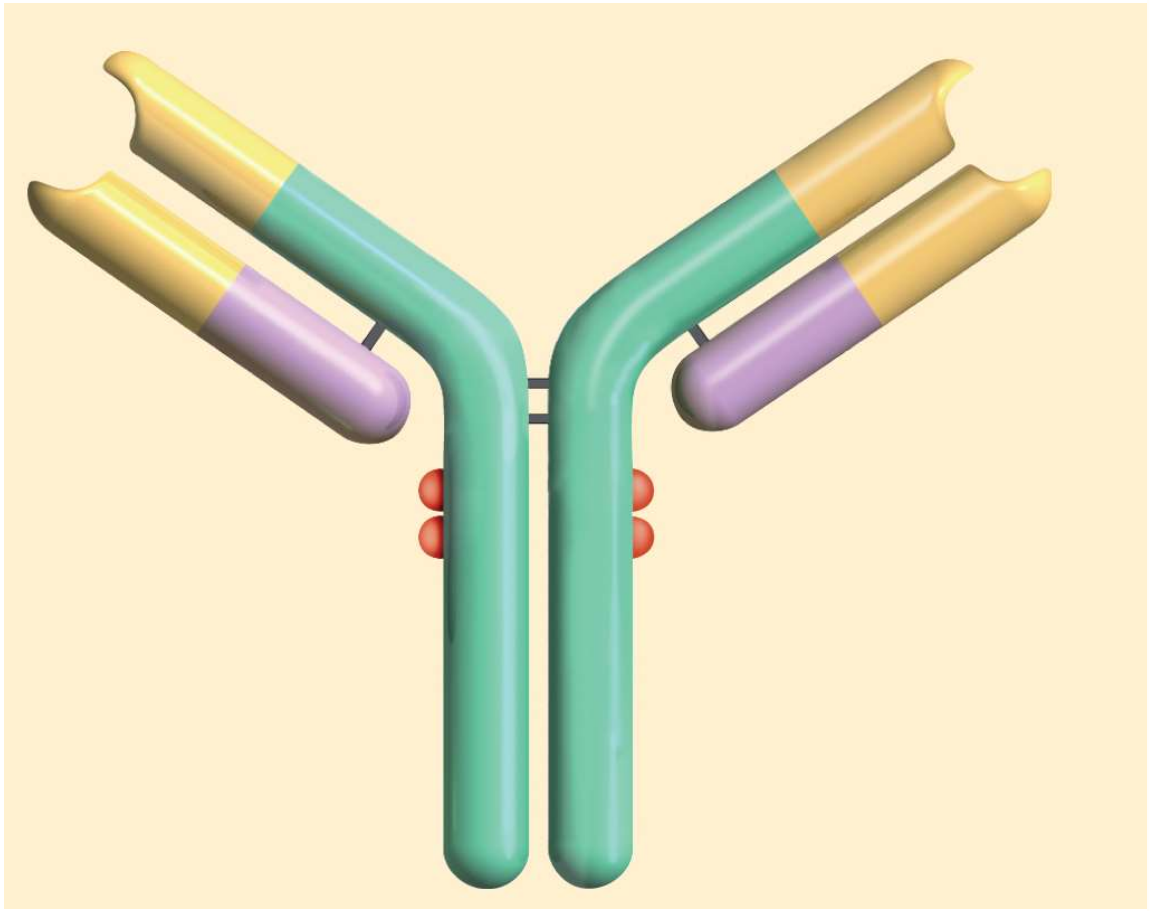
The Third Line of Defense

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



What is immunity?

- *Immunity protects us against internal and external threats.*
- *Two types of immunity - Innate Immunity & Acquired Immunity*
- *Innate immunity exists at time of birth // Relies on numerous factors including cellular phagocytes and many different types of molecules // characterized as "non-specific resistance " to pathogens*
- *Acquired immunity does not exist at birth /// Develops after birth /// characterized as having both "specificity and memory"*
- *We fight infections by using immunity's three lines of defenses:*
  - *#1 - Physical barriers*
  - *#2 - Non-specific resistance*

  (both innate immunity)
  - *#3 - Acquired Immunity*

  (also called adaptive immunity)

What makes acquired immunity so special?

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

What makes “Acquired Immunity” so special?

Two key characteristics (used to distinguish innate immunity responses (also called nonspecific resistance) from acquired immunity)

specificity – immunity directed against a particular pathogen or more correctly against the pathogen’s “antigen”

memory – first exposure initiates an immune response that defeats the pathogen /// when re-exposed to the same pathogen, the body “remembers” the first exposure and reacts so quickly that there is often no noticeable symptoms

Non-self antigen is the stimulus to “activate” acquired immunity.

How Many Types of Acquired Immunity Do We Have?

- *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.

- *After pathogen is eliminated --- activated cytotoxic T cells and plasma cells making antibodies die but their "memory T cells and memory B cells" continue to live /// memory cells "rest" in lymph nodes and throughout the body*

- *Memory cells stored in lymph nodes and other tissues so they can respond immediately to second exposure to a similar pathogen. /// first exposure vs second exposure*

Why do we need two forms of immunity?

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

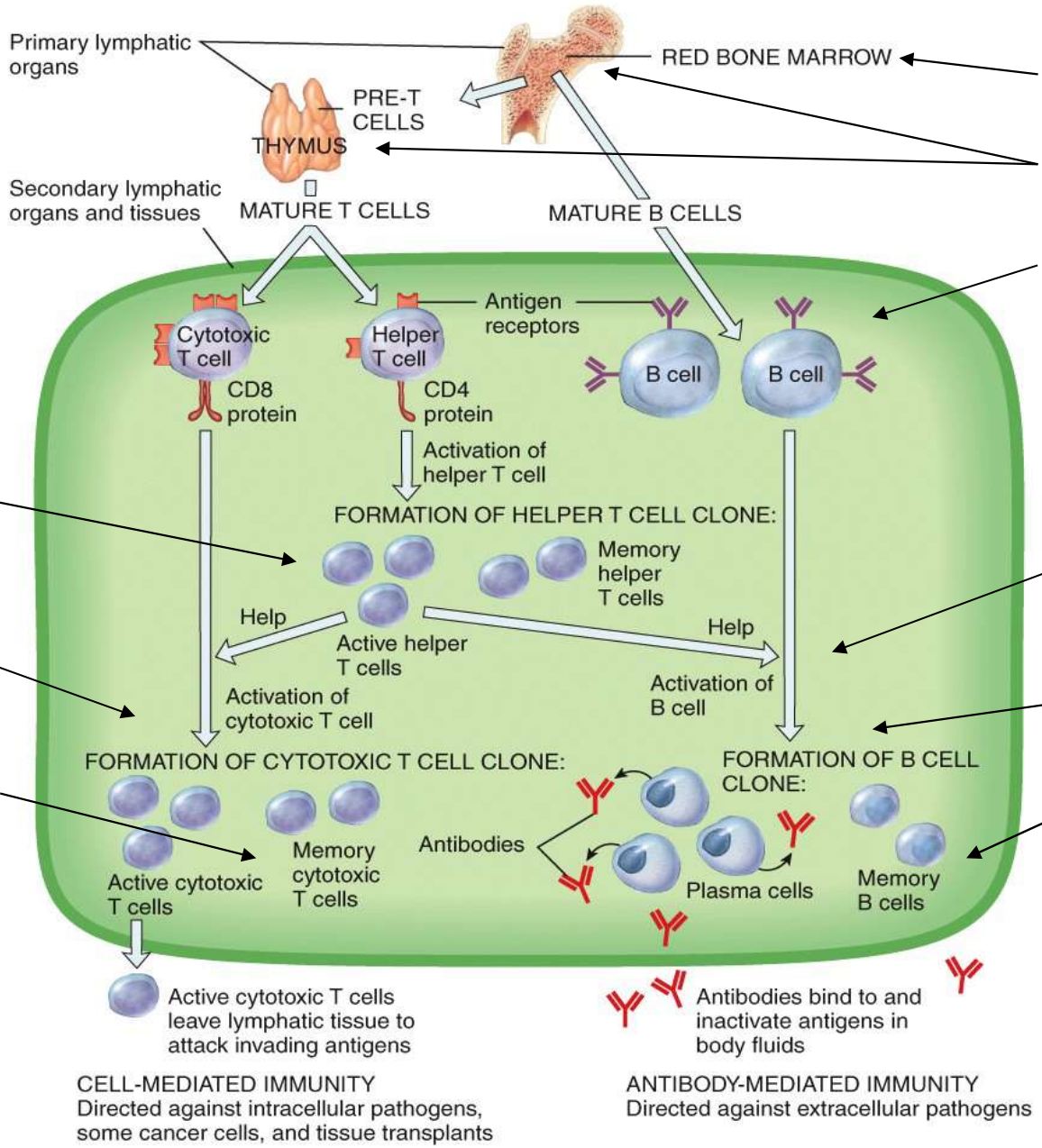
Humoral Immunity: Action of B cell which when stimulated morph into plasma cells // plasma cells make antibodies /// antibodies only attack antigens when they are outside our cells.

Cellular Immunity: Cytotoxic T cells (i.e. cellular immunity) can only recognize foreign antigen when they are "hiding" inside our cells.

Therefore, when we are infected by a bacteria, our acquired immune system activates both T cells and B Cells (i.e. B cells make plasma cells that make antibodies)

Each cell line have similar receptors that are able to recognize the same antigen (i.e. epitope).

