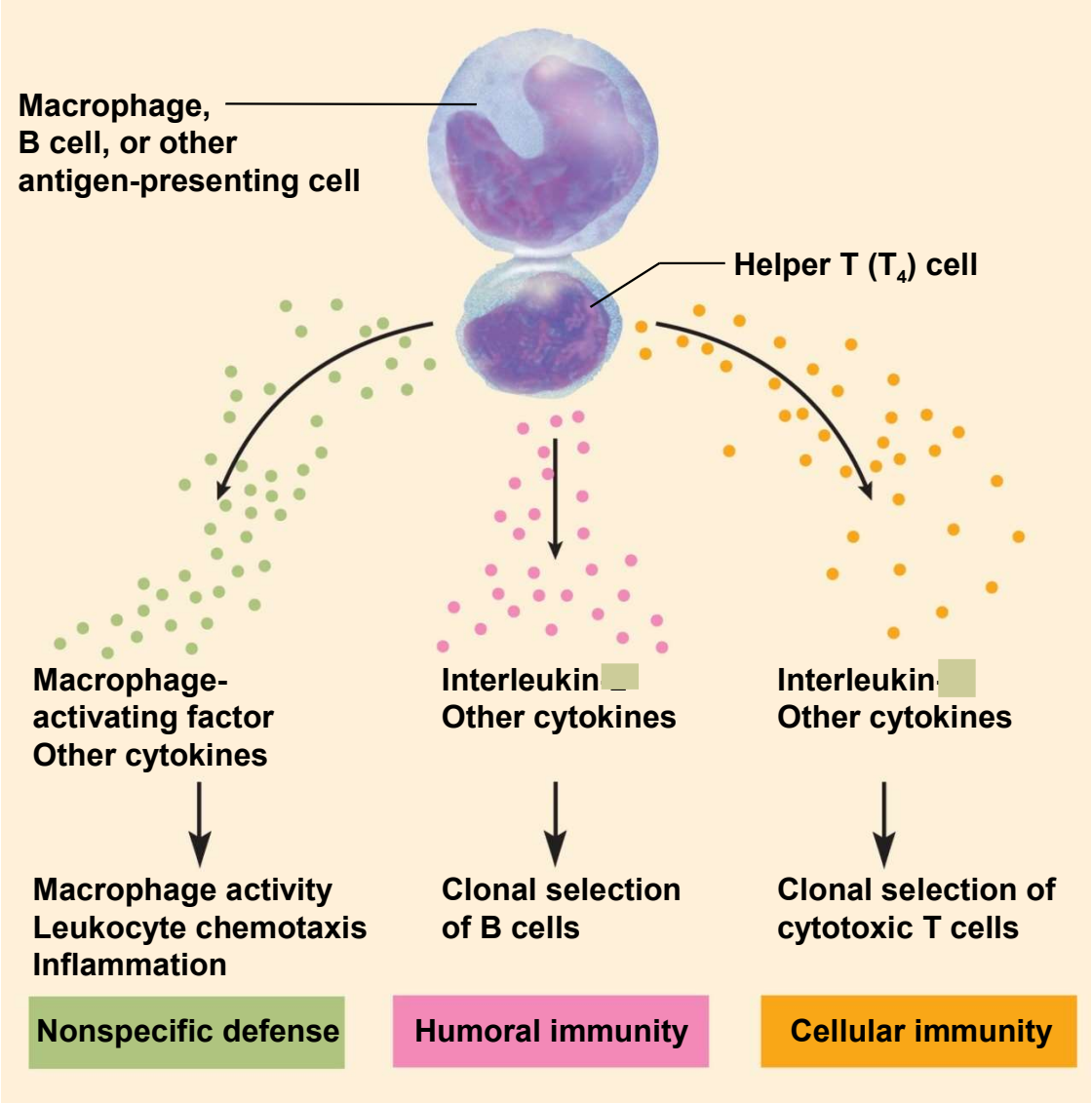
Activated Helper T cell must secrete cytokines (interleukin 2) to complete the activation of both cytotoxic T cells and B cells.

Helper T cells will also attract in area of infection macrophage activity, 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



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

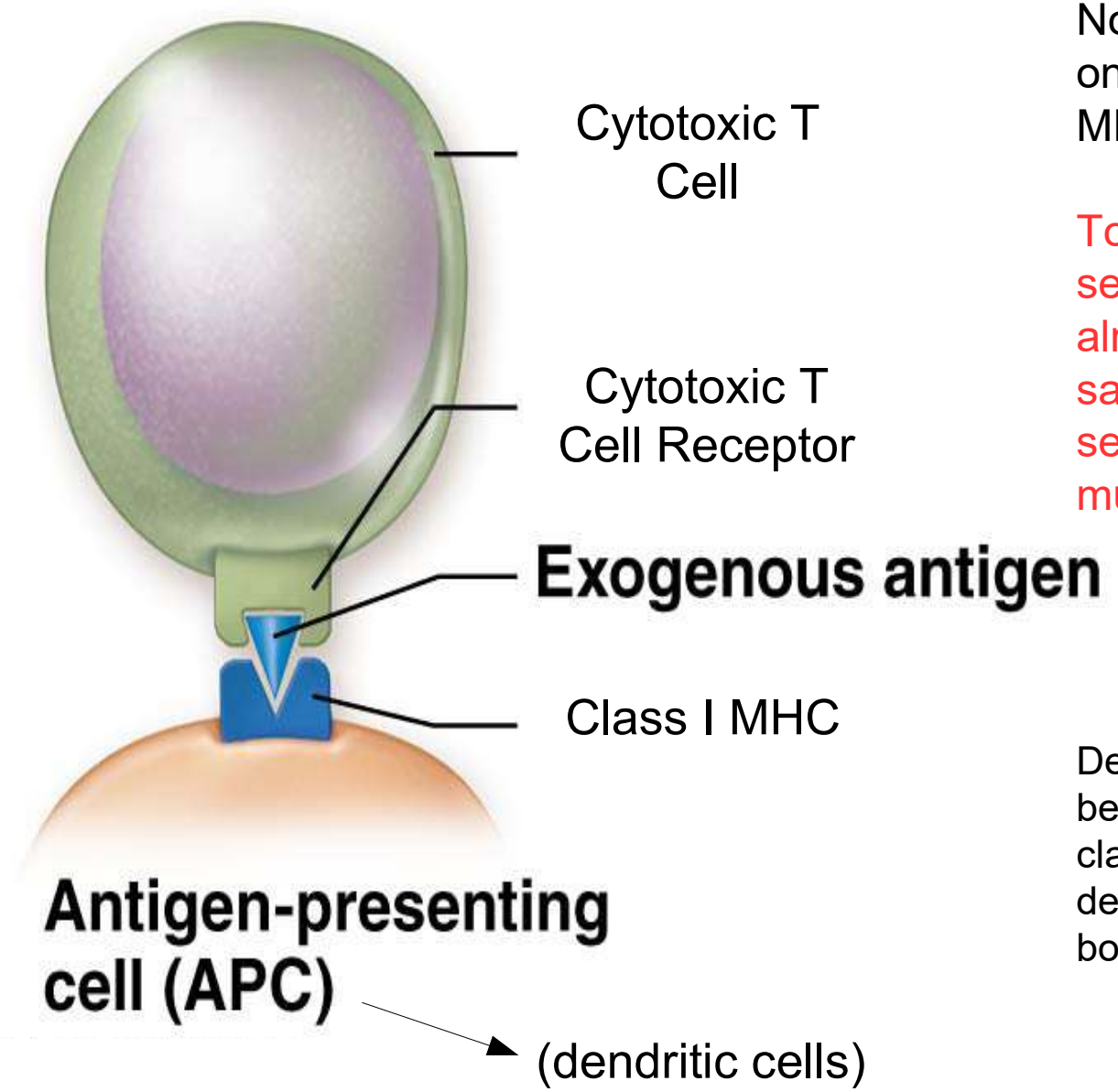


T_H Cells are required to activate both humoral and cellular immunity

TH Cells also releases cytokines which increase the activity of macophage, leukocyte chemotaxis and inflammation.

Without T_H Cells you will lack both the 2nd or 3rd line of defenses against pathogens!

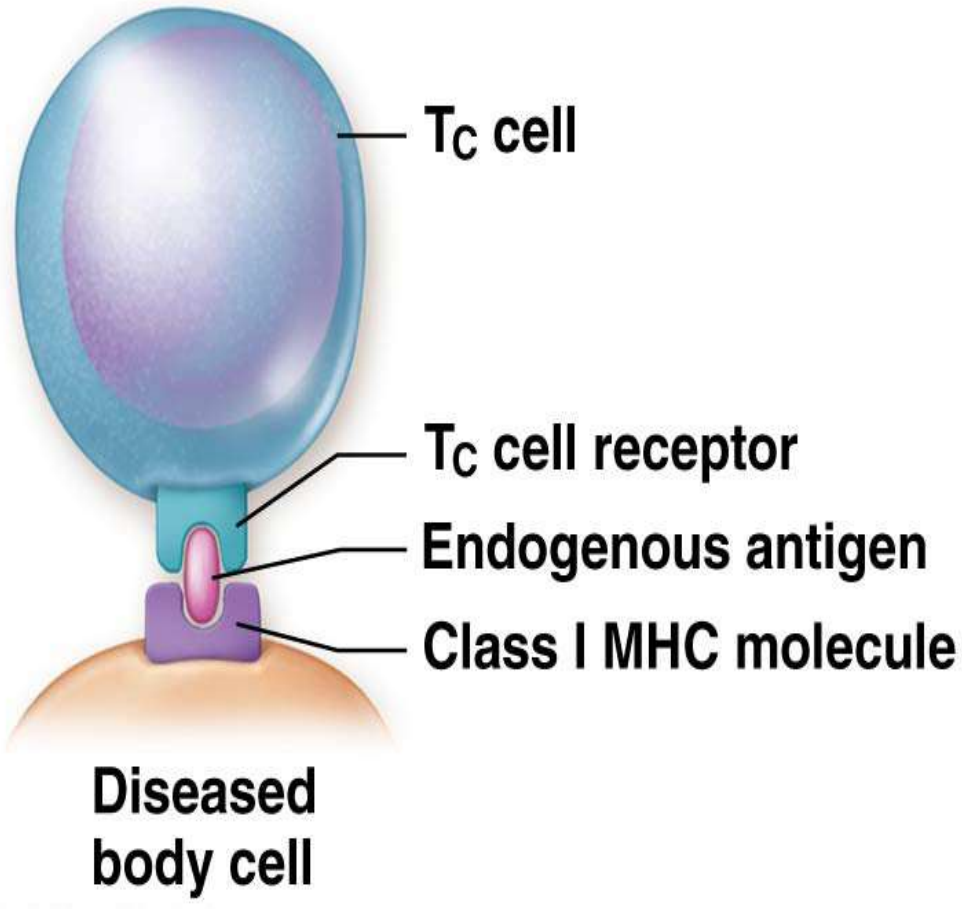
This is how a naive cytotoxic T cell is activated and starts clonal selection.



Note: C-Tcells receptors only recognize class I-MHCP

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

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 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

How Activated Cytotoxic Tc Know How to Dock onto Diseased Host Cell?

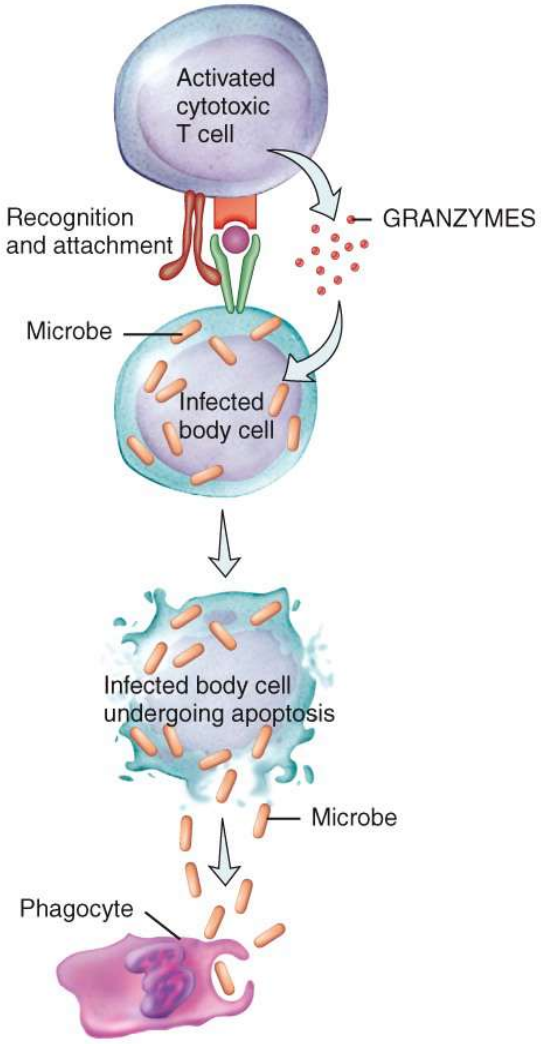
- Inside host cells MHCP-I pickup segments of "non normal proteins" (e.g. cancer or virus proteins) or foreign antigen, (e.g. bacterial antigens)
- These endogenous foreign "epitopes" are placed inside a MHCP-I
- The MHCP-I-epitope complex is then inserted into the plasma membrane
- Receptors on Cytotoxic T Cell (C-Tc) matched to MHCP-I-epitope binds on the surface of the infected host cell /// This complex is associated with only host cells (not APC).
- This allows the C-Tc to recognize a "specific" bacterial type that infects cell /// NK cells bind to cancer and viral epitopes

The Kiss of Death Delivered by the Cytotoxic T Cells

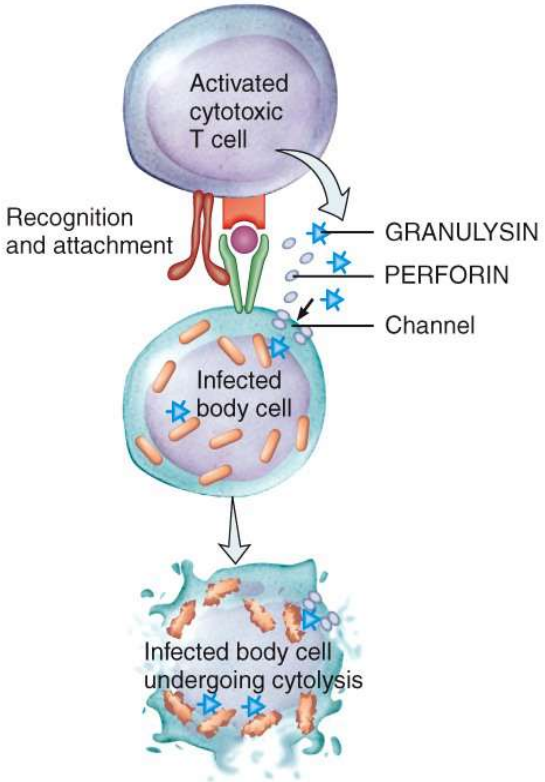
This is the react stage of the “three R”

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

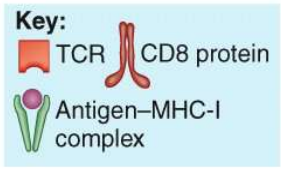
There is also a third way for C-Tc to kill host cells by releasing cytokines (e.g. cytokine storm)



(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 granulysin



The Car Metaphor to Cytotoxic-T-cell Activation

- If you want to drive your car then you must put the key into the ignition and turn the key to start the engine. /// This is the cytotoxic-T-cell receptor must bind to the dendritic cell MHC-I-epitope.

- If you want the car to move then you must shift car into drive. /// This occurs if a H-Tc secretes interleukin-2 onto the C-Tc bound to the MHC-1 epitope.

- Now the C-Tc is activated and undergo clonal selection (mitosis). These newly formed cells may now kill infected host cells that display foreign epitope-MHC-I complexes. /// During clonal selection memory H-Tc are also produced and these M-Tc rest in lymphoid tissues for future use.

- However, if you shift the car into neutral then the engine will continue to run but the care will not move. The car engine runs until there is no gas. /// This is what happens if a C-Tc binds to infected host cell without H-Tc interleukin-2. These C-Tc can not kill infected host cells.