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

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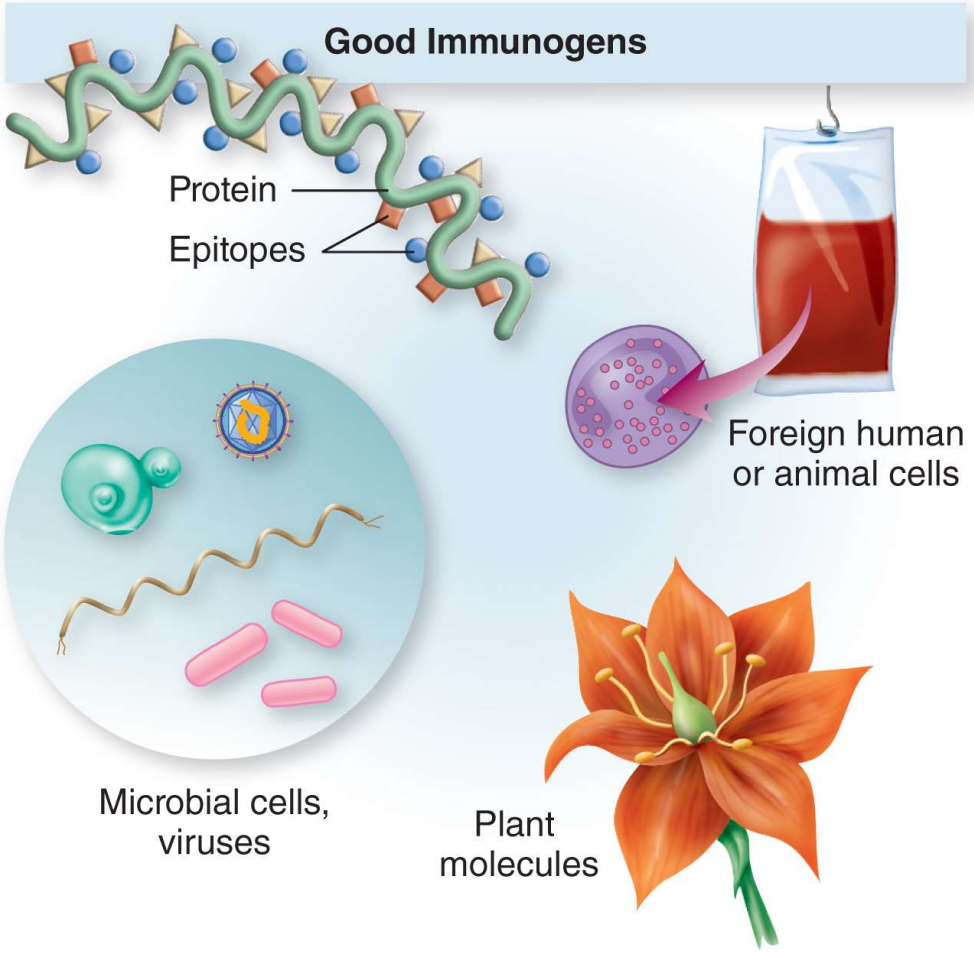
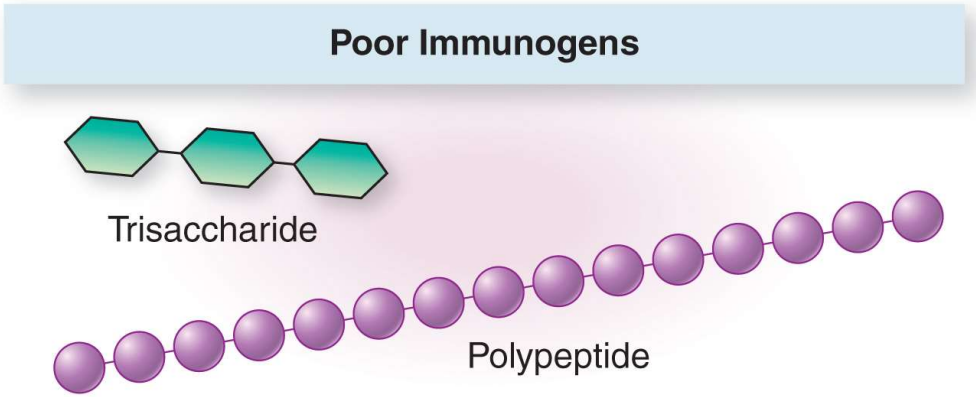
More About Antigens

- An antigen is a molecule // protein or large polysaccharides
- Allows immune cells to tell difference between self antigen vs foreign antigen
- Non-self antigen is any molecule that triggers an immune response
  - Normally large molecular weight - over 10,000 amu
  - Pathogen's have non-self antigen which are transmembrane molecules /// foreign cell or virus (e.g. pathogen)
  - May also be an plant molecule or toxin made by microbe
  - Many different antigens can be on the surface of the same pathogen /// each molecule starts unique immune response
  - E.g. - The flagella and the glycocalyx may each induce a separate immune response activated by different antigens from the same bacteria





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

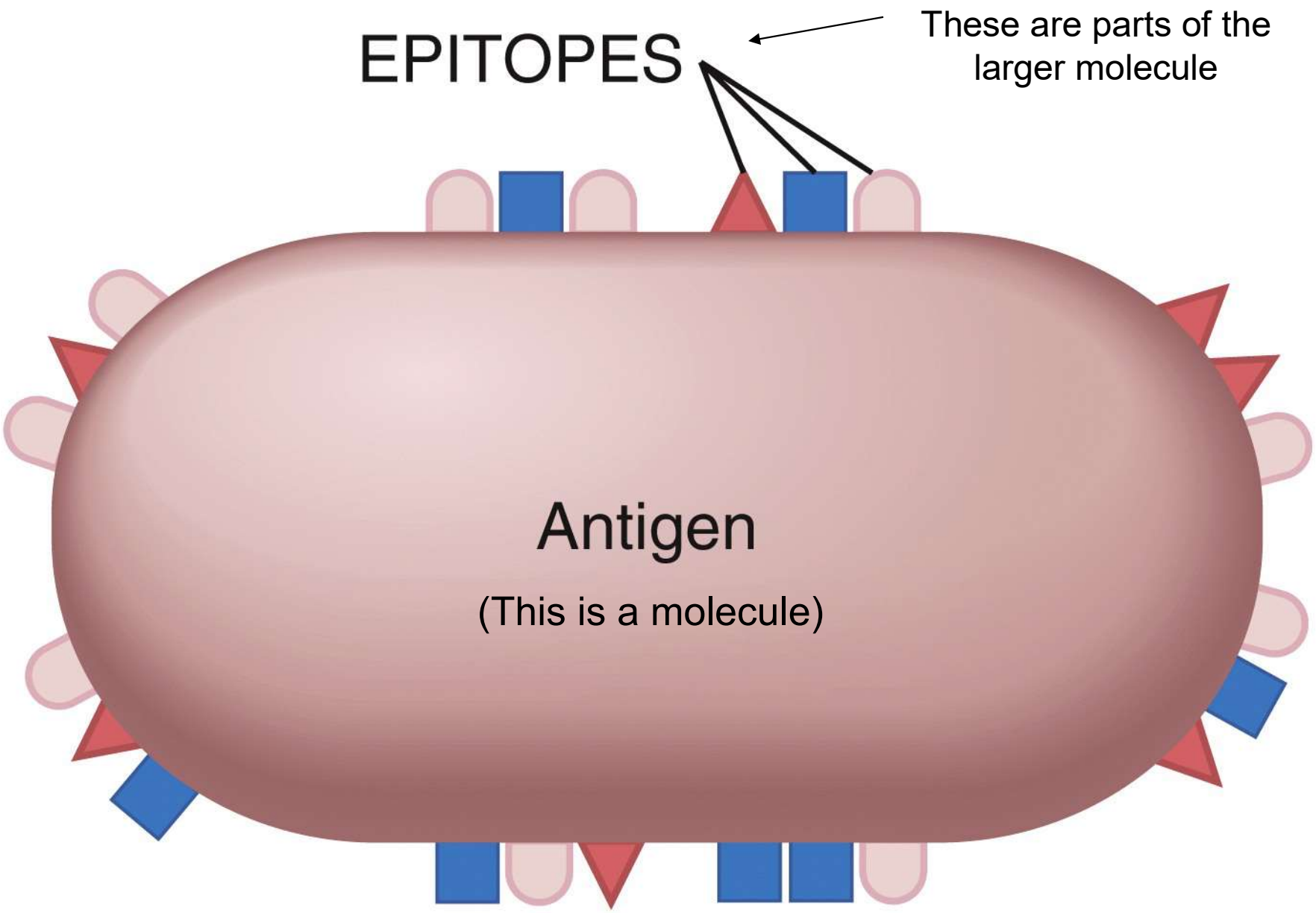
What is a self antigen?

We have antigens in our plasma membranes that are unique to our cells /// These antigens are “self-antigen”

- Our immune system can tell the difference between our cells (self-antigen) and foreign cells (non-self antigen)
- Our antigens are unique to each individual // only identical twins may have similar antigen!!!
- Antigens are either proteins, polysaccharides, glycoproteins, glycolipids /// these molecules embedded into plasma membranes
- Two Key Idea:
  - immune system can differentiate between self and non-self (‘foreign’) antigens
  - Immune system function is to either destroy or render harmless foreign cells (or their toxins) that exhibit non-self antigens // note: this is also the basis of tissue rejection

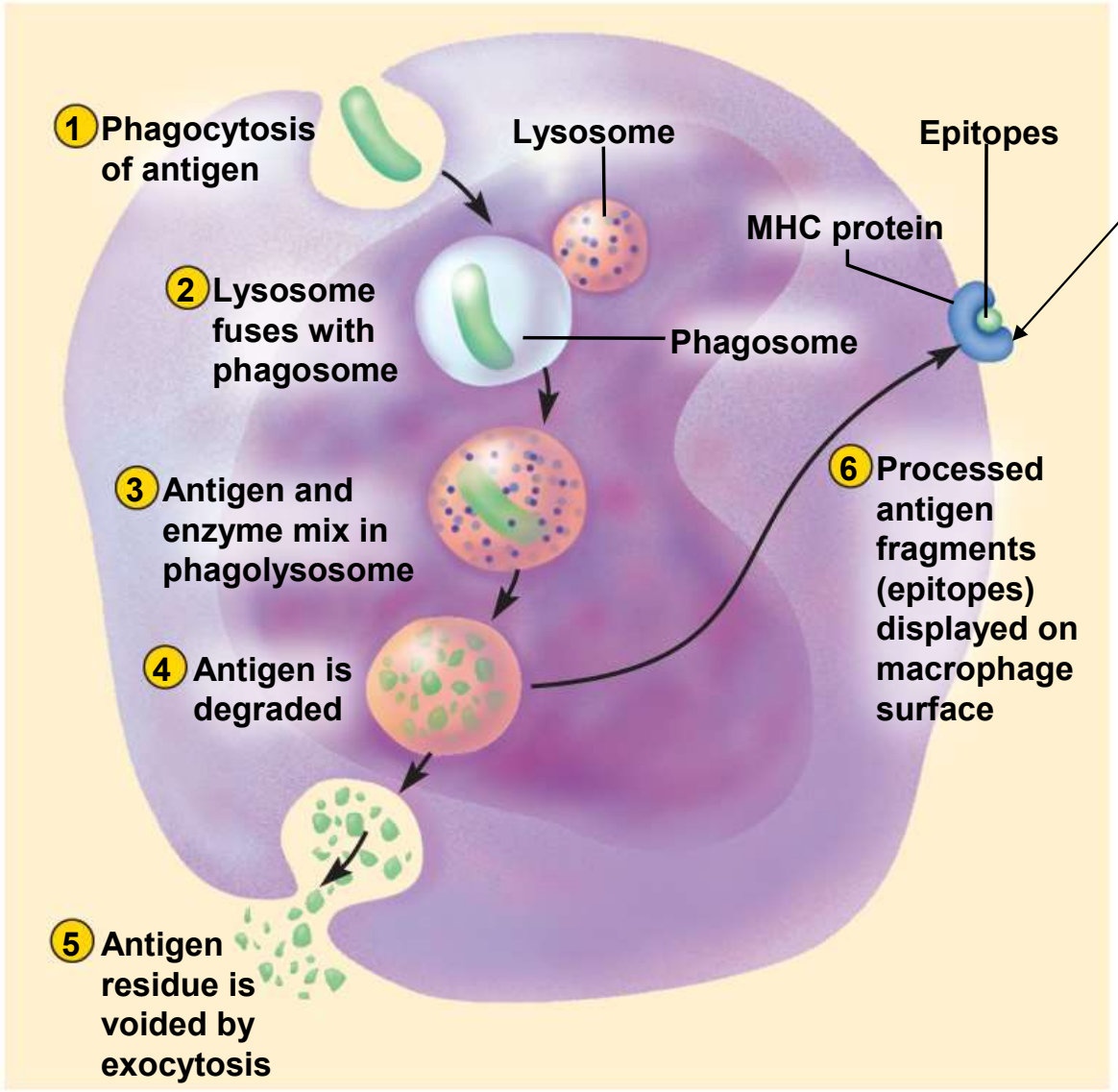
What is the difference between an epitope and an antigen?

- Epitopes = the antigenic determinant
  - smaller segment of the larger antigenic molecule
  - represents a certain regions of an antigen molecule but only this smaller molecule is required to stimulate the immune response
  - large antigen digested by lysosomes and their smaller epitope placed in holder (i.e. MHC protein) which displays 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 molecule
Antigen
(This is a molecule)

APC Process Antigen into an Epitope

The Epitope is then inserted into the plasma membrane. Why?



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

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

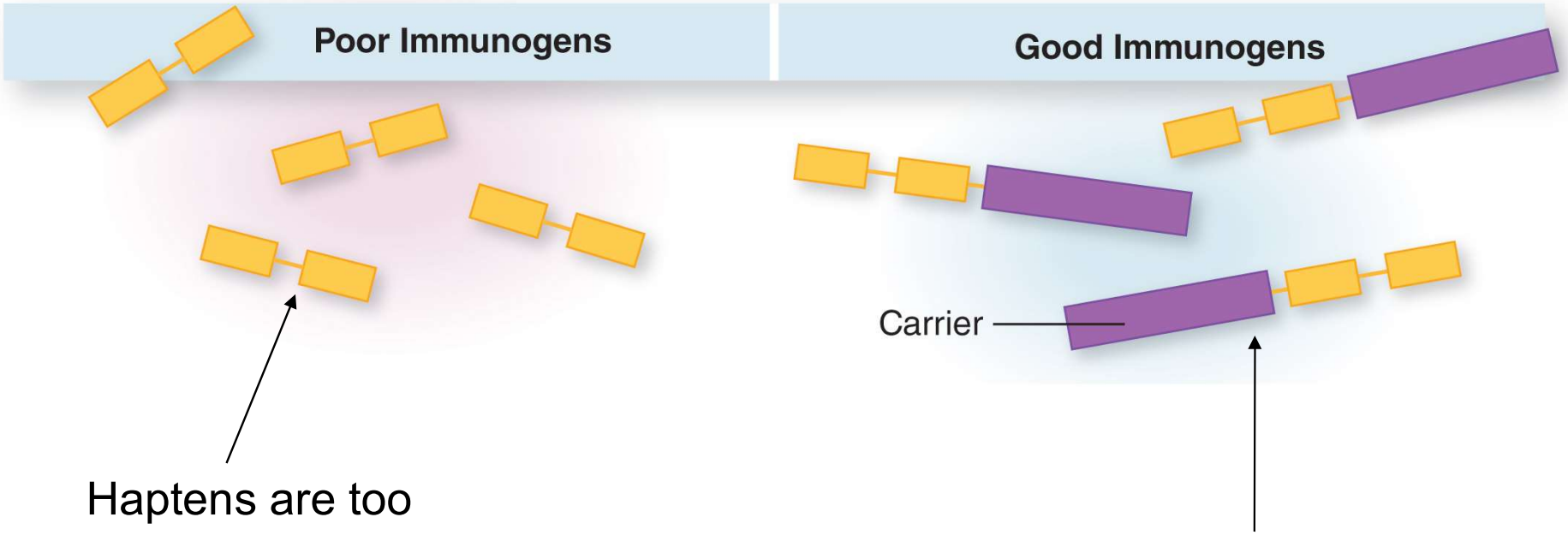
All other nucleated cells in host use MHC-I

NK cells also able to recognize MHC-I

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

- Haptens = term describes a molecule to small to be antigenic /// penicillin is a hapten
  - haptens able to combine with a host macromolecule (e.g. albumin)
  - create a unique complex that the body recognizes as foreign
  - cosmetics, detergents, industrial chemicals, poison ivy, and animal dander
  - penicillin binds to host proteins in allergic individuals

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.

More About Cellular Immunity

- *Cellular Immunity requires the action of four different T Cells*
  - *Different classes of T Cells (helper, regulatory, memory, cytotoxic)*
  - *Each class has special function*
  - *These cells communicate with each other using cytokines*
  - *Cytotoxic T cells (Tc) are the only cell in the T Cell family that are abler to kill infected host cells*
  - *NK cells (also a lymphocyte) able to kill infected host cells but not specifically // NK cells provide "immune surveillance.*

More About Humoral Immunity

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 come from B cells /// only plasma cells 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*

What Are Major Histocompatibility Complex Proteins (MHCP)?

- These cytoplasmic proteins allow APC to show immune cells pathogens
- Two type = MHCP-I and MHCP-II
- Constantly being made by the endoplasmic reticulum
- These proteins migrate from the cytosol to be embedded in the plasma membrane // embedded into plasma protein's outer face
- They are shaped like a “hot dog buns”
- As MHCP move through cytoplasm they “pick up” cytoplasmic proteins
- MHCP with protein are embedded into plasma membrane outer face
- Now WBCs can see the different types of proteins that are inside cytoplasm /// both normal and pathogenic

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

- MHCP-I are associated with all nucleated cells (not RBC)
- MHCP-II are only associated only with antigen presenting cells
  - Macrophage
  - Dendritic cells
  - B cells
  - Macrophage and dendritic cells present epitopes to CD4 cells (i.e. help T cells)
  - B cells function as their own APC to self-activate themselves /// their activation is very different than T cells

What is the function of the Epitope-MHCP-I complex ?

- Inside MHCP-I cells “non normal proteins” (i.e. cancerous proteins) or foreign antigen, (e.g. virus and bacterial antigens) are partially digested
- These foreign “epitopes” are placed inside a MHCP-I
- The MHCP-I-epitope complex is then inserted into the plasma membrane
- Cytotoxic Tc can now see the MHCP-I-epitope complex on the surface of the cell
- The Tc cells now binds to this complex
  - Note: naive immunocompetent CD8 (inactive Tc) cell makes first contact with MHCP-I /// this is first step to forming active cytotoic T cells
  - To complete activation complex must get second signal from an already activated Helper T Cell (more to come on this process) /// costimulation

What is the end game?