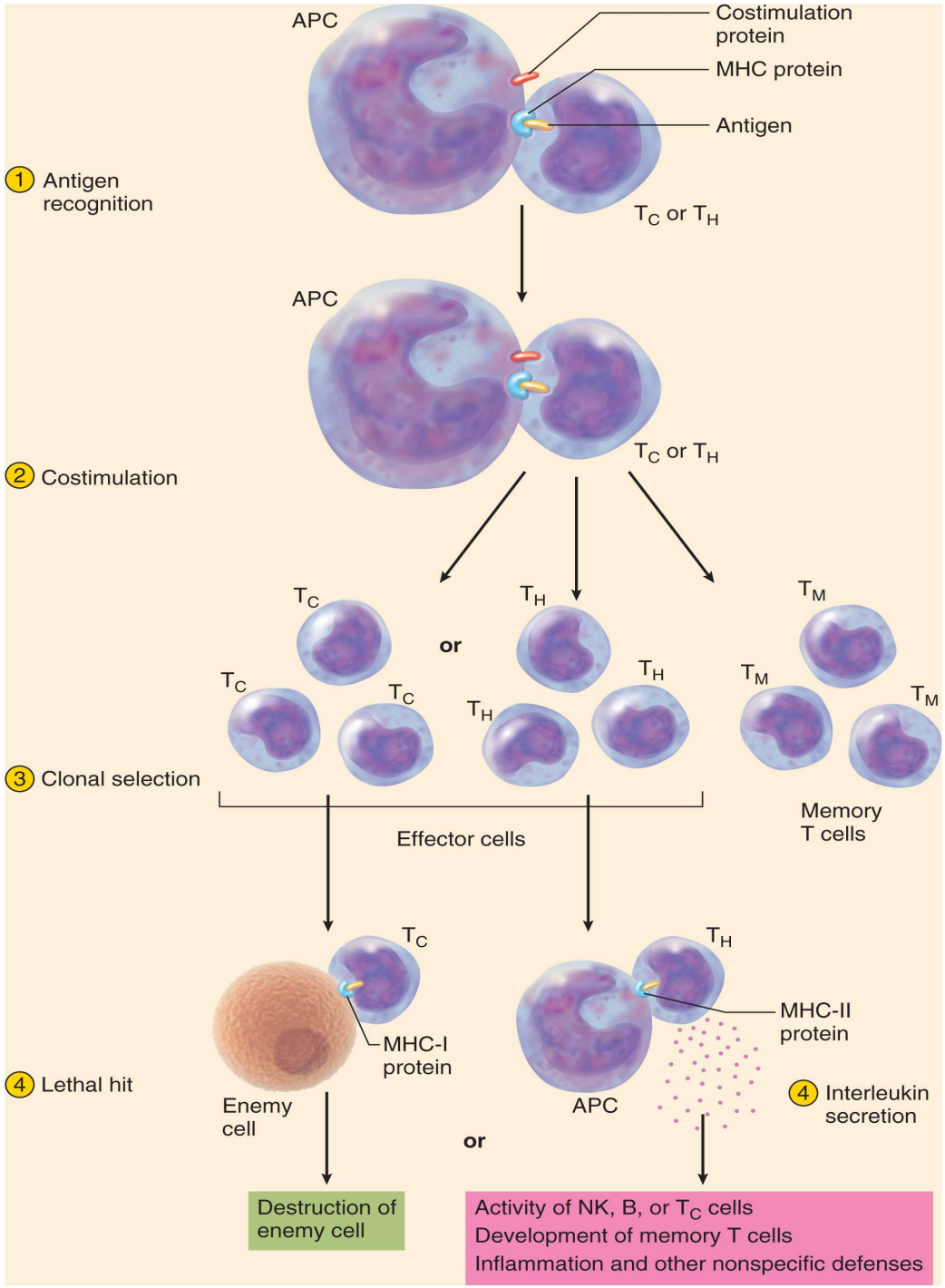
Activation of Cytotoxic T Cells

- 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)

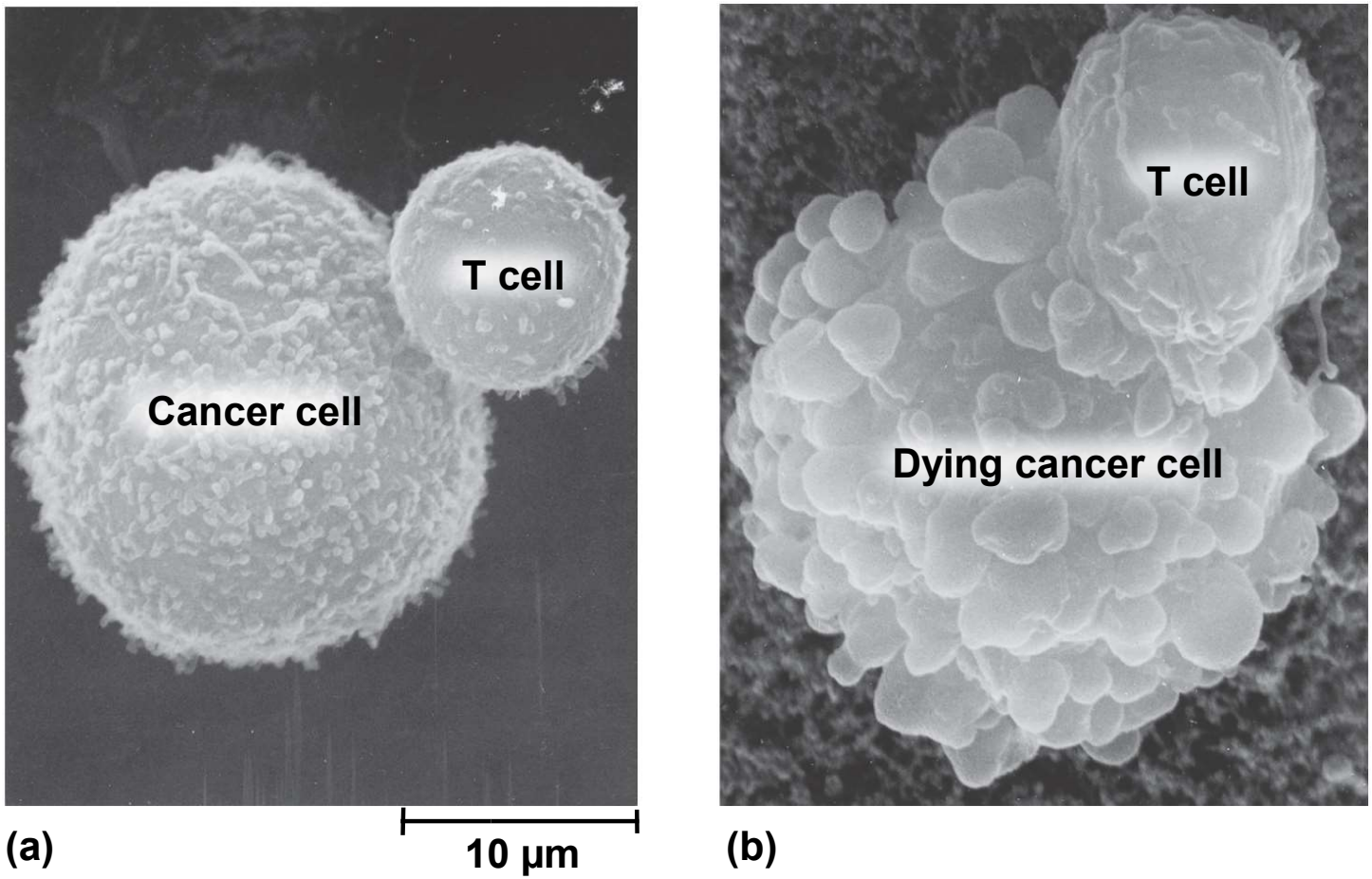
- Note CD8 protein on T cell binds to dendritic cell costimulation protein = "second check" for proper MHC-I receptor complex = costimulation

- 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)



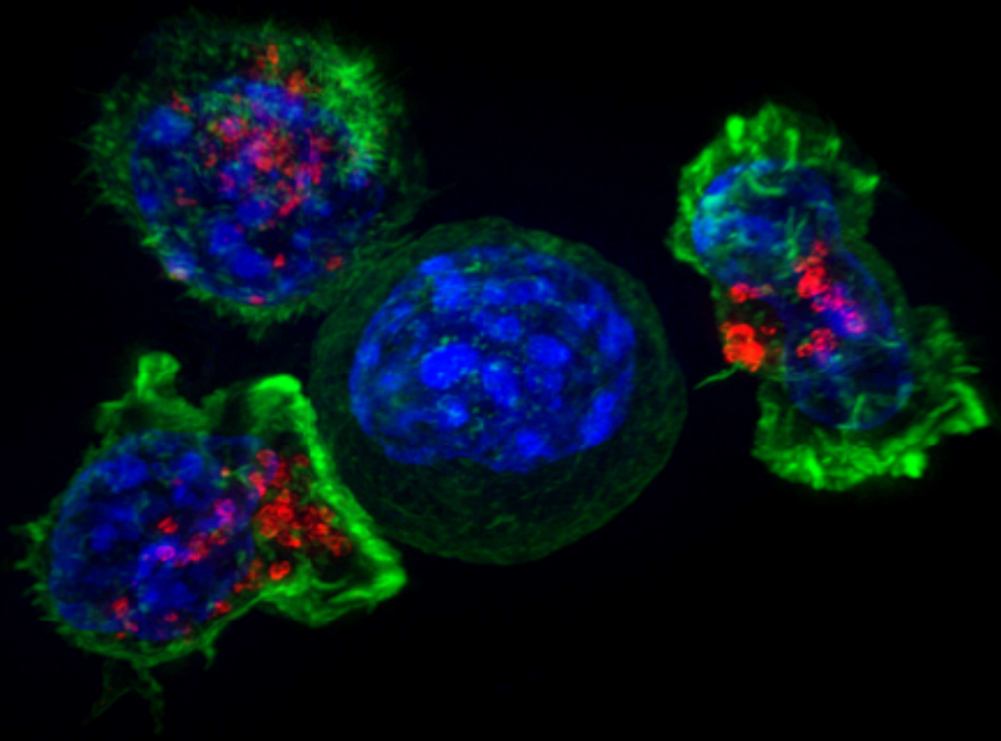
Cytotoxic T Cell Function



Dr. Andrejs Liepins

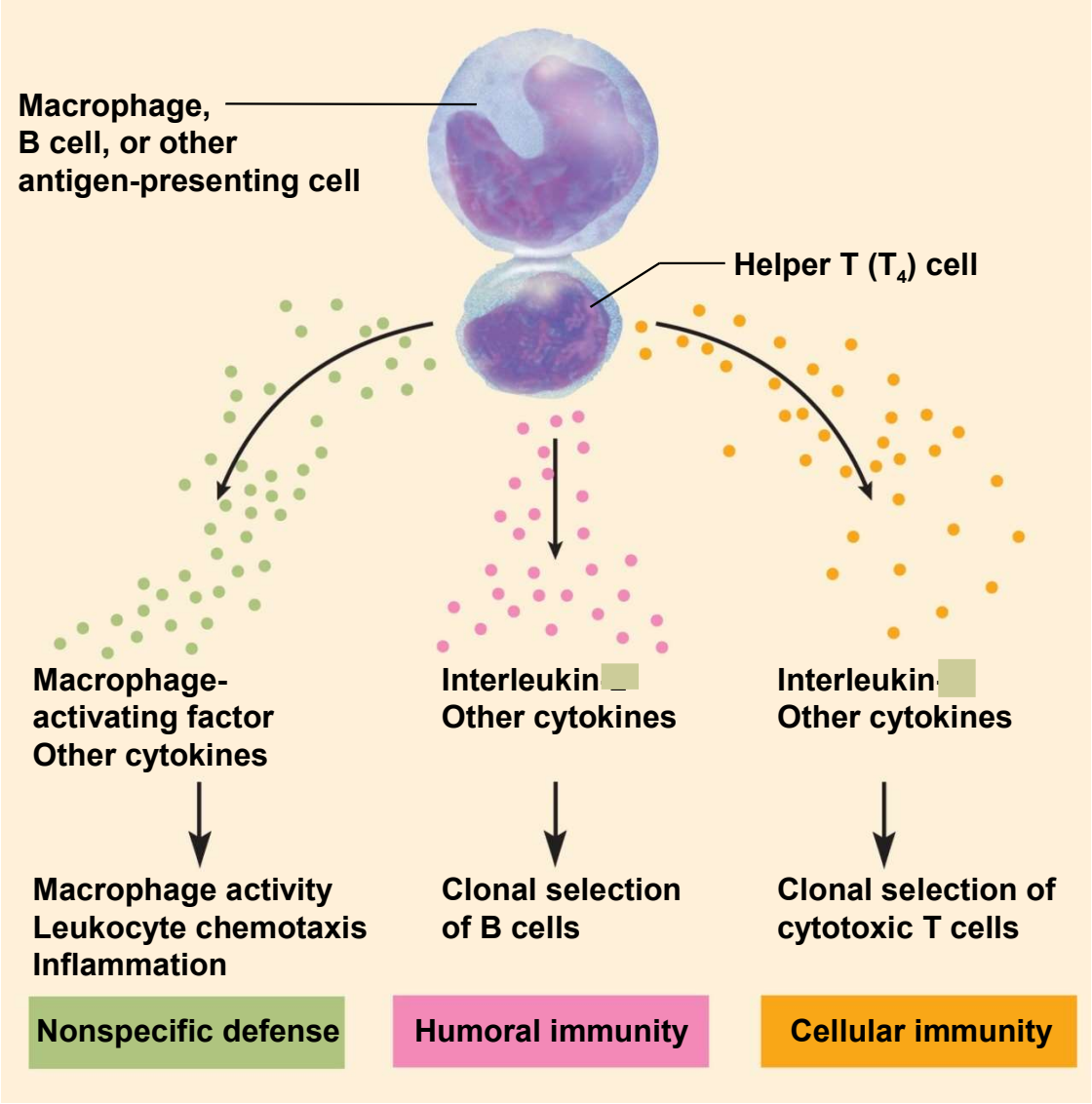
- cytotoxic T cell binding to cancer cell

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.

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

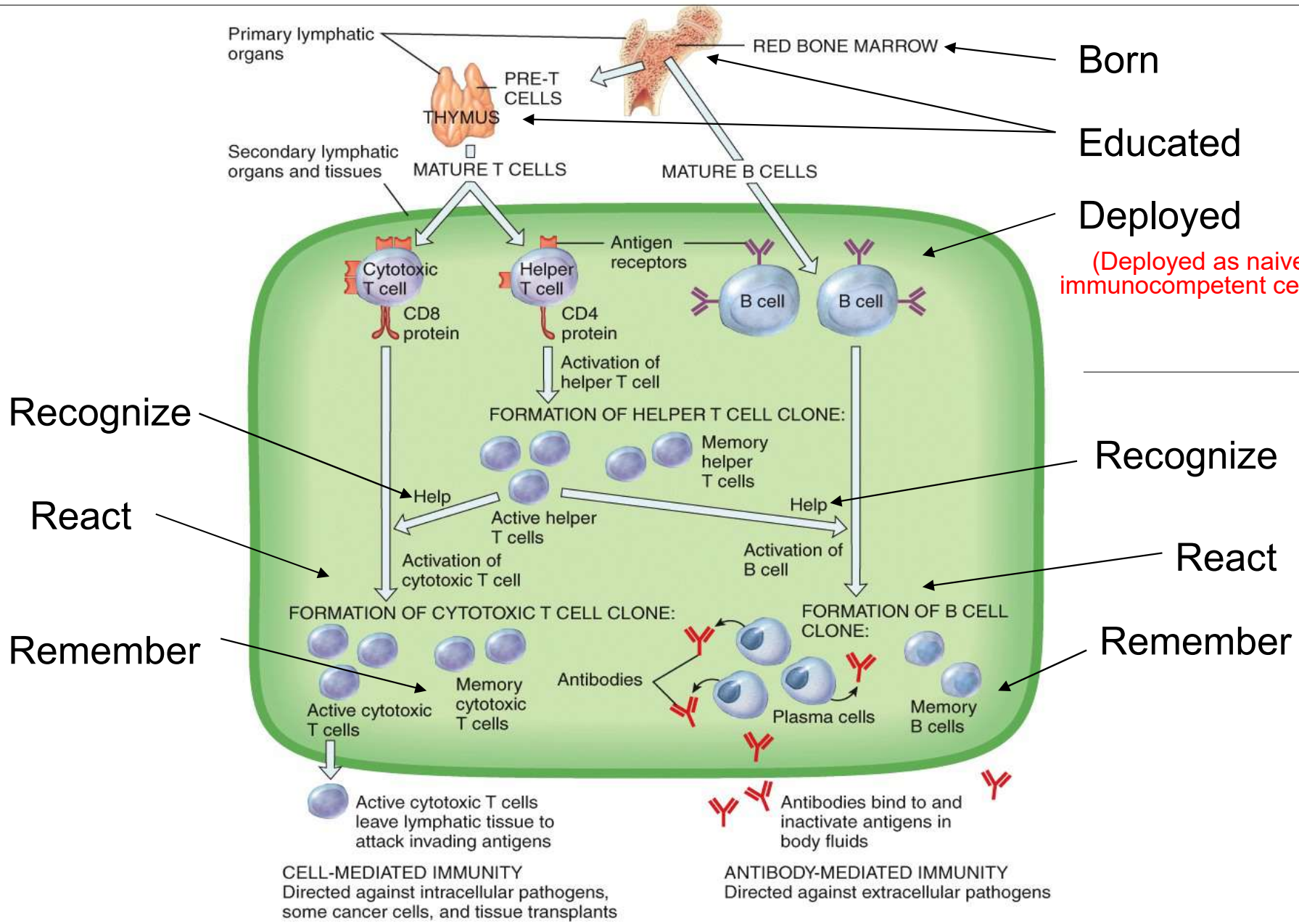


T_H Cells are required to activate both humoral and cellular immunity

TH Cells also releases cytokines which increase the activity of macophage, leukocyte chemotaxis and inflammation.

Without T_H Cells you will not have 2nd or 3rd line of defenses against pathogens!

Look at the H-Tc pathway. To complete C-Tc and B-cells activation, you must have activated H-Tc. All these cells have like receptors matched to same bacterial antigen.



Review of Developmental Stages in the Formation and Activation of Cellular and Humoral Immunity

Both systems (cellular and humoral immunity) undergo similar steps.