- If a naive cytotoix Tcell (CD8 cell) binds to an infected cell displaying an epitope-MHCP-I-complex then this *completes first step in the activation of the cytotoxic T cell*

- The *second step is for an already activated Helper T Cell (with similar receptor to same epitope) – to "costimulate" the CD8-epitope-MHCP-I complex* // this completes the activation of the Tc and now clonal selection occurs – producing many activated Tc cells and Tc memory cells /// active helper T cell secretes interluken 2

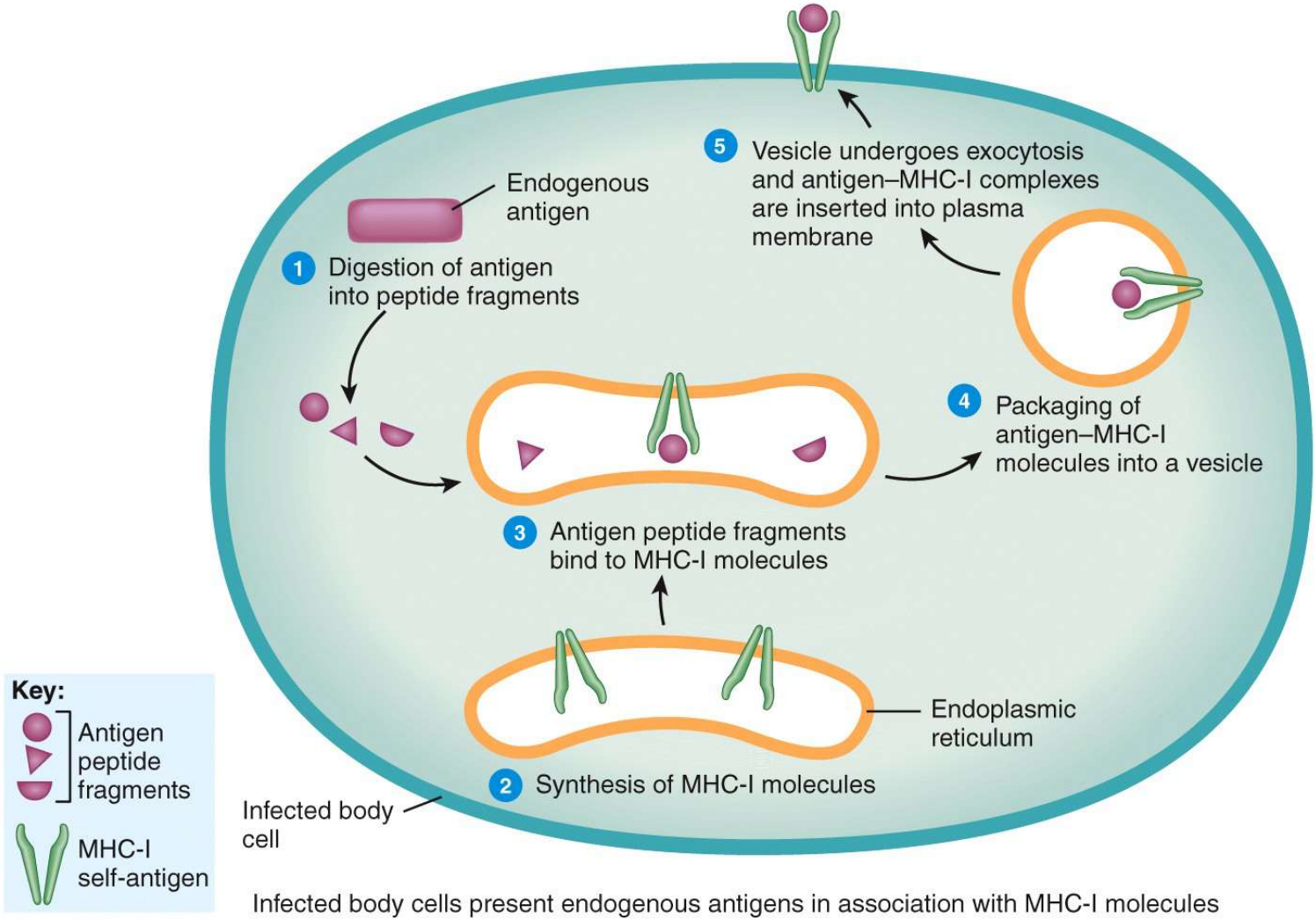
- Clonal selection now results in production of many, simular *cytotoxic T cells all with similar cytotoxic T cell receptors matched to the pathogens' epitope*

- Clonal selection means activated cytotoxic T cells undergoes rapid mitosis /// make many similar Tc as well as many memory Tc matched to same epitope /// the memory cells migrate to lymph nodes where they will "rest "

- Infected cells displaying MHCP-I-epitope can now be killed by newly activated Tc cells when they "dock" onto the MHCP-1 epitope complex

Antigens Processed by Host Cells Using MHC-I

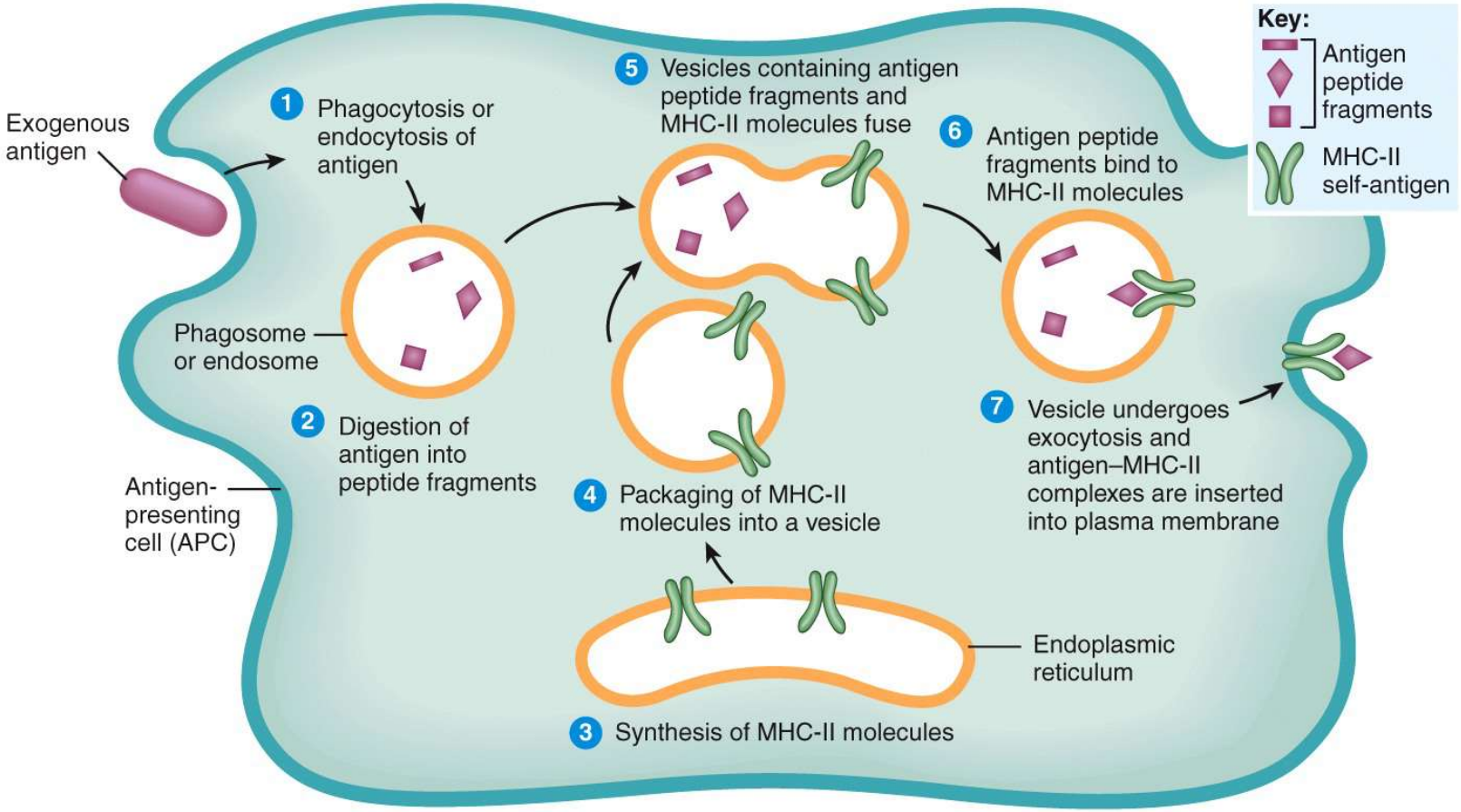
(Note: This is used as the first step to activate a CD8 cell. Activation requires costimulation by activated Helper T cell which then starts CD8 colonal selection which actives cytotoxic T cells. After CD8 cells become Cytotoxic T cells, they use similar epitope-MHCP-I complexes to initiate infected cells destruction by cytotoxic T cells)



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

Antigens Processed by APCs Using MHC-II

(Note: this is how a naïve immunocompetent CD4 cells – the Helper T Cell - become aware that there is a foreign antigen now present in the host)



APCs present exogenous antigens in association with MHC-II molecules

What Are Antigen-Presenting Cells (APCs)?