The first phase involves the formation and preparation of the immune cells. (born – educated - deployment)

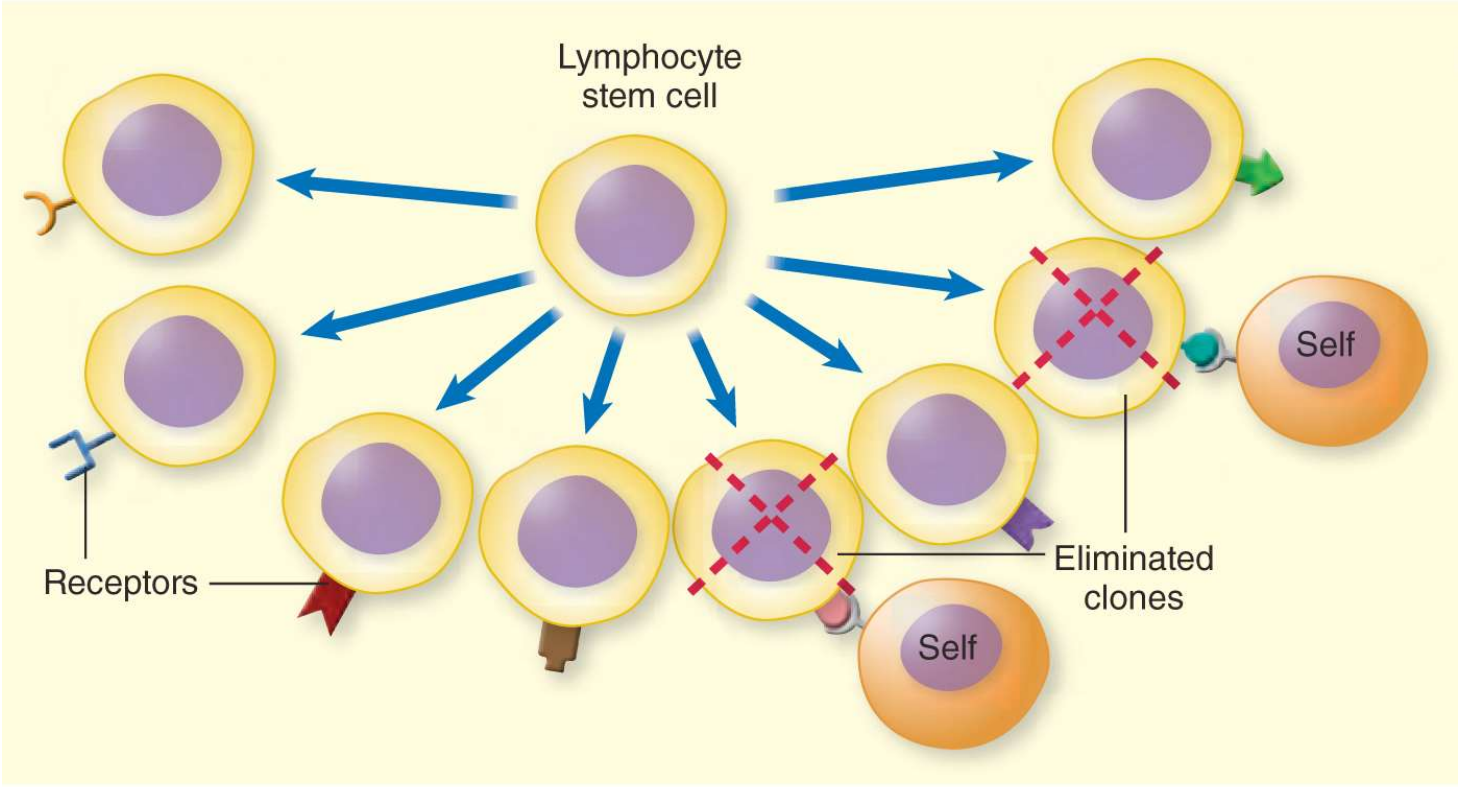
The second phase involves how these cells are transformed from inactive cells into active cells (i.e. able to kill pathogen or render pathogen harmless and tag for destruction). This is where colonal selection occurs and memory cells are made.

Second phase stages = the 3 R's

> recognize (two aspects = antigen presentation plus Tc activation)
> react (the attack or kill stage)
> remember (prevent future disease from same antigen)

After T Lymphocytes are “Educated” Each T Cell Has a Unique Receptor

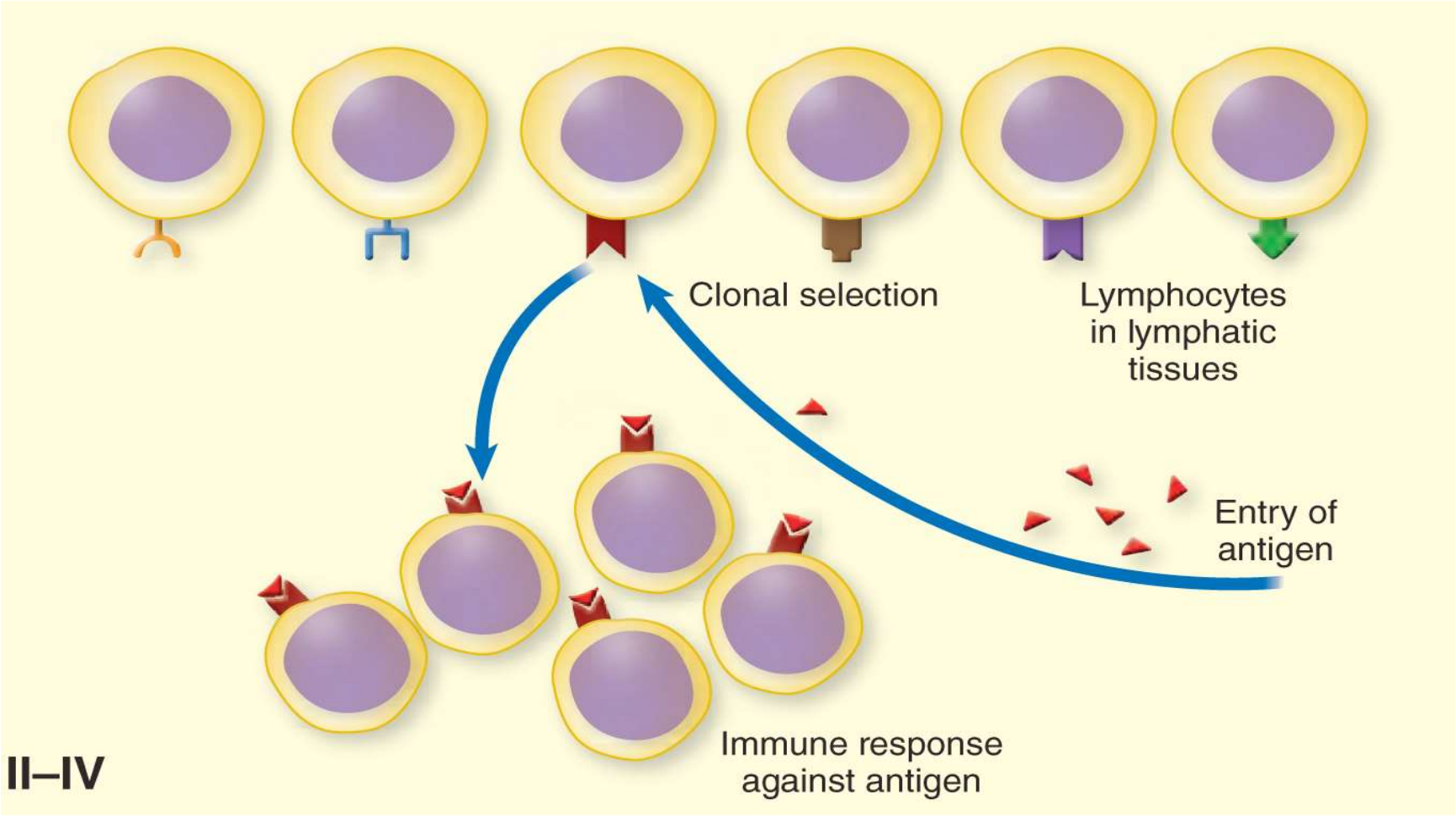
Deployed as “Naïve Immunocompatent” T Lymphocytes (helpers and cytotoxic)



Repertoire of lymphocyte clones, each with unique receptor display

Naïve Immunocompatent T Cells Activated by

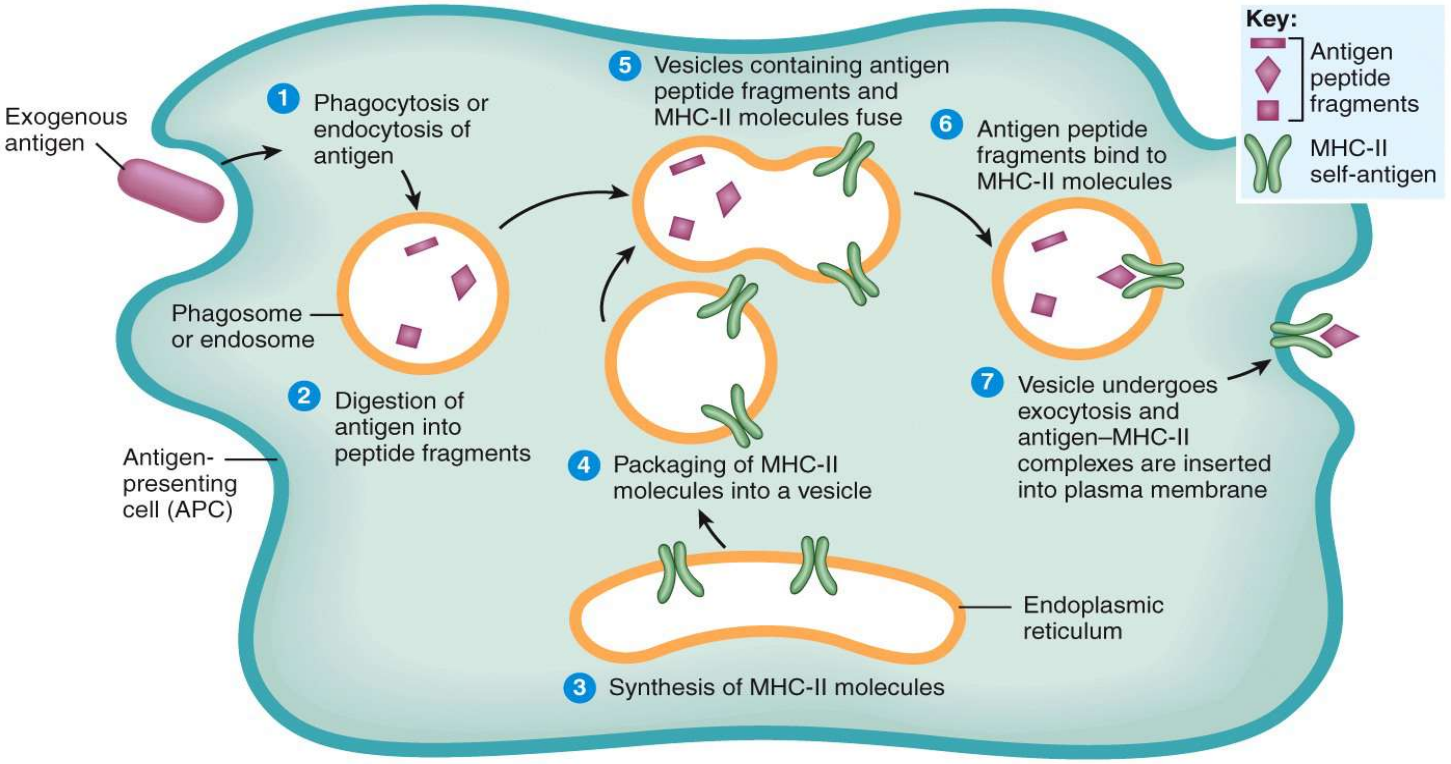
Unique Antigen (epitope) That Then Initiates Clonal Selection



Clonal selection results in mitosis where millions of similar cells are formed. All activated with similar receptors.

Antigens Processed by APCs Using MHC-II

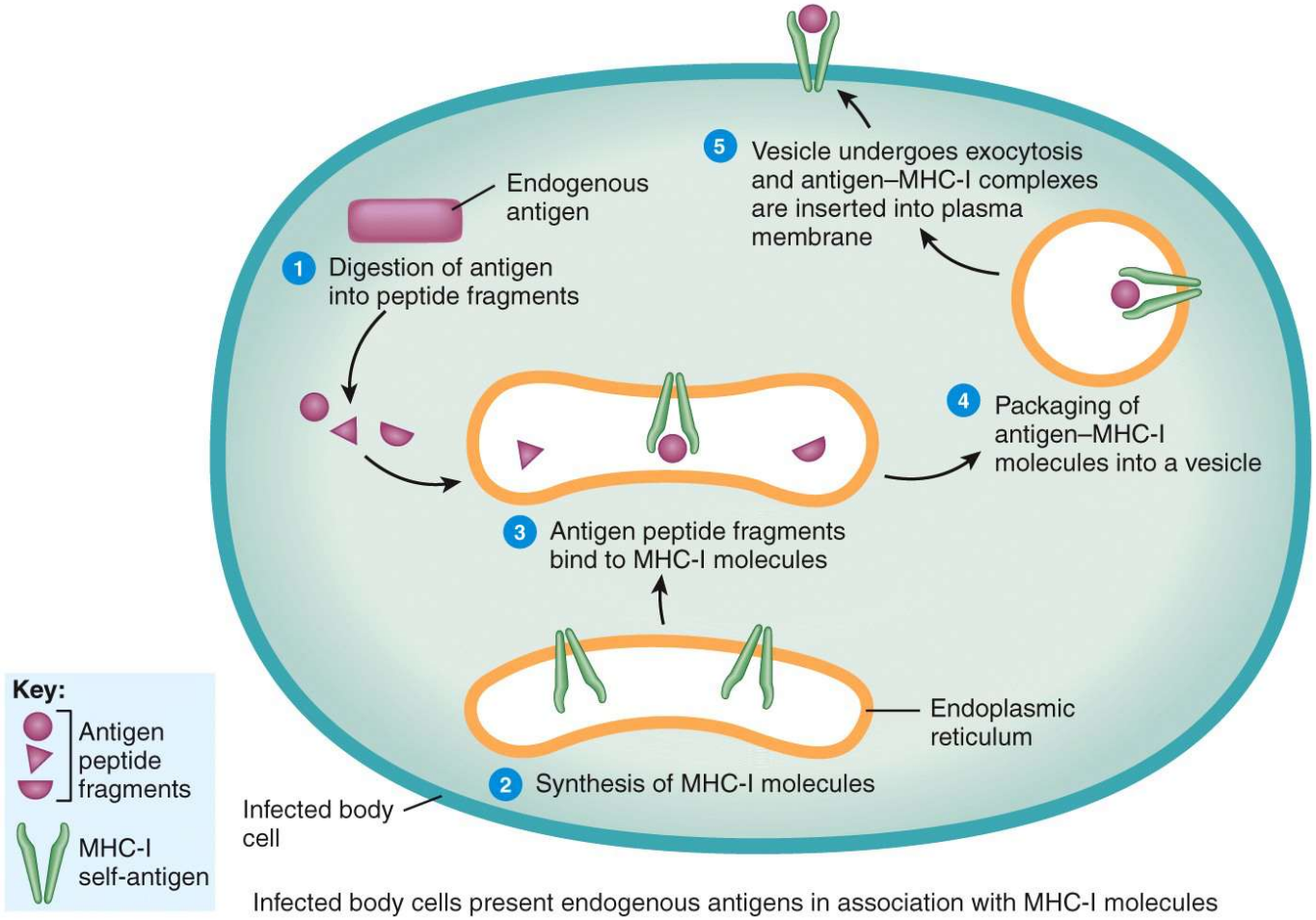
Macrophage and dendritic cells are antigen processing cells that use MHC-II proteins. The APCs engulf exogenous antigen and present epitope-MHC-II complex in plasma membrane. Naïve immunocompetent helperTcells (CD4) with matched receptors bind to the APC. This activates the helper Tcell.



APCs present exogenous antigens in association with MHC-II molecules

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

Placing a piece of the endogenous protein into the cell's plasma membrane will allow cytotoxic T cells" to recognize which cells are infected. If the cell is infected then the cytotoxic T cell will form a T-cell-receptor-MHC-1 complex. Endogenous implies the proteins are from the cell's cytoplasm. This may also include proteins from bacteria that are living inside the cell or proteins from virus that are multiplying inside the cell. // Only cytotoxic T cells recognize MHC-I type molecles. // Helper-T-cells secrete interleukin 2 to complete cytotoxic-T-cell complete activation.



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

How are B cells activated?

Humoral Immunity requires the action of B cells

- *Different classes of B cells (B cells, plasma cells, memory B cells, regulatory B cells)*
- *Each class has a special function*
- *Plasma cells are formed from B cells /// its the plasma cells that make antibodies // each plasma cell make 2,000 antibodies per second for approximately 7 days*
- *Antibodies attach directly 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*

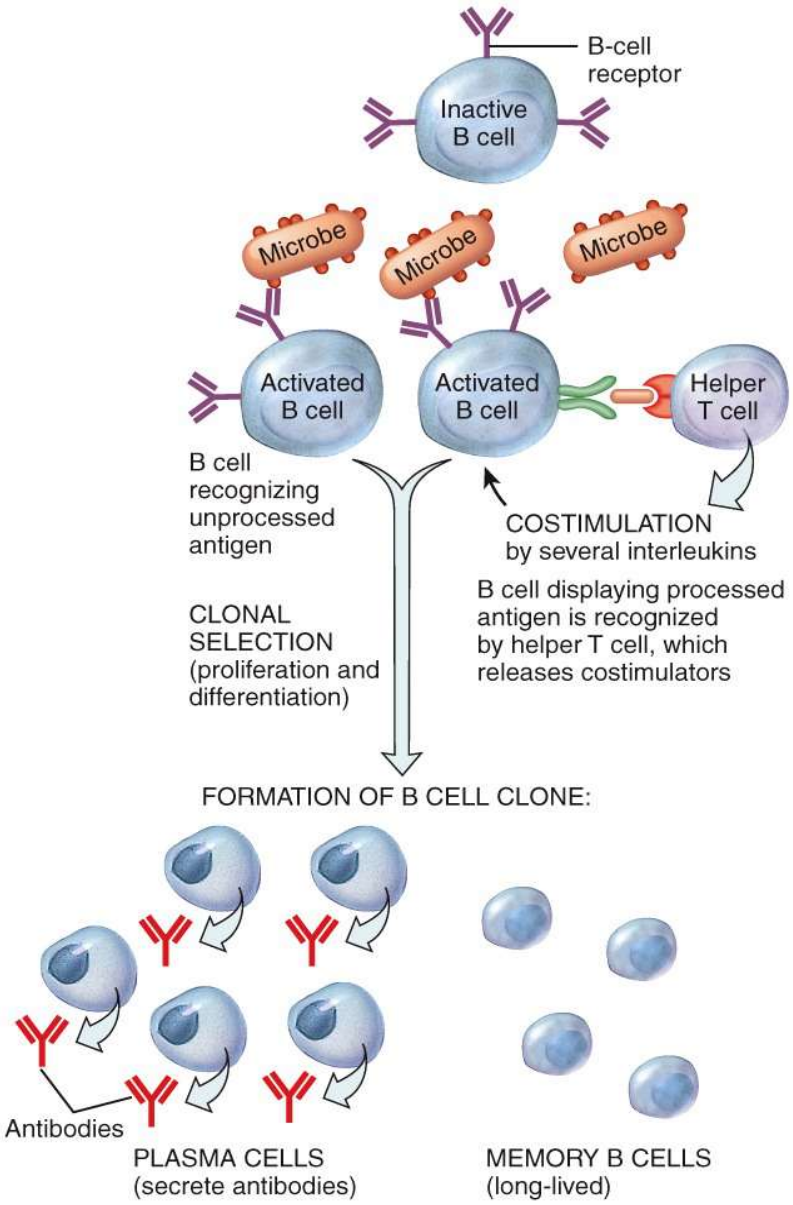
Activation of B Cells

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

Naïve immunocompetent B cells have two distinct activation methods with different outcomes // TH cell dependent and TH cell independent.

If B cells enter clonal selection without the Helper T cell – (no costimulation known as T cell independent) then… /// the B cell activation is less robust /// results in fewer plasma cells and less antibodies /// key idea: 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

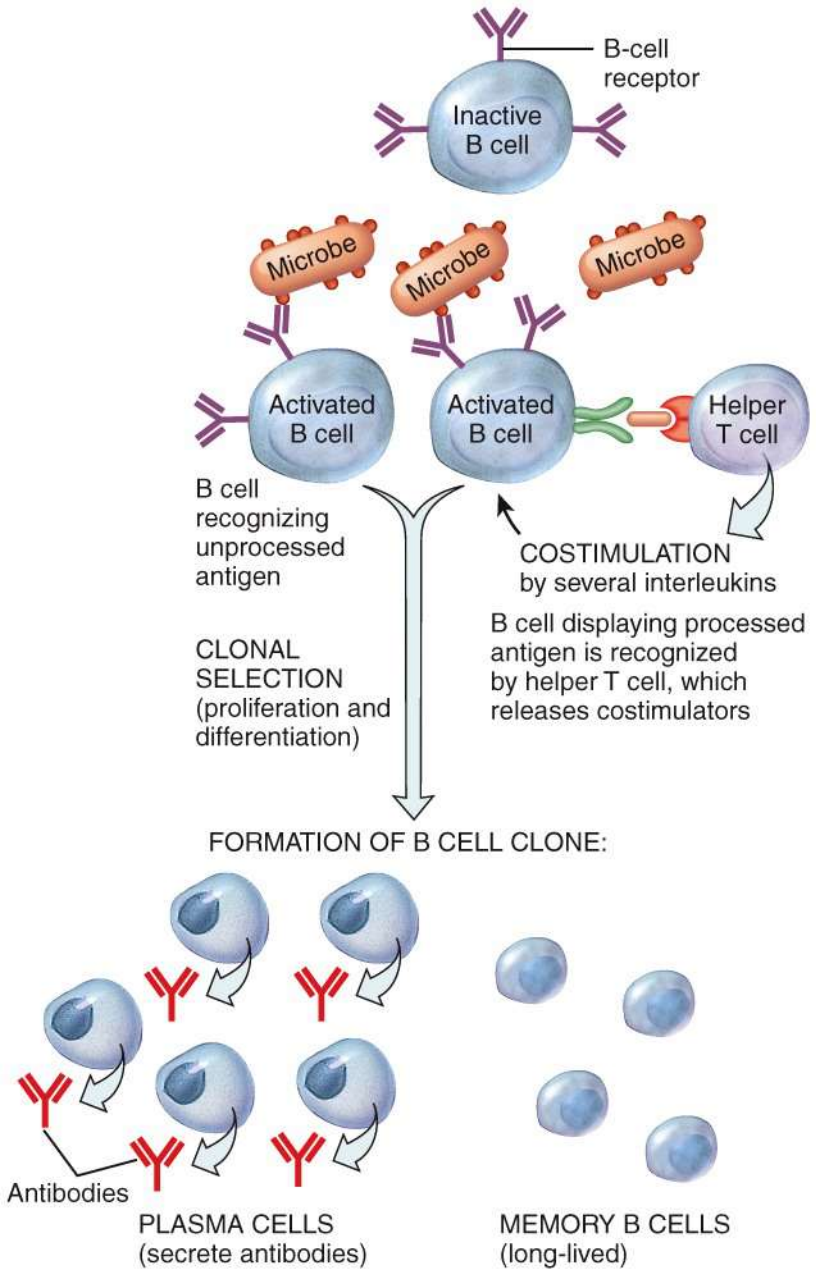
First step in “recognition” (activation) is pathogen binds to a B cell receptor.

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

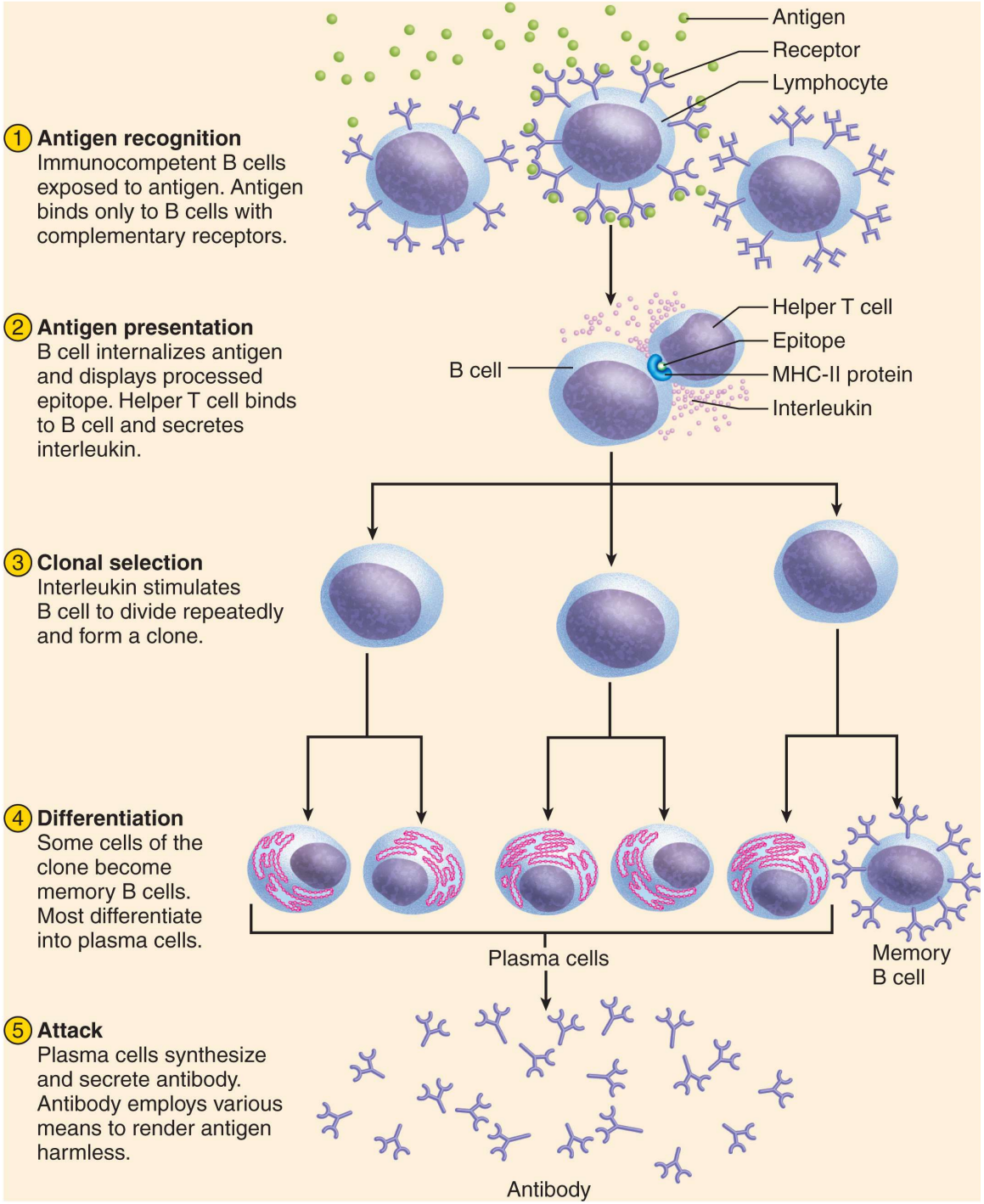
Previously activated Helper T cell with similar pathogen now binds it's T cell receptor with MHCP-II-epitope complex (second step)

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

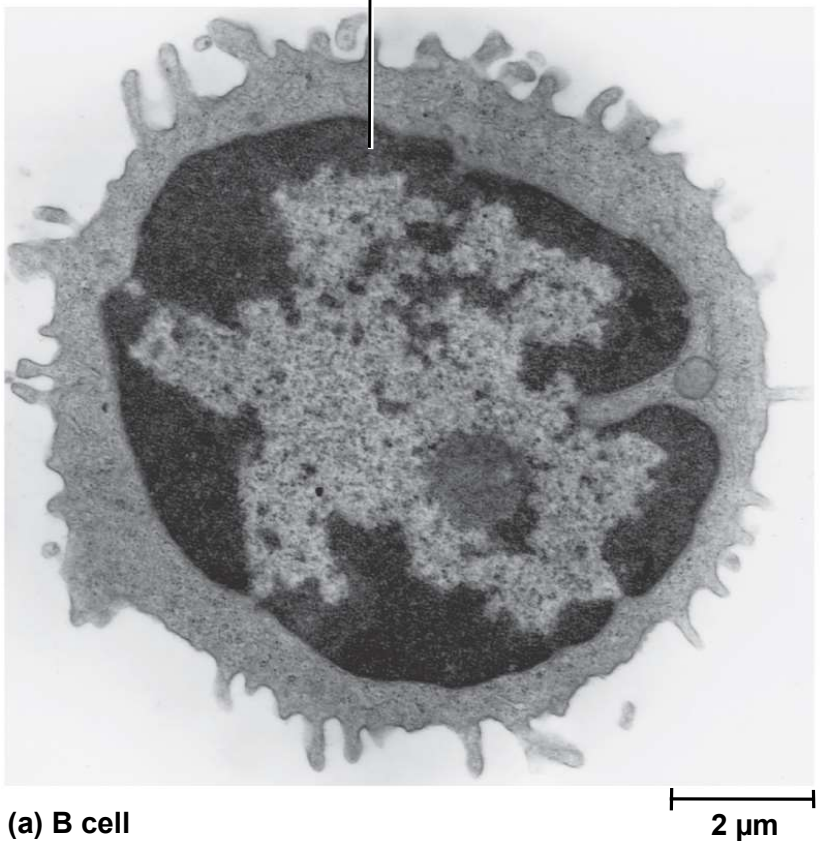
Plasma cells and memory B cells formed // Plasma cells make 2,000 antibodies per second per cell for 7 days.



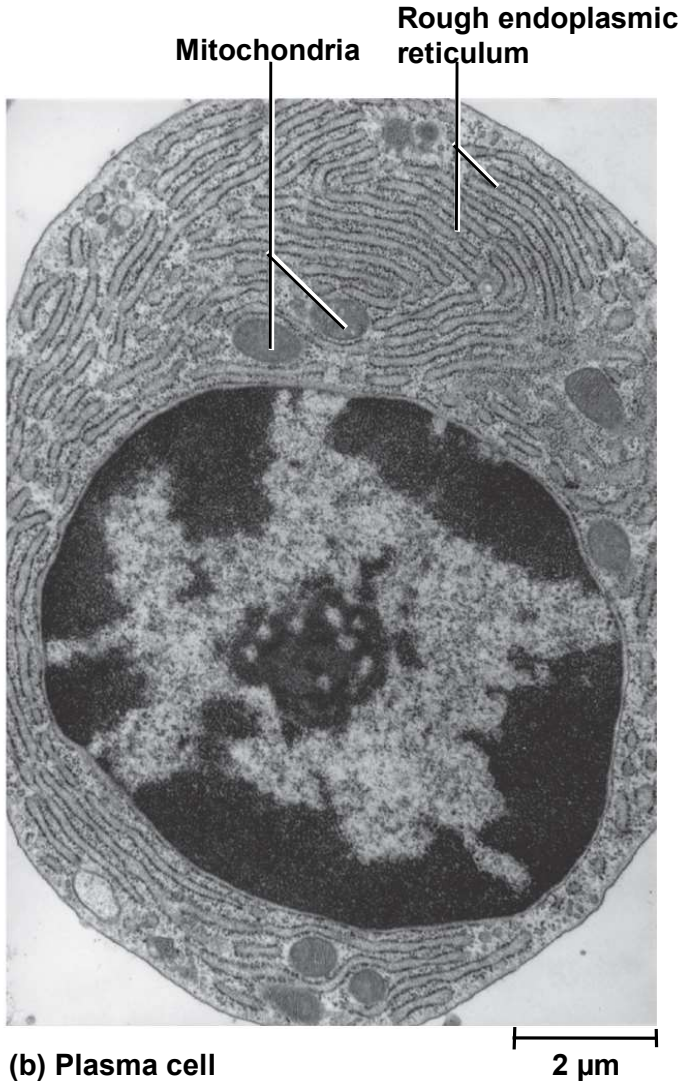
B Cells to Plasma Cells



B cells to Plasma cells

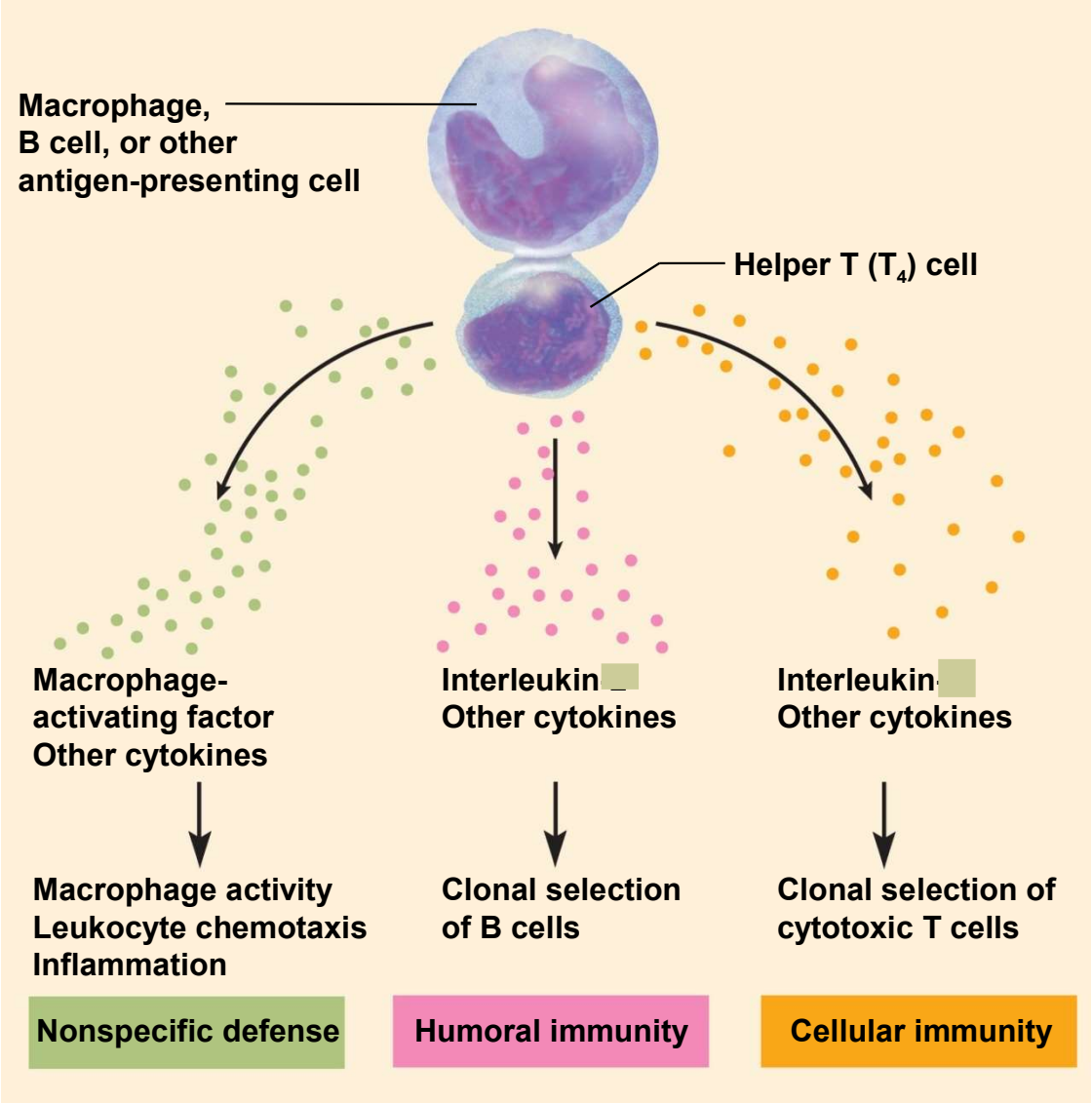


(a) B cell



(b) Plasma cell

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



T_H Cells are required to activate both humoral and cellular immunity

TH Cells also releases cytokines which increase the activity of macophage, leukocyte chemotaxis and inflammation.

Without T_H Cells you will not have 2nd or 3rd line of defenses against pathogens!

Review of Cellular Immunity

- *Cellular Immunity requires the action of four different T Cells*
  - *Different classes of T Cells (helper, regulatory, memory, cytotoxic)*
  - *Each class has specific functions*
  - *These cells communicate with each other using cytokines*
  - *Cytotoxic T cells (Tc) are the only T cell that kill with specificity infected host cells*
  - *NK cells (also a lymphocyte) are able to kill infected host cells but without specificity // NK cells provide "immune surveillance killing host cells infected with cancer or virus.*

What is the end game?

- If a naive cytotoixic Tcell (CD8) binds to an infected cell displaying an epitope-MHCP-I-complex then this is *the first step in the activation of the cytotoxic T cell /// the CD8 protein of the Tcell receptor must also link to the infected cell (co-stimulation).*

- The *second step requires that an already activated Helper T Cell (that has similar receptor type) must "co-activate" the cytotoxic-Tcell-CD8-epitope-MHCP-I complex* by secreting the cytokine – interleukin 2 //// interleukin 2 allows clonal selection of the C-Tc to occur – producing many active C-Tc cells as well as the formation of M-Tc- /// critical step was helper T cell secreting interluken 2

- Clonal selection now results in production of millions of identical activated *cytotoxic T cells //// all with similar cytotoxic T cell receptors matched to the pathogens' epitope --- these C-Tc can now bind to and kill infected host cells*

- During clonal selection mitosis of m-Tc are also formed /// migrate to lymph nodes where they will "rest " until "second exposure" occurs

- All host cells that now display the MHCP-I-epitope can now be killed by newly activated cytotoxic-Tc cells when they "dock" onto the MHCP-1 epitope complex of the host cells

Key Questions

These are key factoids that you need to know about acquired immunity.