- Only three cells = APCs
  - *Dendritic cells*
  - *Macrophages*
  - *B cells*
  - *These three cell lines display foreign antigen on their plasma membranes using major histocompatibility proteins (MHCP-II)*
  - *All other host cells display antigen using a second type of MHCP called MHCP-I /// are found on all host cells except RBC*

How Are Epitopes Used?

- Helper T Cells with appropriate receptor are able to bind to foreign antigen on APCs which display antigen in MHCP II

- This activates Helper T Cells //// they then play critical role in clonal selection to make the following T cells

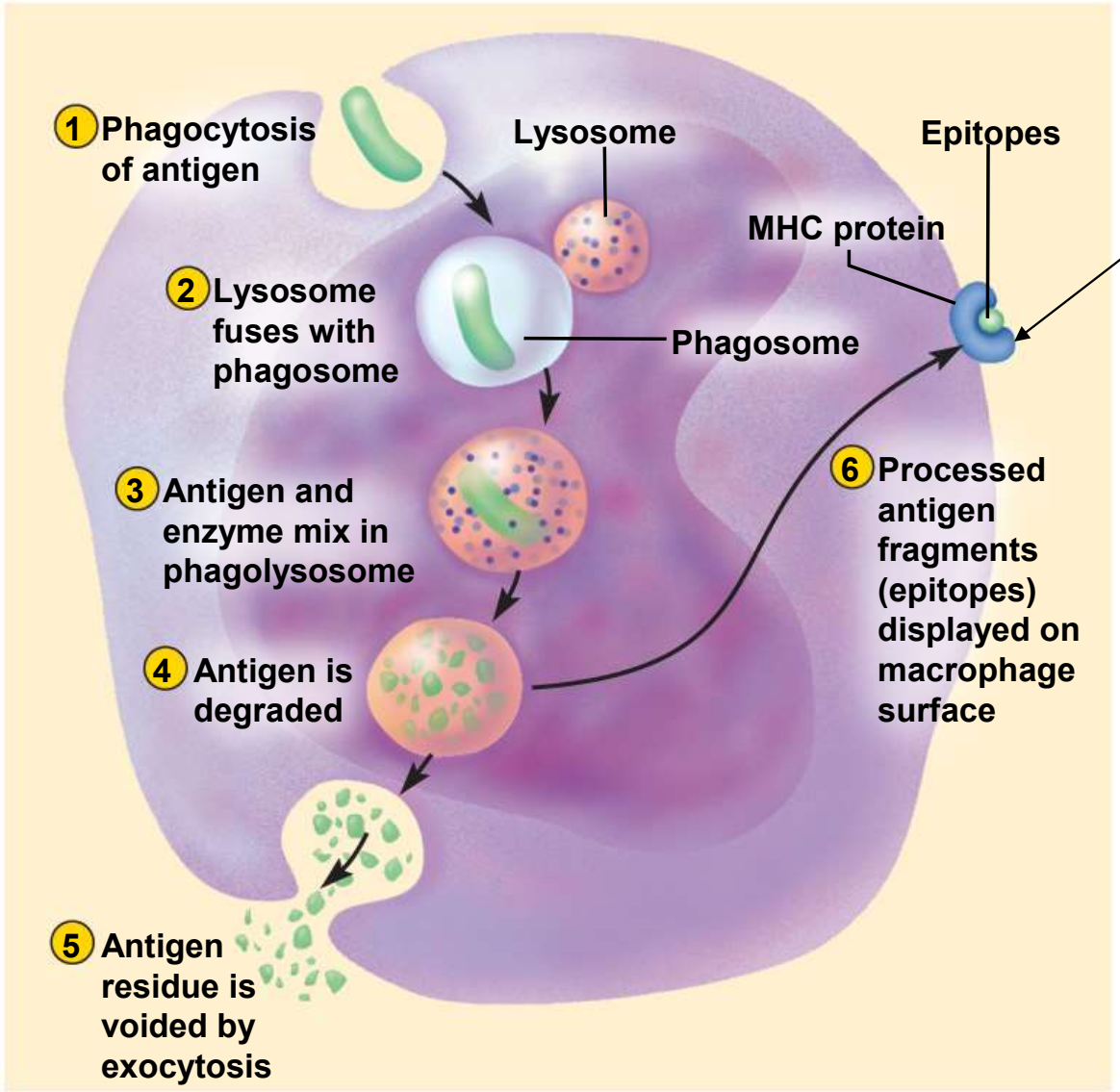
  - cytotoxic T cells – kills infected cells with MHC-I
  - memory T cells – saved for future use
  - regulatory T cells – controls immune response

- These activated Helper T cell have the ability to "co-activate B cells" which have also captured similar foreign antigen via their independent antigen processing

- Activated T Helper cells now able to also stimulate non-specific defenses / stimulate macrophage, NK cells, and inflammation!

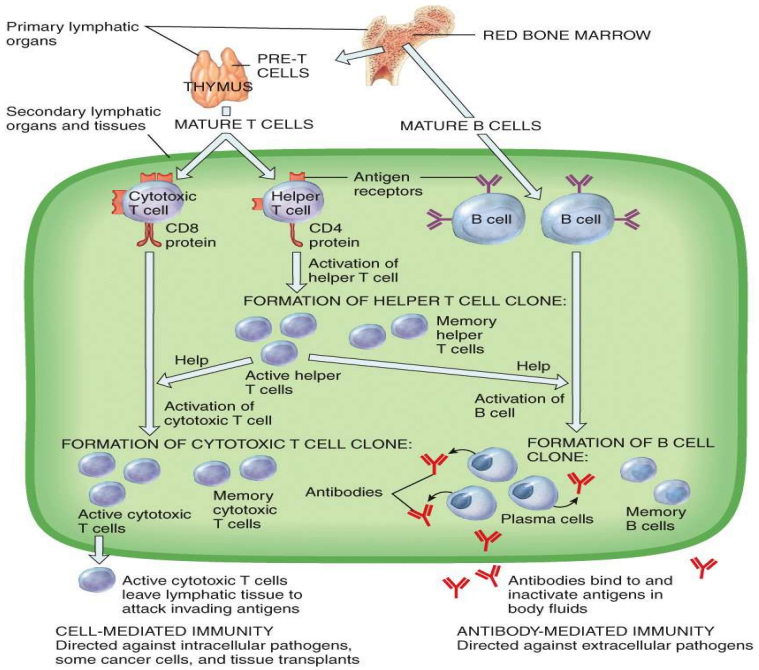
Antigen Processing

The first step to initiate an acquired immunity response.

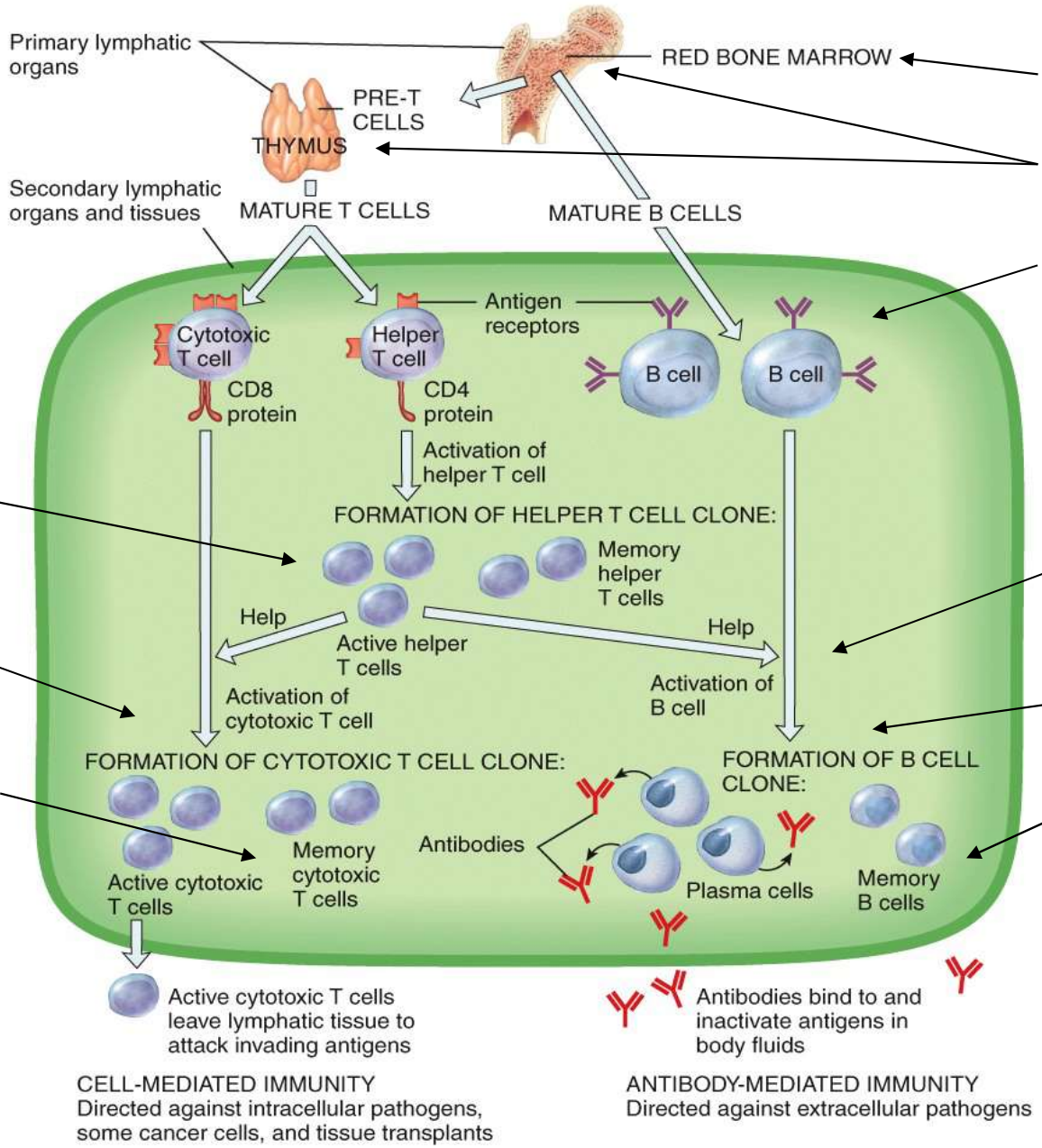


MHC protein type-II for all antigen presenting cells

- The **immune system** is complex and difficult to understand on the first pass.
- It helps to visualize the overall process first before you try to learn the details of the immune system.
- After you grasp the overall process, then you can drill down for greater understanding about adaptive immunity.
- This graphic is an overview of how the immune system works. You will need to memorize this graphic to fully understand how the the immune system works.