- Where are the B and T immune cells produced (i.e. born)?
- Where do immune cells go to mature (i.e. get educated)? What does this mean?
- What must happen to an immature immune cell before they become functional (complete their education)?
- After immune cells are educated, where do they go (i.e. deployment)?
- What does it mean to be naive immunocompetent?

Key Questions About Acquired Immunity

- How are the educated deployed immune cells *(now called naive immunocompatent T and B cells)* "activated"?

- *Note: Activation means these cells will be able to recognize and react to the pathogens.*

- What is the sequence of events that follows T and B cells activation? (The Three Rs)

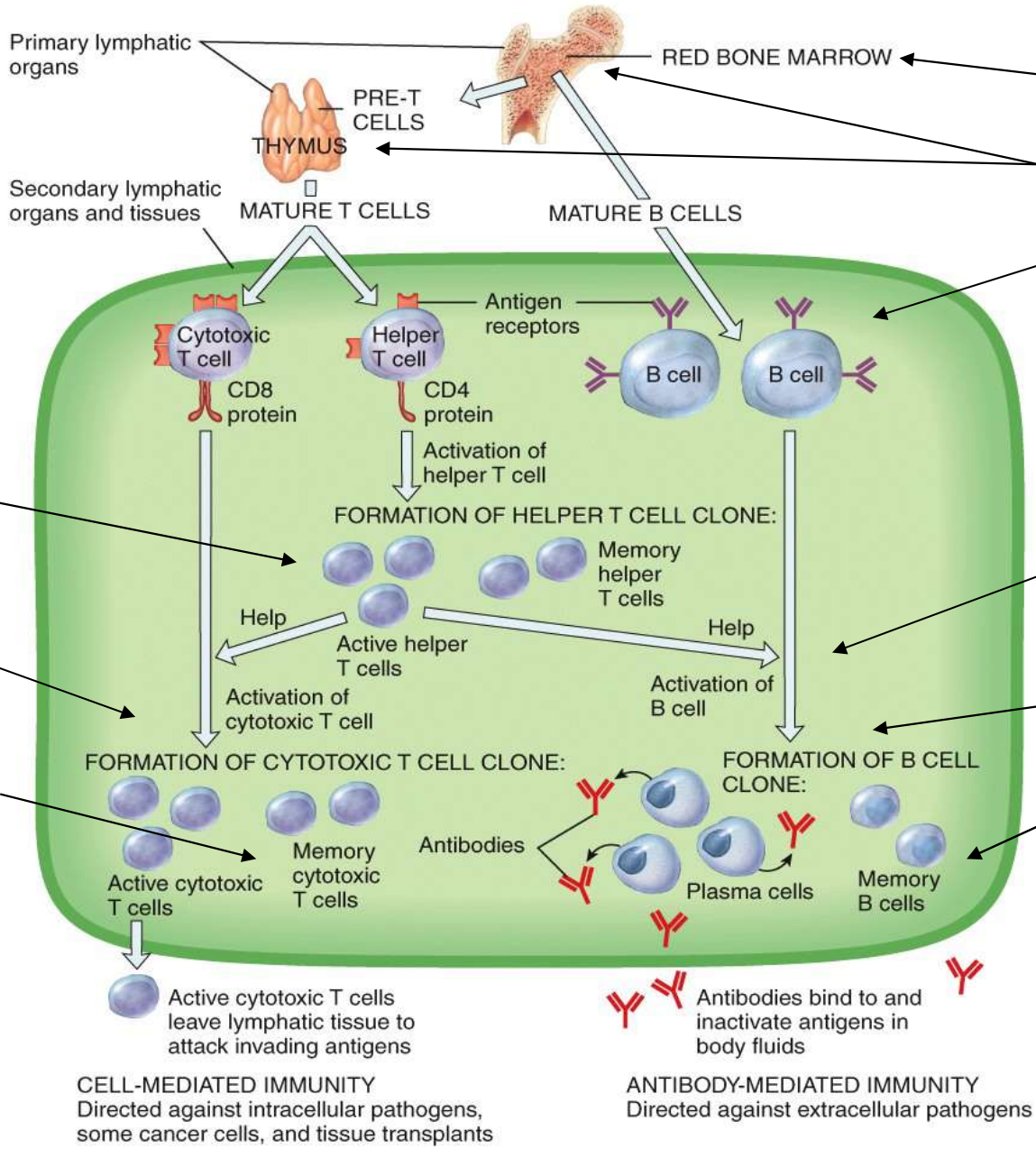
  - 1) recognize (means the immune cells have been activated – able to bind to MHCP)

  - 2) react (able to attack)

  - 3) remember

- What will happen to activated immune cells after the pathogen is defeated? *(apotosis for both the cytotoxic T cells and plasma cells // but memory T cells and memory helper B cells live on /// some are reported to live for over 70 yrs within the lymph nodes!)*

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

React

Remember

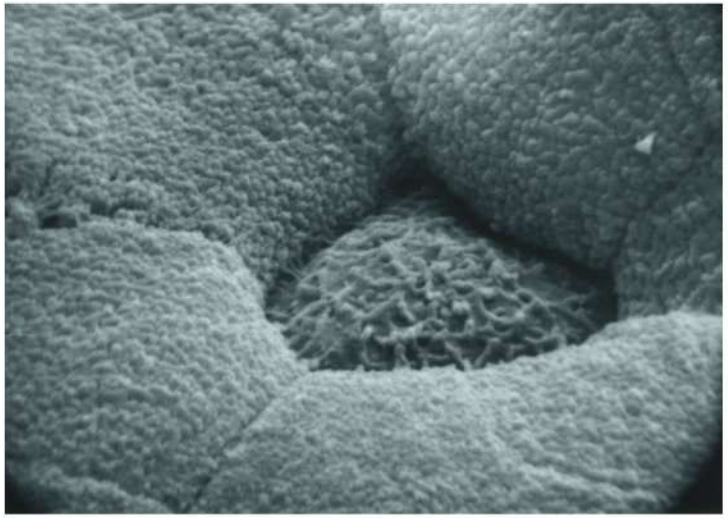
M Cells

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.

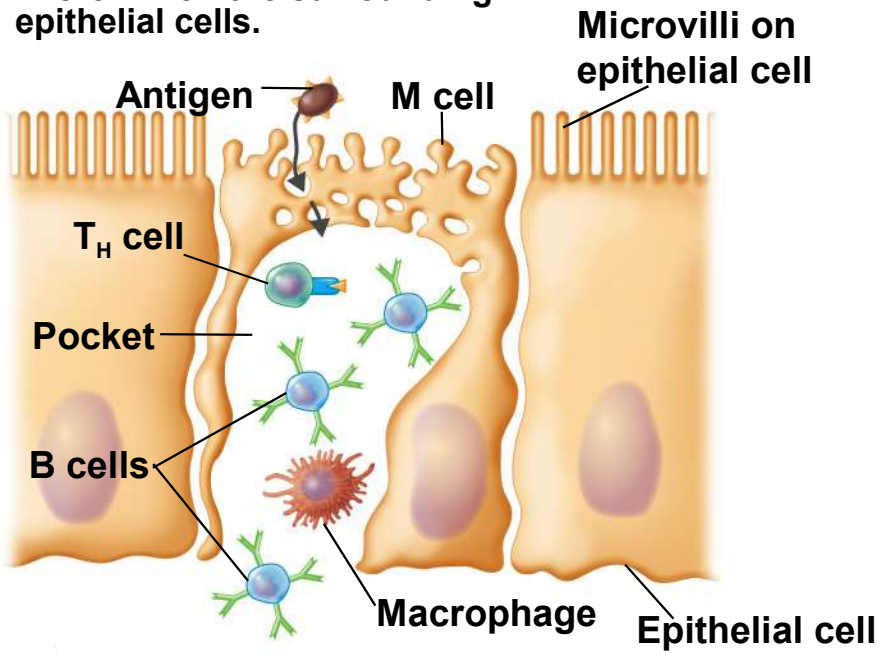
Immune system recognize bacteria even before it is in our bodies

Immune system starts to prepare defenses against bacteria.

Tonsils have a similar function in bucal cavity!

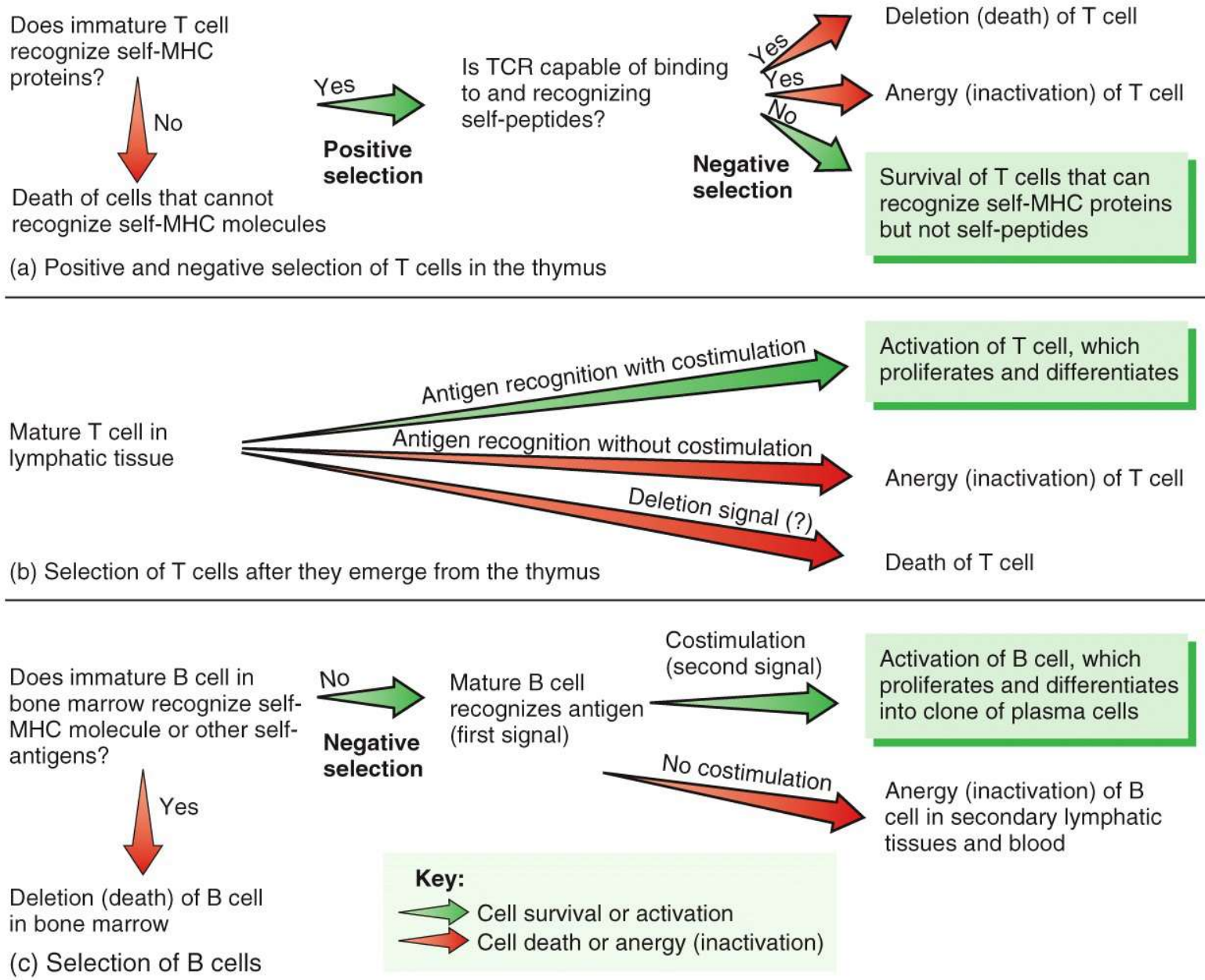


(a) M cell on Peyer's patch. Note the tips of the closely packed microvilli on the surrounding epithelial cells.

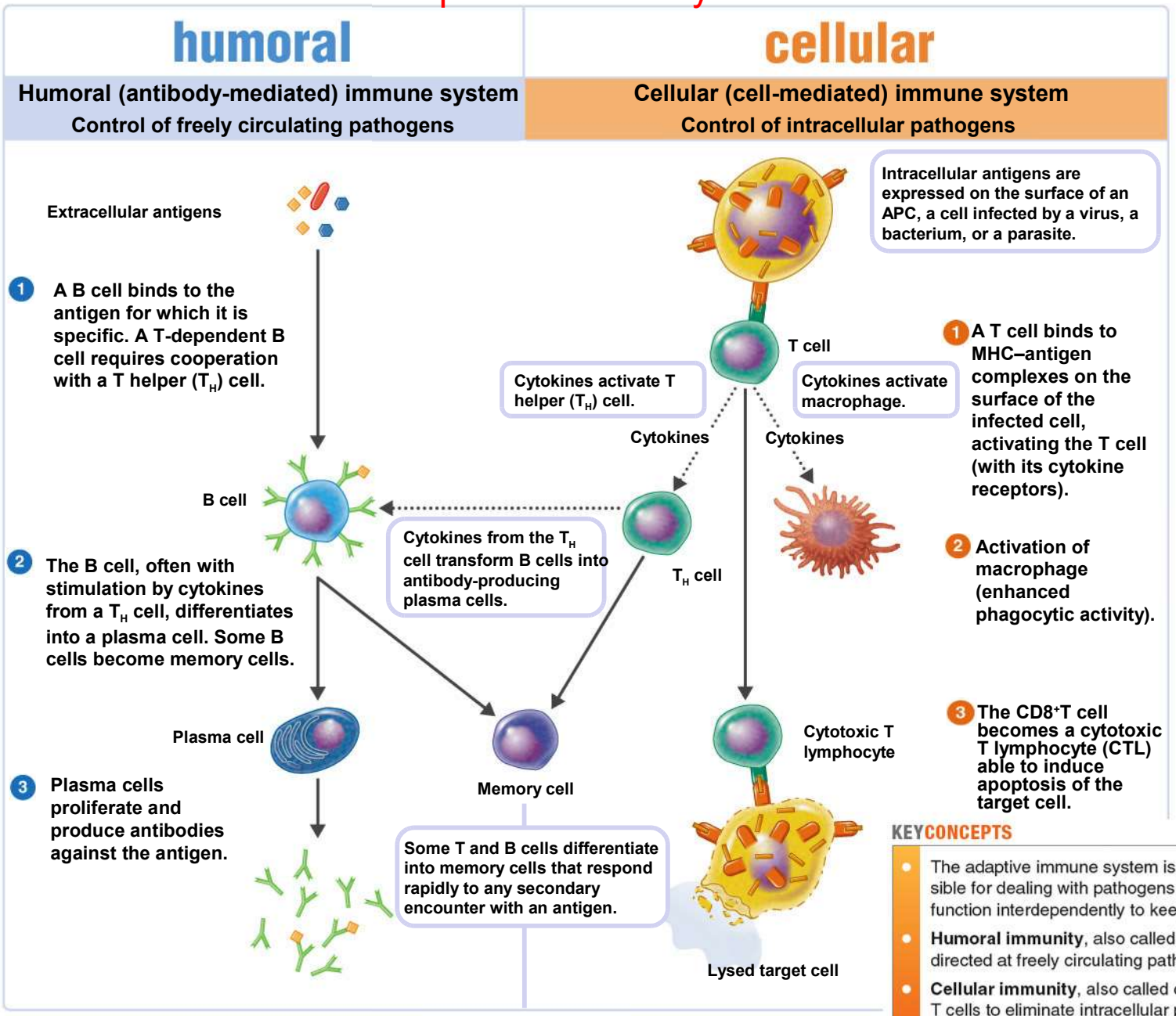


(b) M cells facilitate contact between the antigens passing through the intestinal tract and cells of the body's immune system.

Summary of Immunity



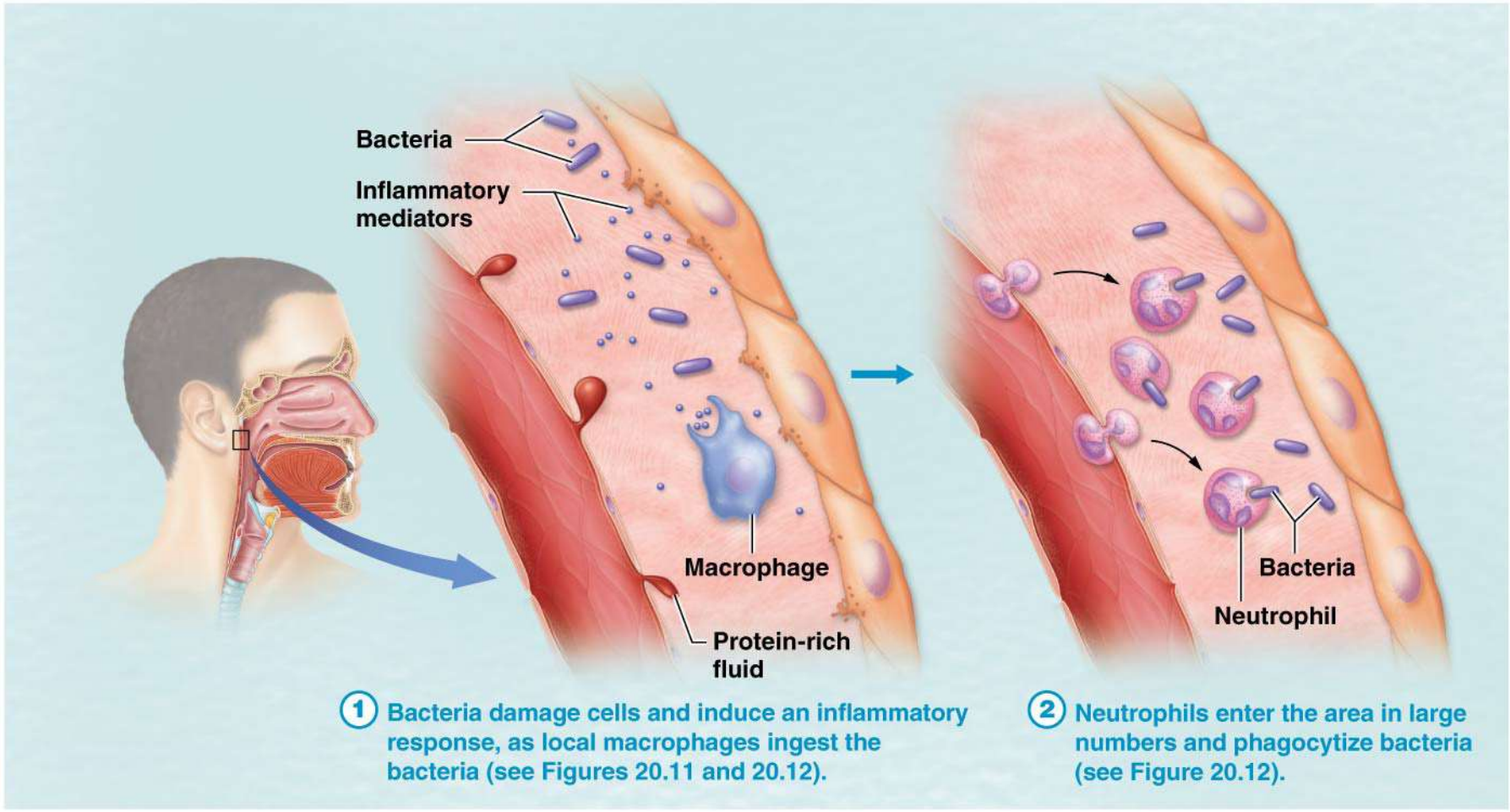
The dual nature of the adaptive immune system.



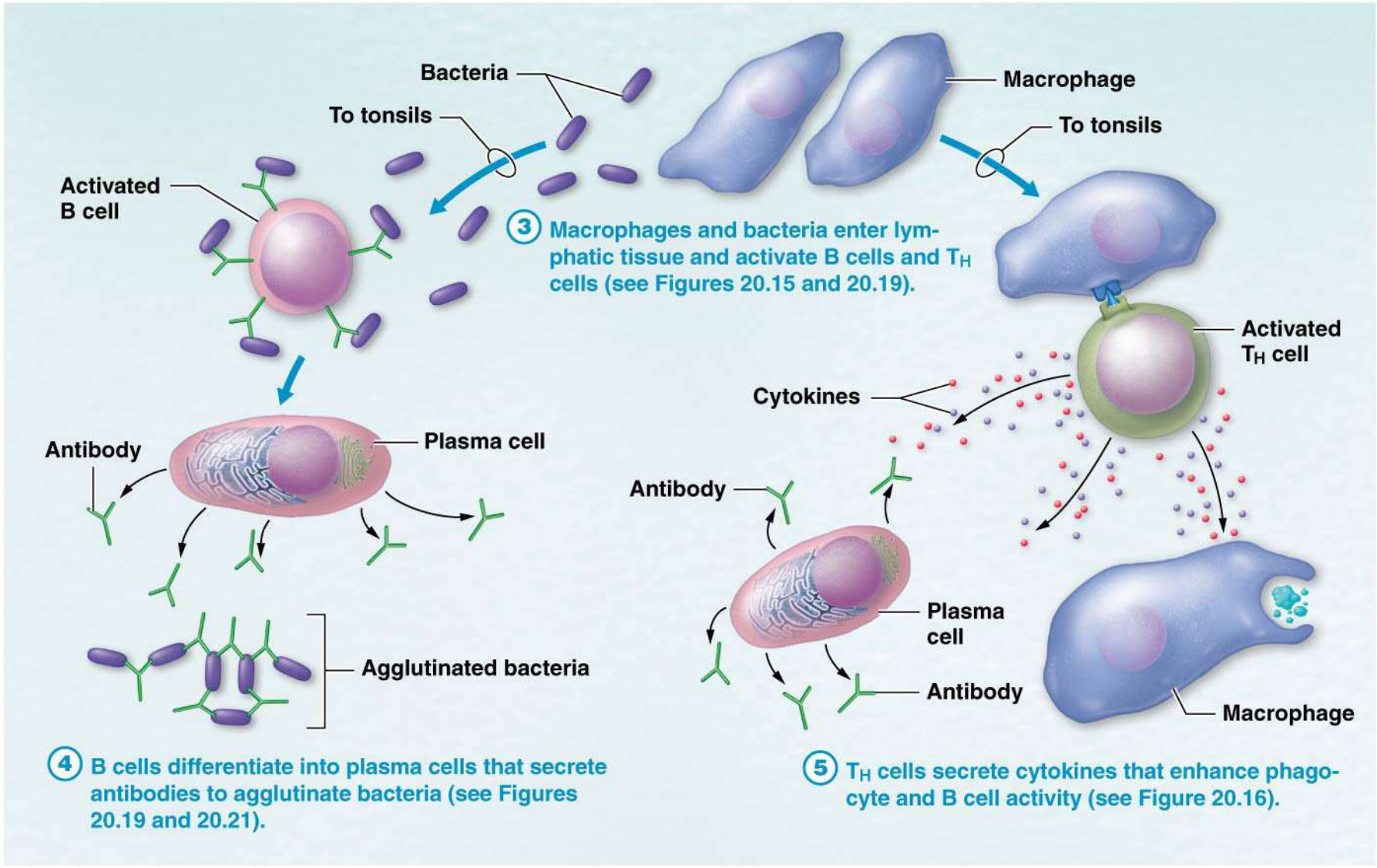
KEY CONCEPTS

- 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.

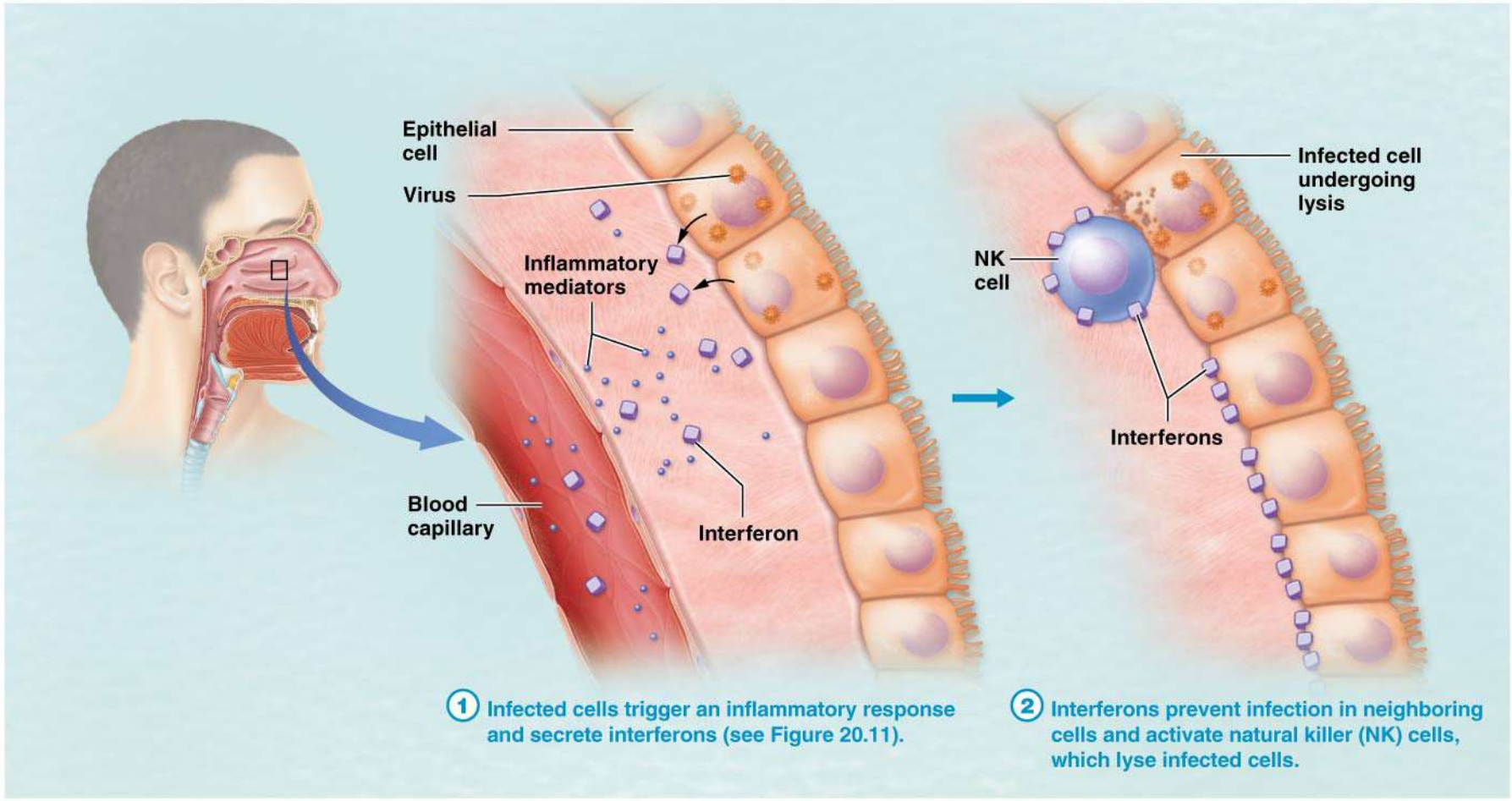
The Big Picture of the Immune Response to a Bacterial Infection (slide 1 of 2).



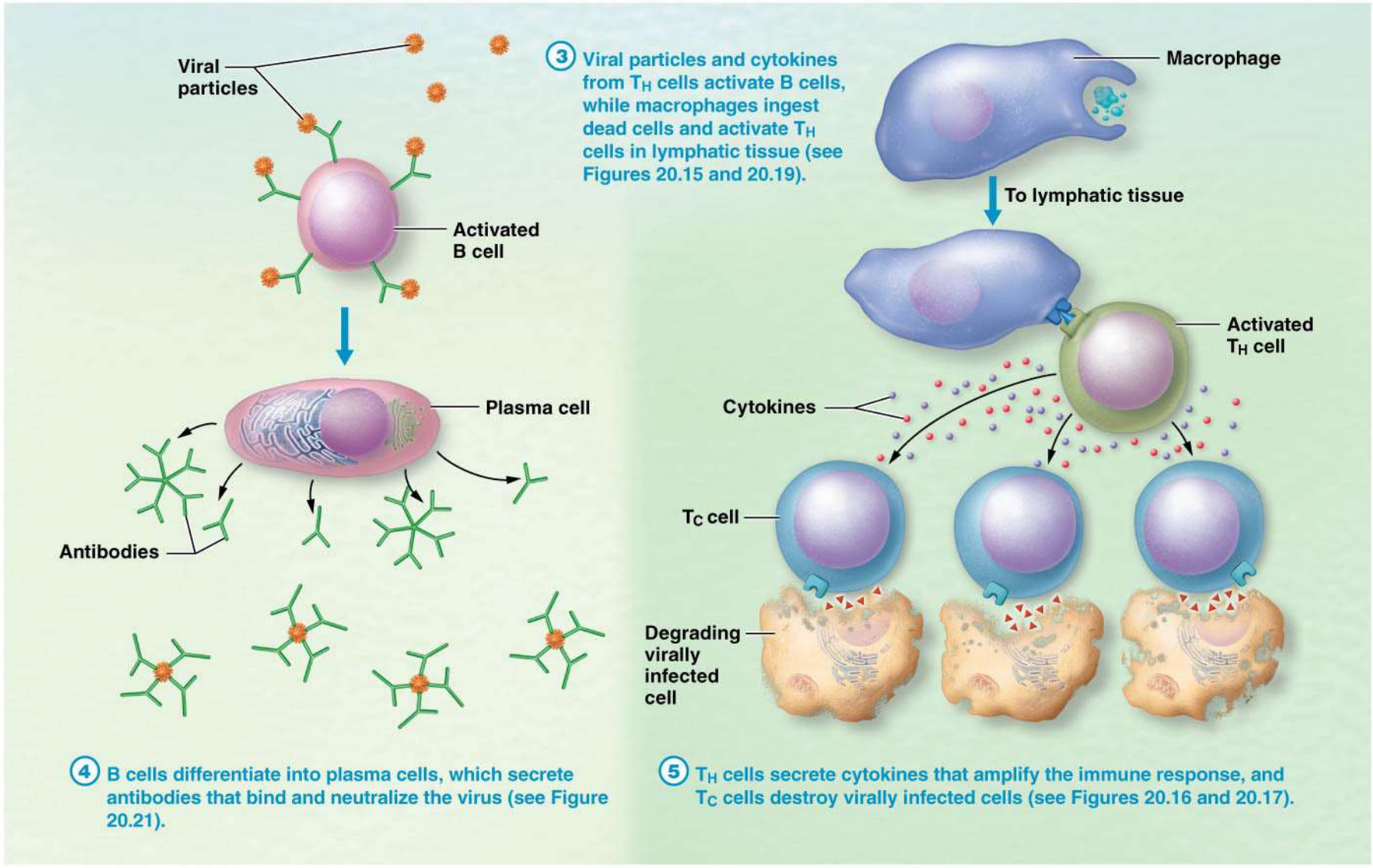
The Big Picture of the Immune Response to a Bacterial Infection (slide 2 of 2).



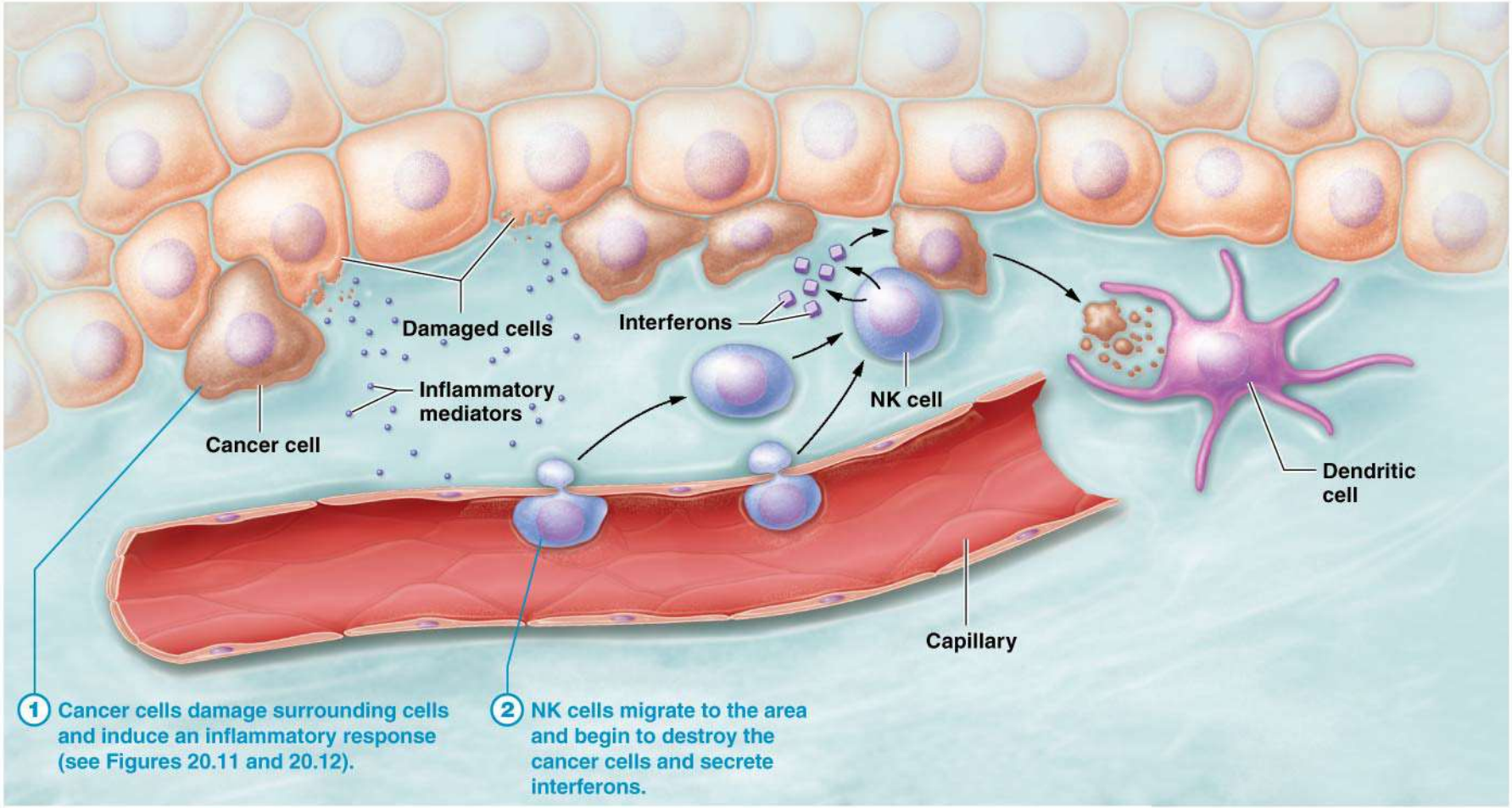
The Big Picture of the Immune Response to the Common Cold.
This is a viral infection. (slide 1 of 2)