This is an overview of adaptive immunity.



Born

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Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

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Remember

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

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

The first step involves the formation and preparation of the immune cells.

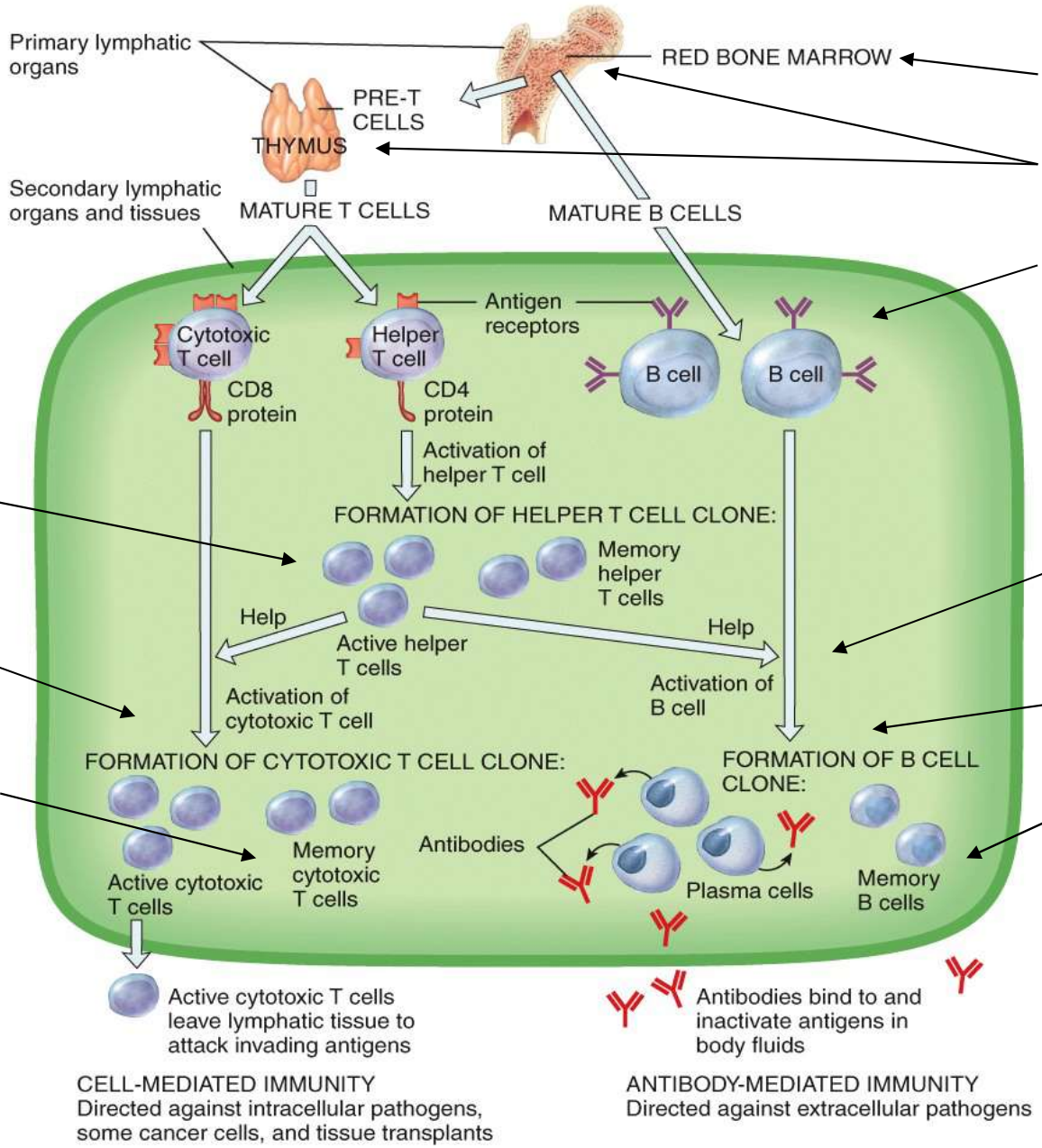
The second step involves how these cells are transformed from inactive cells into active cells (i.e. able to kill pathogen) and memory cells

First step stages = cells are born – education – deployed

Second step 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)

This is an overview of adaptive immunity.



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Key Questions

This is what you need to know about acquired immunity.

- Where are the B and T immune cells produced (born)?
- Where do these immune cells mature (get educated)?
- What must happen to an immature immune cell to make them functional (complete education)?
- After immune cells are educated, where do they go (deployment)?

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)

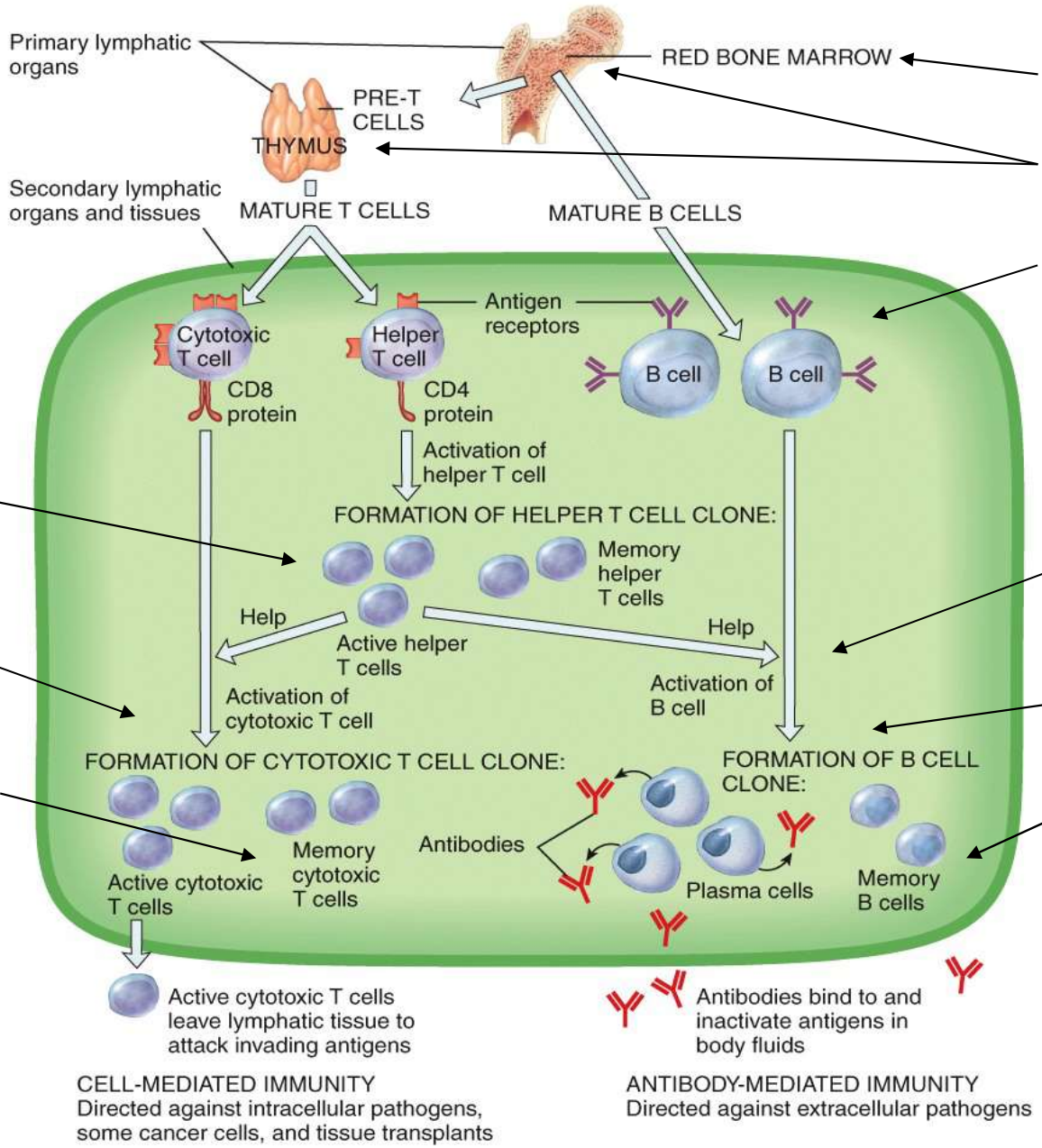
  - 1) recognize (means the immune cells have been activated – able to bind to MHCP)

  - 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.