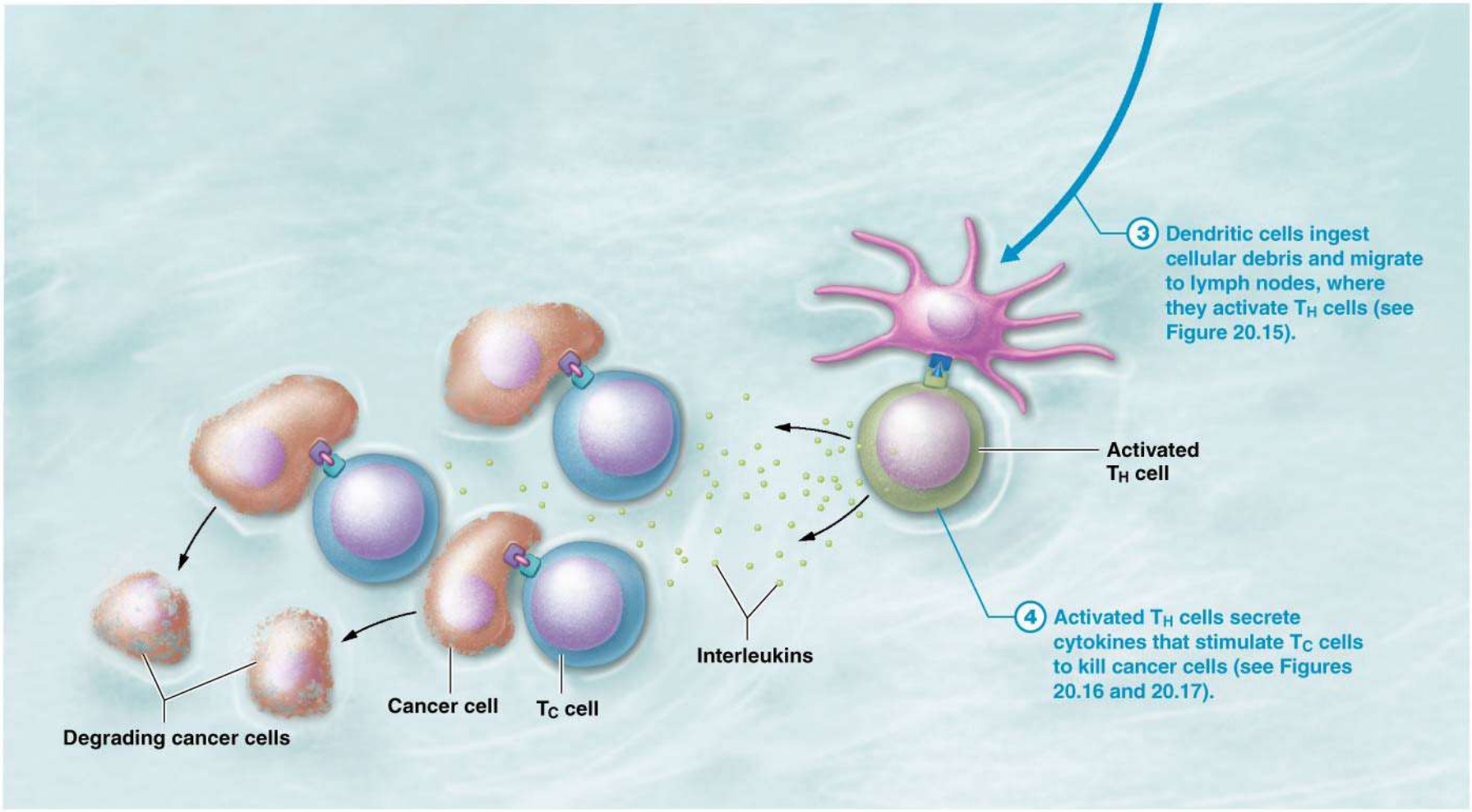
The Big Picture of the Immune Response to the Common Cold.
This is a viral infection. (slide 2 of 2)



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



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



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 C-Tc and B-cells to kill cancer cells.

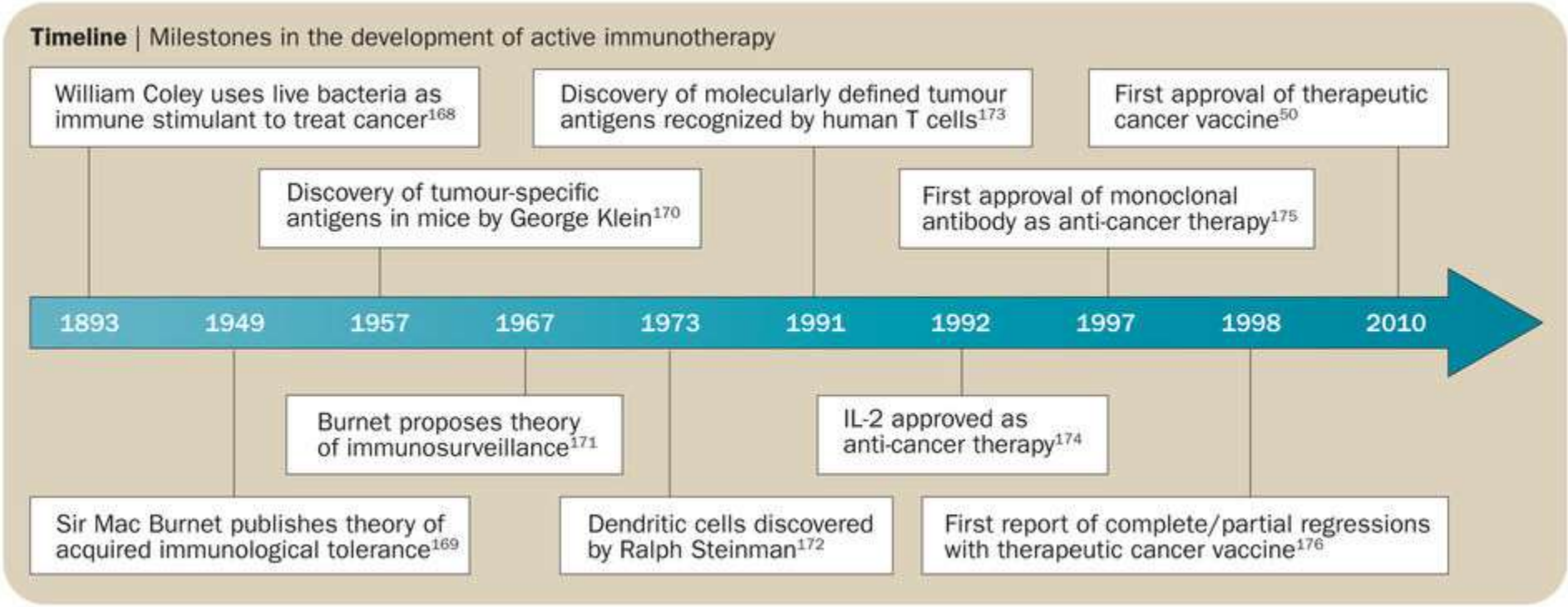
- Cancer immunotherapy's leverage our knowledge about the immune system to direct immune system cells to identify “specific types of molecules only on cancer cells” or remove factors that inhibit cancer cells ability to turn off our immune cells from attacking cancerous cells.

- These new cancer immunotherapy's target only cancerous cells.

- Early “clinical trials” have demonstrated that we can kill some types of cancer cells. These new therapies now offer people diagnosed with certain types of cancers a viable cure.

- New Therapies = Checkpoint Inhibition, Dendritic Cell Vacines, and CAR T Cells

See Next Slide


Timeline | Milestones in the development of active immunotherapy
William Coley uses live bacteria as immune stimulant to treat cancer[168]
Discovery of molecularly defined tumour antigens recognized by human T cells[173]
First approval of therapeutic cancer vaccine[50]
Discovery of tumour-specific antigens in mice by George Klein[170]
First approval of monoclonal antibody as anti-cancer therapy[175]
1893
1949
1957
1967
1973
1991
1992
1997
1998
2010
Burnet proposes theory of immunosurveillance[171]
IL-2 approved as anti-cancer therapy[174]
Sir Mac Burnet publishes theory of acquired immunological tolerance[169]
Dendritic cells discovered by Ralph Steinman[172]
First report of complete/partial regressions with therapeutic cancer vaccine[176]

THREE IMMUNE STRATEGIES

Surgery, radiation and chemotherapy have long served as the standard treatments against cancer. But clinical trials over the past five years have shown that supercharging the body's immune cells—which evolved to fight harmful bacteria and viruses, among other things—offers a powerful new addition to the mix by helping the cells to find and destroy tumors. The approaches shown here are being tested alone or in combination with other treatments.

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 cells' immune-dampening signals, allowing the immune system to do its job.

Dendritic Cell Vaccine

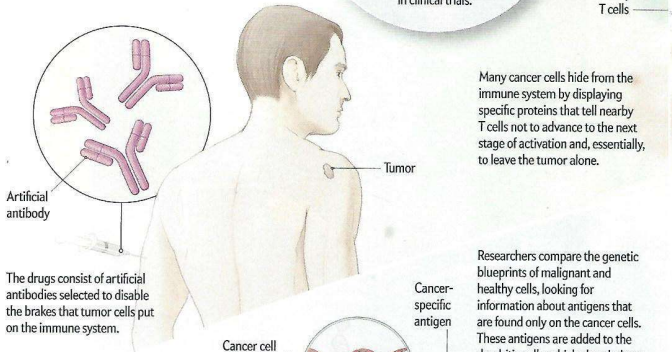
Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found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

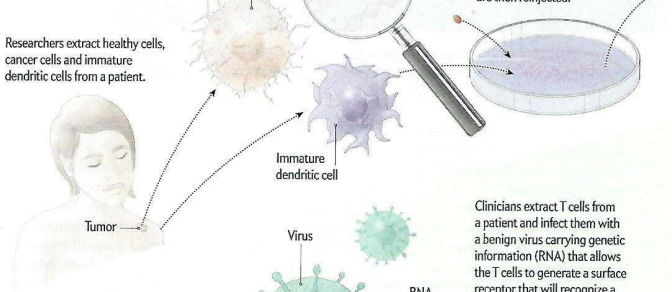
CAR-T Cells

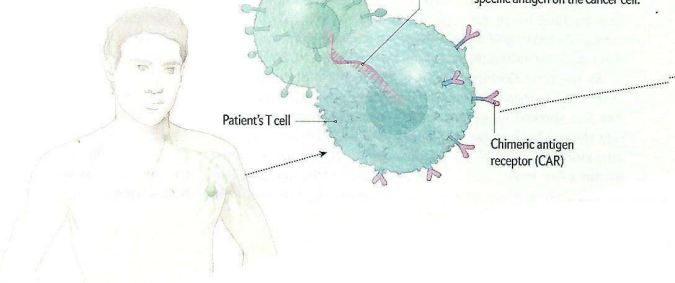
Chimeric antigen receptor (CAR) T cells combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy 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.

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.



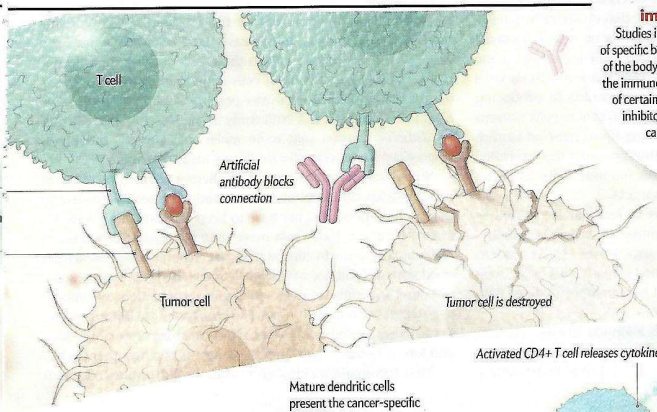




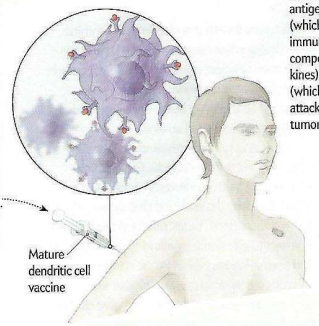
Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.

Researchers compare the genetic blueprints of malignant and healthy cells, looking for information about antigens that are found only on the cancer cells. These antigens are added to the dendritic cells, which absorb them. The now mature dendritic cells are then reinjected.

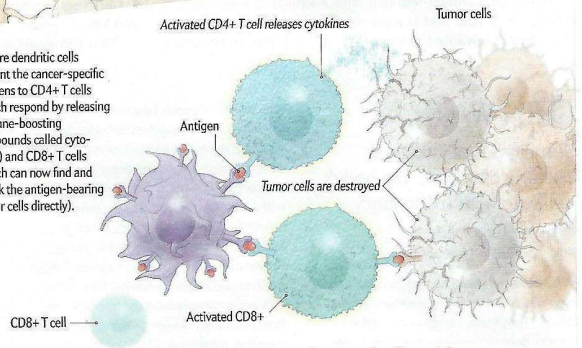
Clinicians extract T cells from a patient and infect them with a benign virus carrying genetic information (RNA) that allows the T cells to generate a surface receptor that will recognize a specific antigen on the cancer cell.

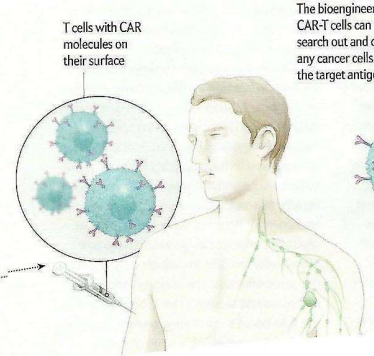


By preventing tumor cells from interacting with the checkpoint system for T cells, checkpoint inhibitors free the T cells to attack a tumor with newfound vigor.

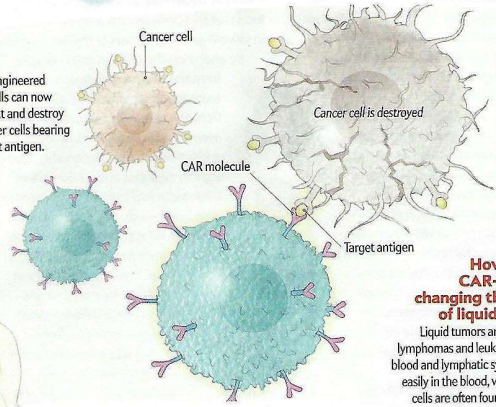


Mature dendritic cells present the cancer-specific antigens to CD4+ T cells (which respond by releasing immune-boosting compounds called cytokines) and CD8+ T cells (which can now find and attack the antigen-bearing tumor cells directly).





The bioengineered CAR-T cells can now search out and destroy any cancer cells bearing the target antigen.



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.

How are CAR-T cells changing the treatment of liquid tumors?

Liquid tumors are cancers (such as 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 in as many as 90 percent of patients studied with an aggressive leukemia.

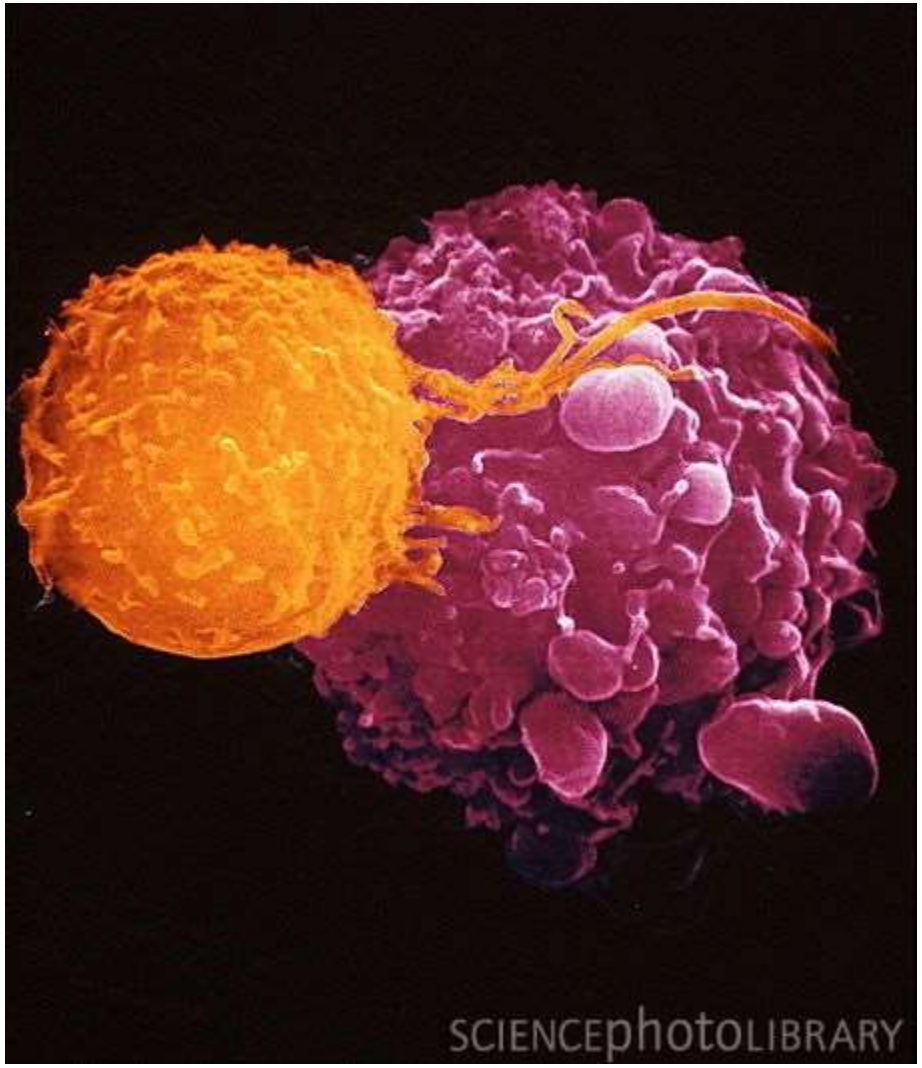
2016 FUTURE OF MEDICINE

Illustration by Shizuka N. Aoki

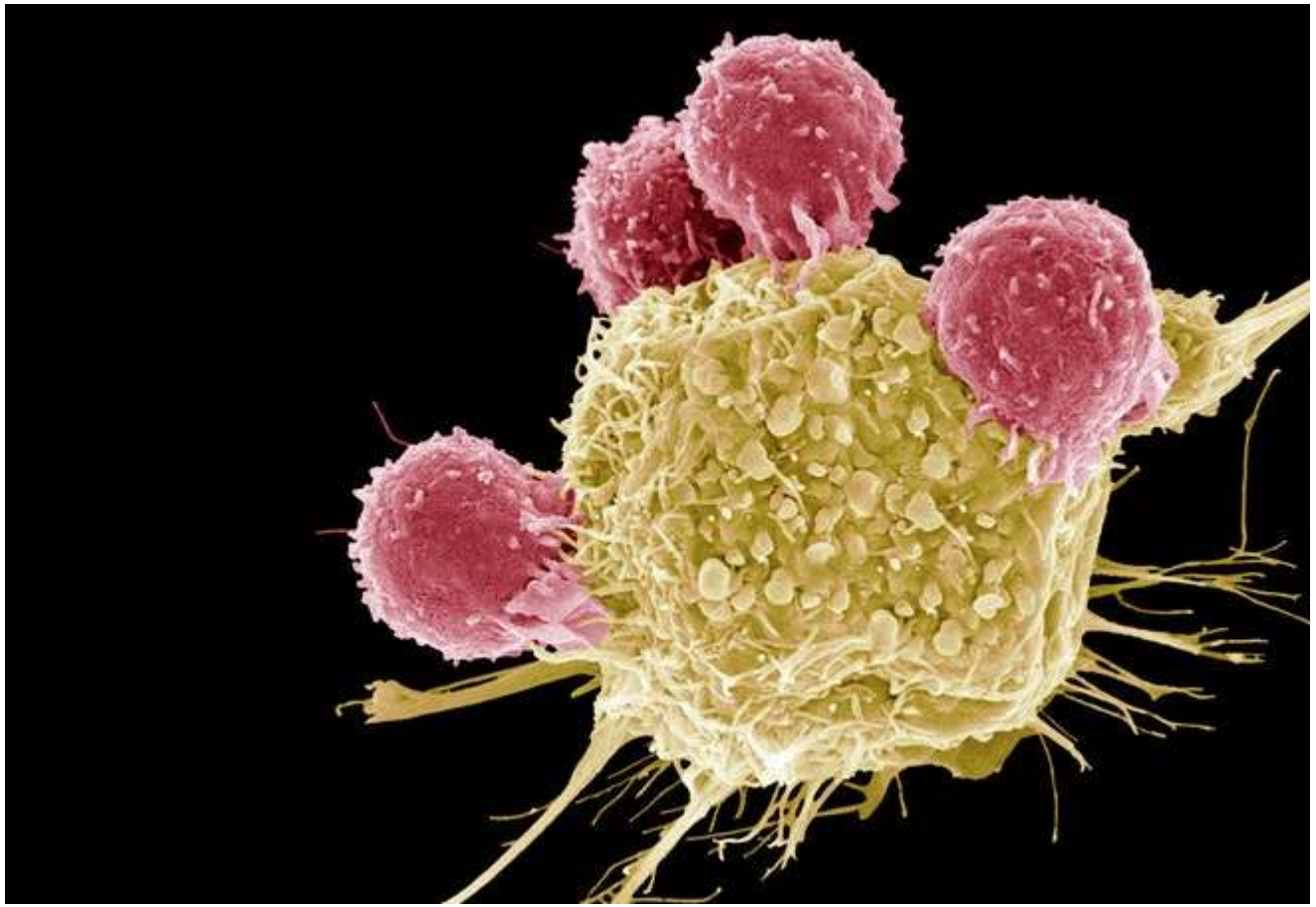
See Slide Presentation // Three Immune Strategies - Unit 3 Online Lecture Resources

Immune system fighting a cancer cell.

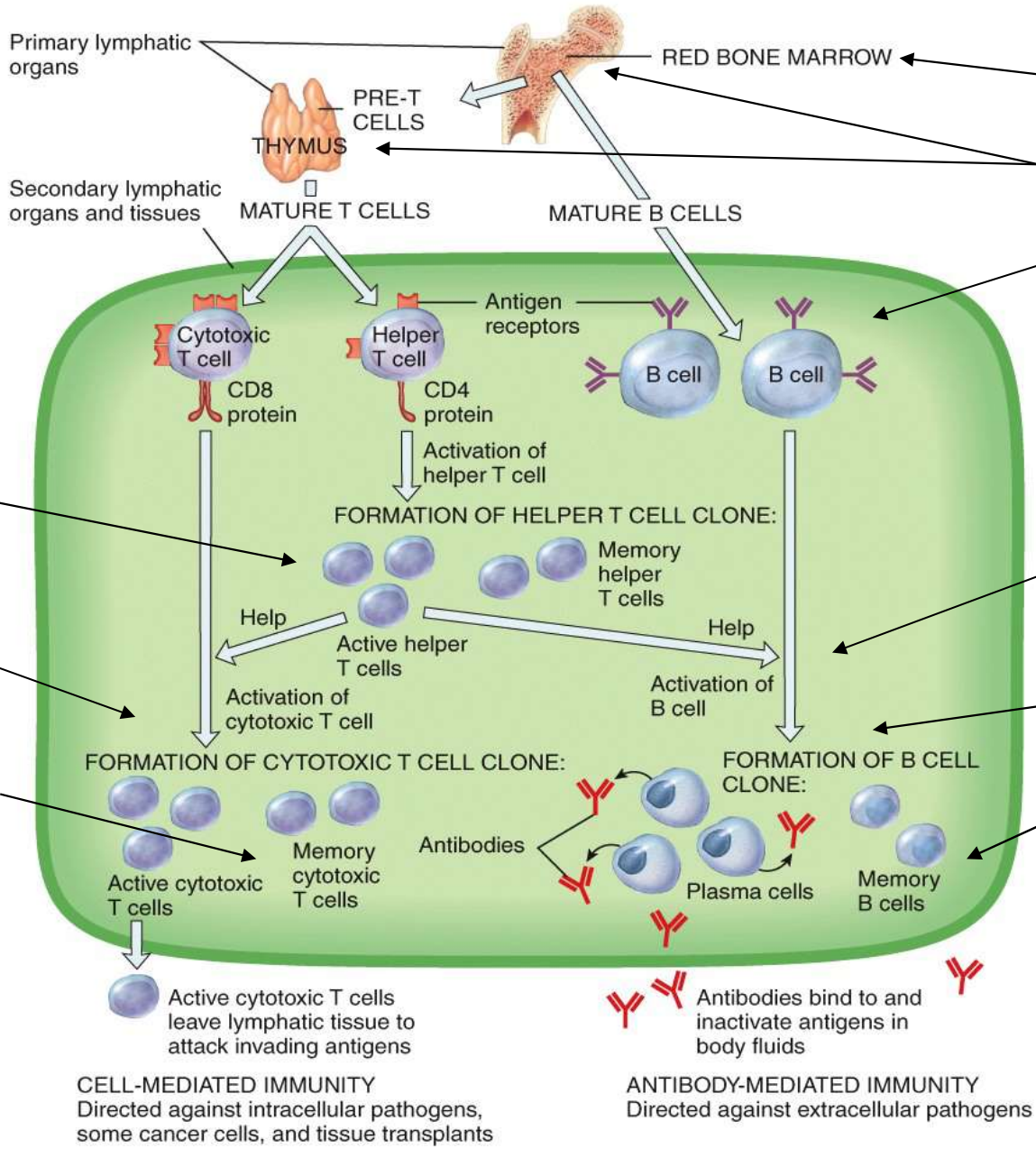
A killer T-lymphocyte (orange) inducing a cancer cell to undergo Programmed Cell Death (apoptosis).



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



This is an overview of adaptive immunity.



Born

Educated

Deployment

naive immunocompatent cells (resting cells)

Recognize

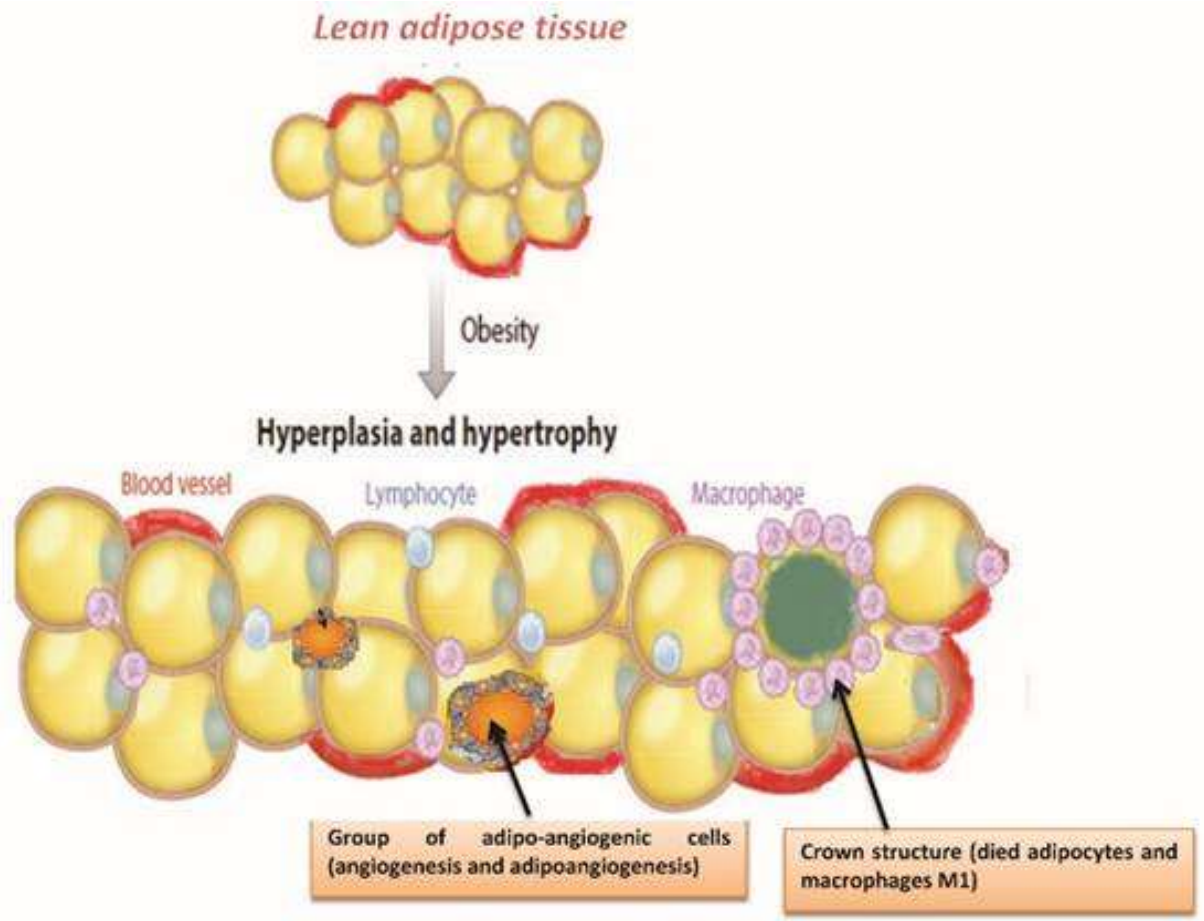
React

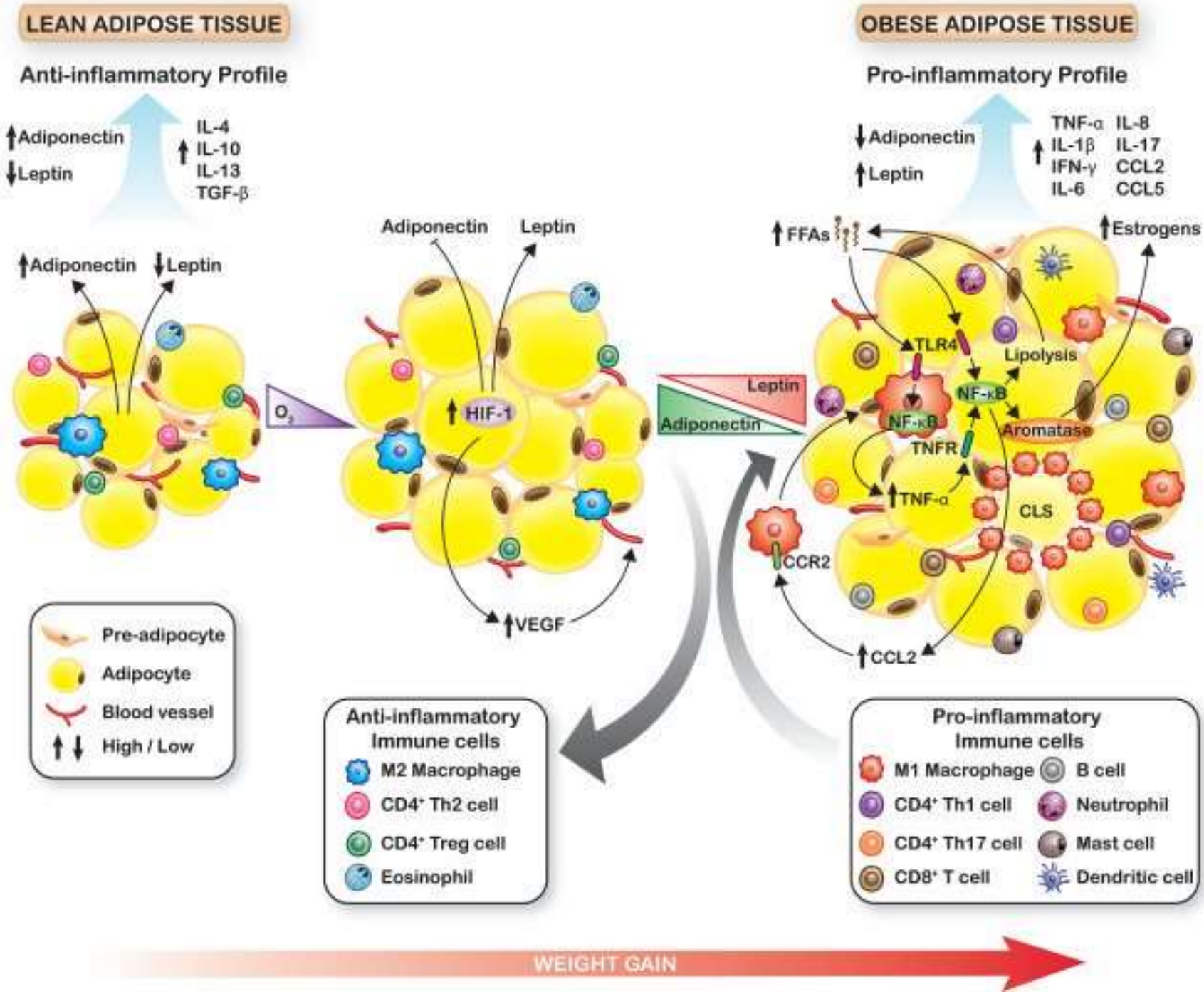
Remember

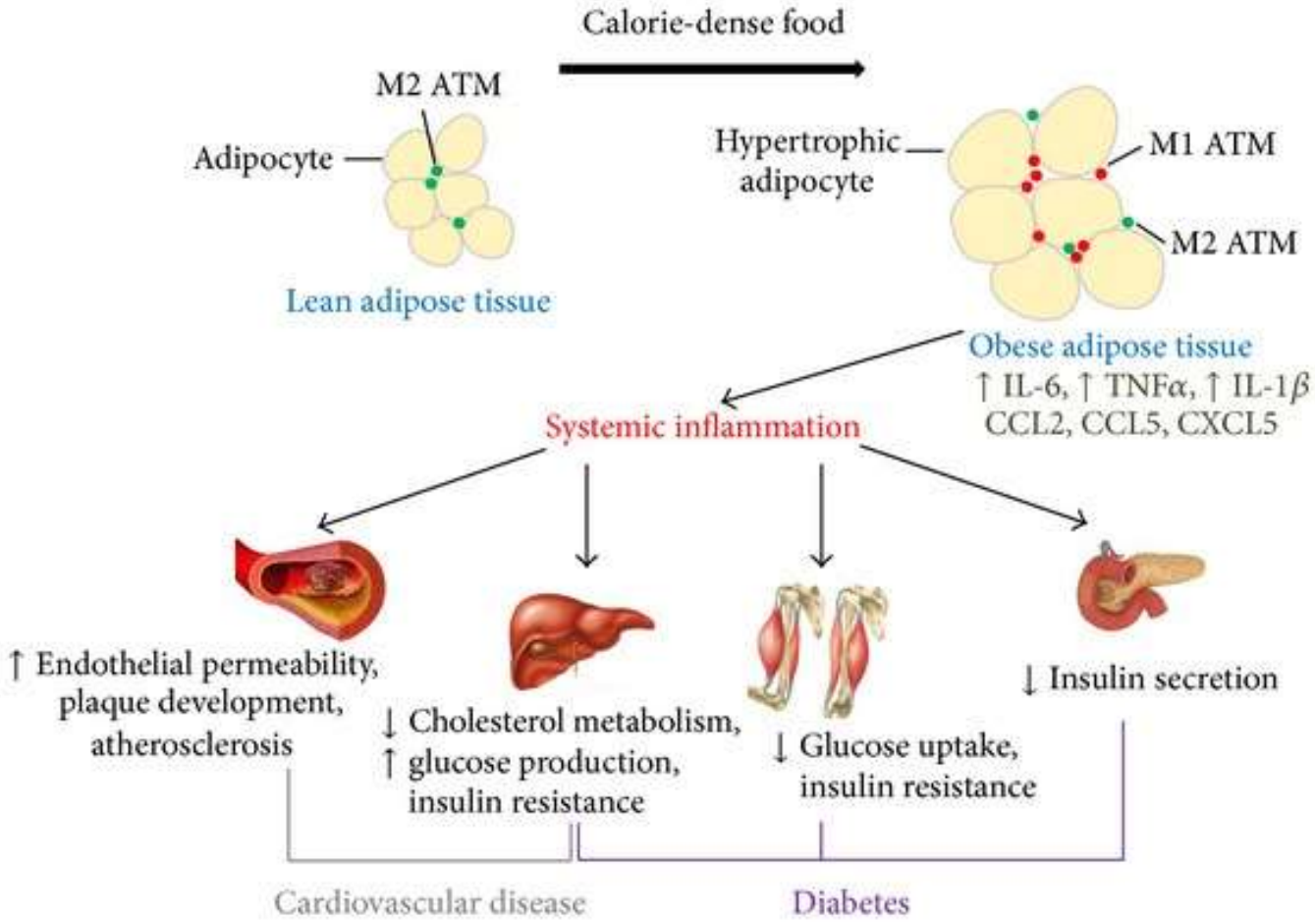
Recognize

React

Remember


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
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



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.