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Activation of Helper T Cells

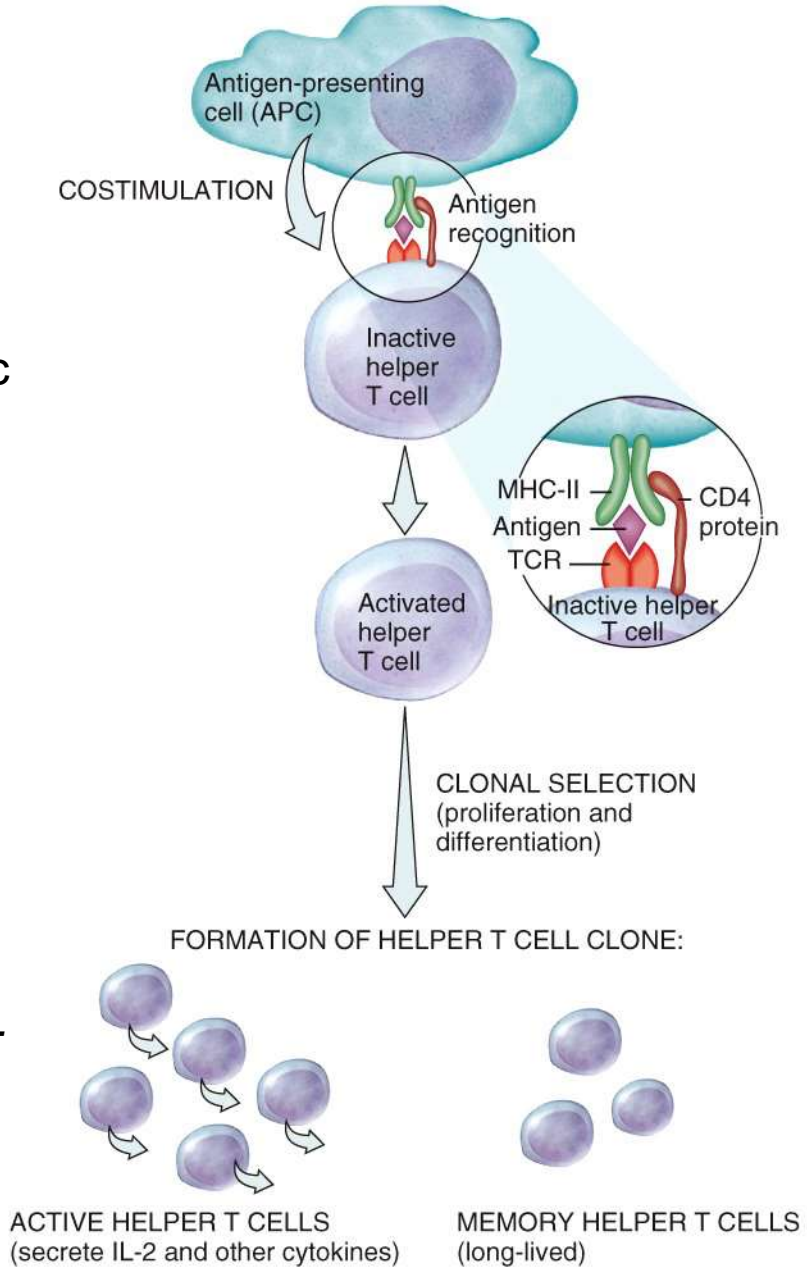
This is a critical step in the recognition process.

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

Activated Helper T cell are required to complete the activation of both naïve immunocompetent cytotoxic T cells and naive immunocompetent B cells.

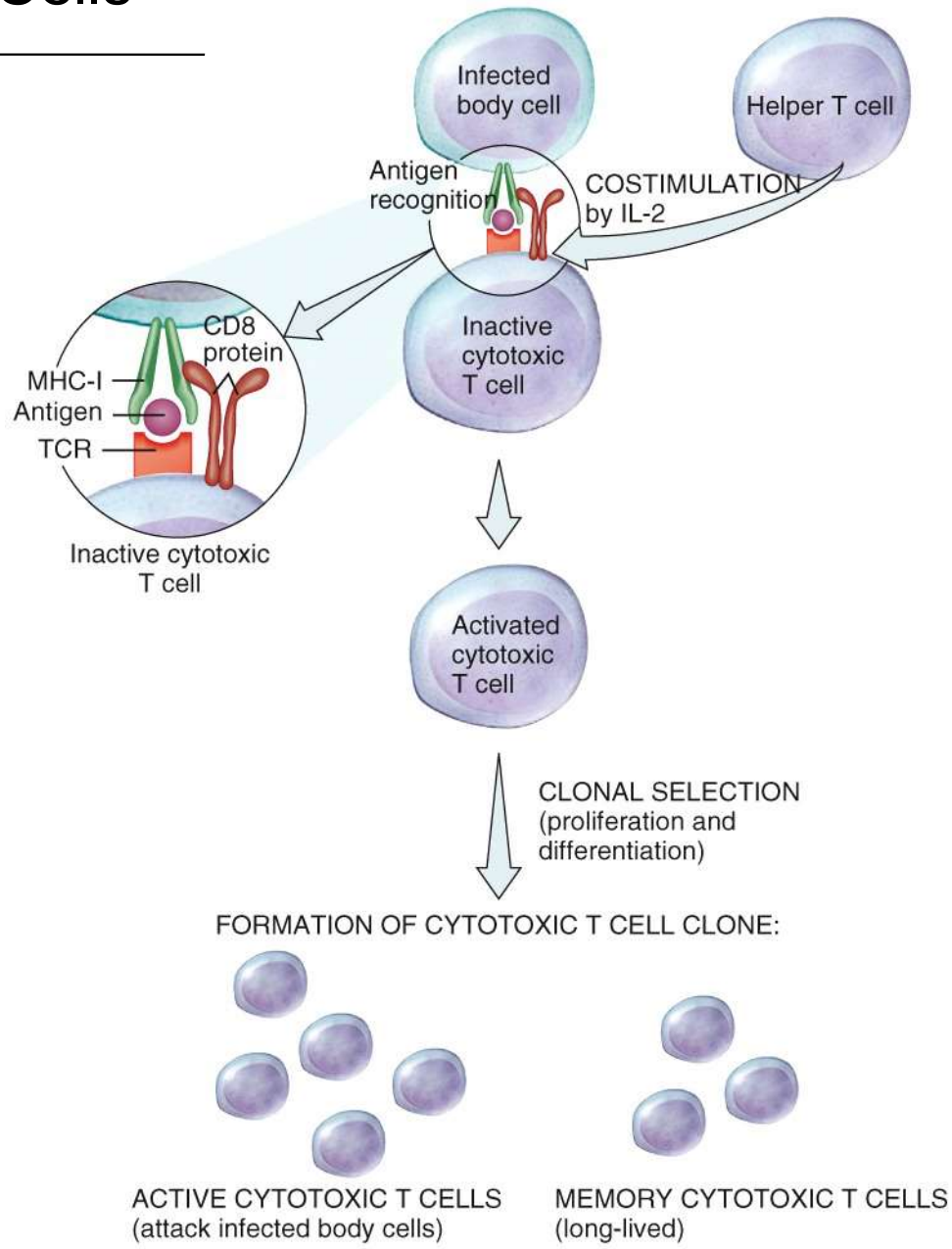
Helper T cells will also enhance macrophage activity and other events associated with inflammation

Note: the CD4 protein on helper T Cell function as a costimulatory factor in activation of helper T Cell /// costimulation is a type of second check to insure helper T Cell will activate only the appropriate cytotoxic T cells and B cells



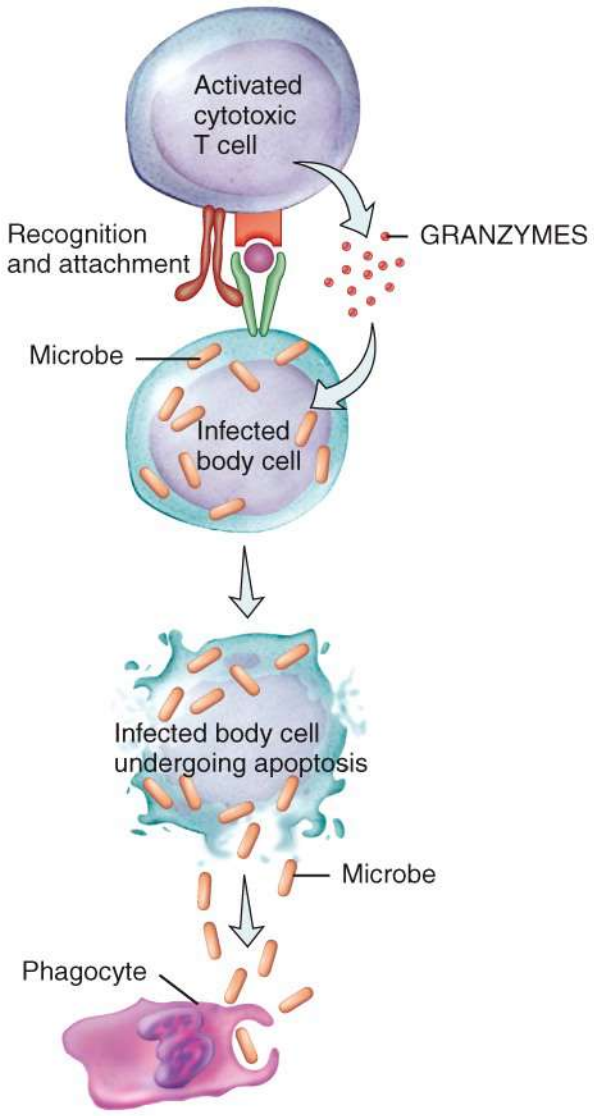
Activation of Cytotoxic T Cells

- The first step of the recognition process for the CD8 cell occurs when they binds to an infected cell displaying the “foreign epitope”
- Note CD8 protein provides a “second check” for proper MHC-I receptor complex
- Now Helper T cell (previously activated by similar pathogen) now secretes interlukin-2 /// this is the costimulation /// This completes the activation
- Now clonal selection occurs producing many activated cytotoxic T cells /// Now these activated cytotoxic T cells are able to dock and kill infected cells that display MHCP-I with foreign epitopes

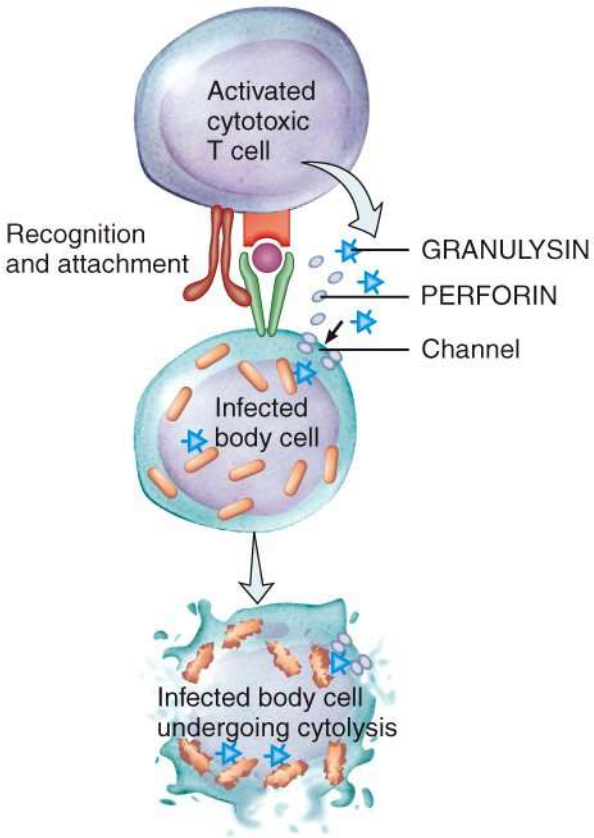


React Stage of Cytotoxic T Cells

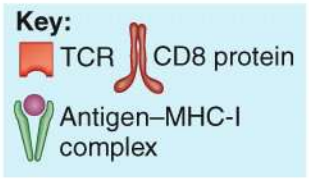
Note two different methods to destroy infected cells with exogenous antigen



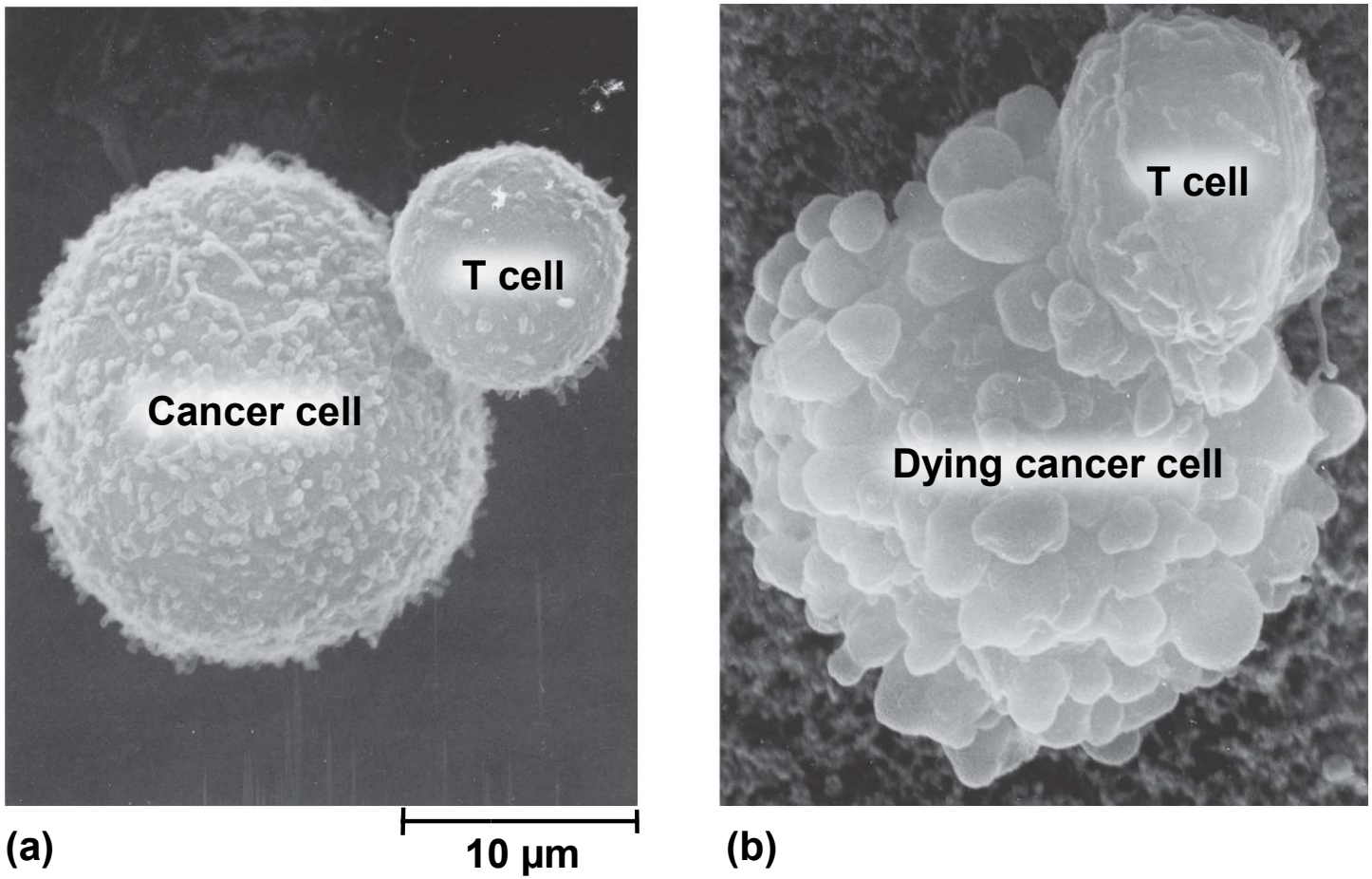
(a) Cytotoxic T cell destruction of infected cell by release of granzymes that cause apoptosis; released microbes are destroyed by phagocyte



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



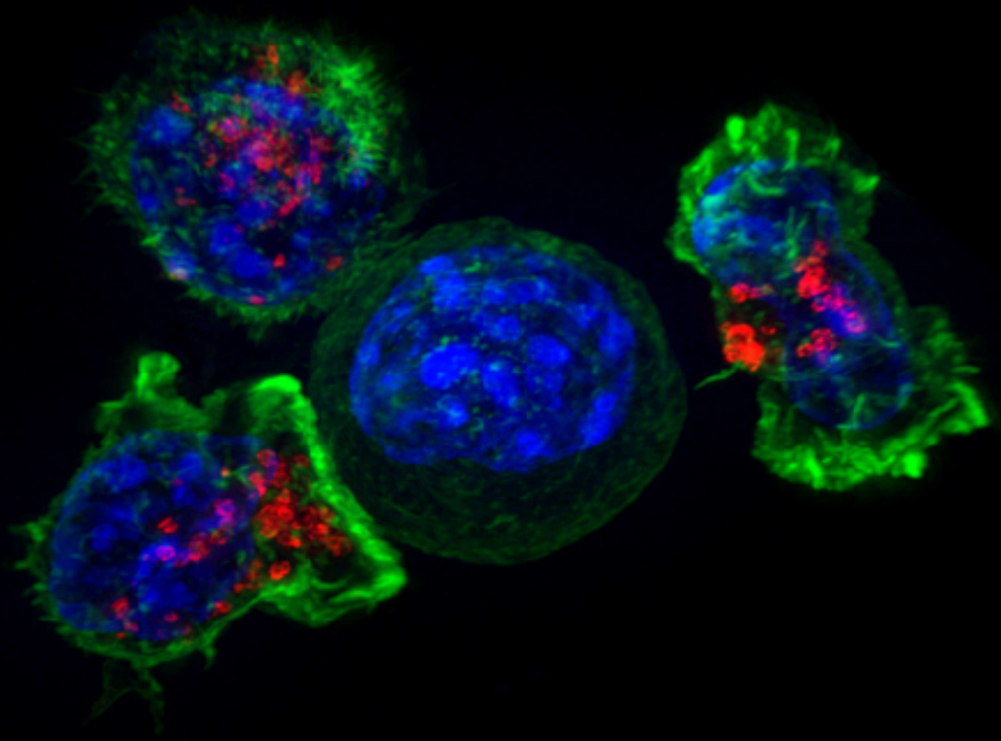
Cytotoxic T Cell Function



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) is 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.

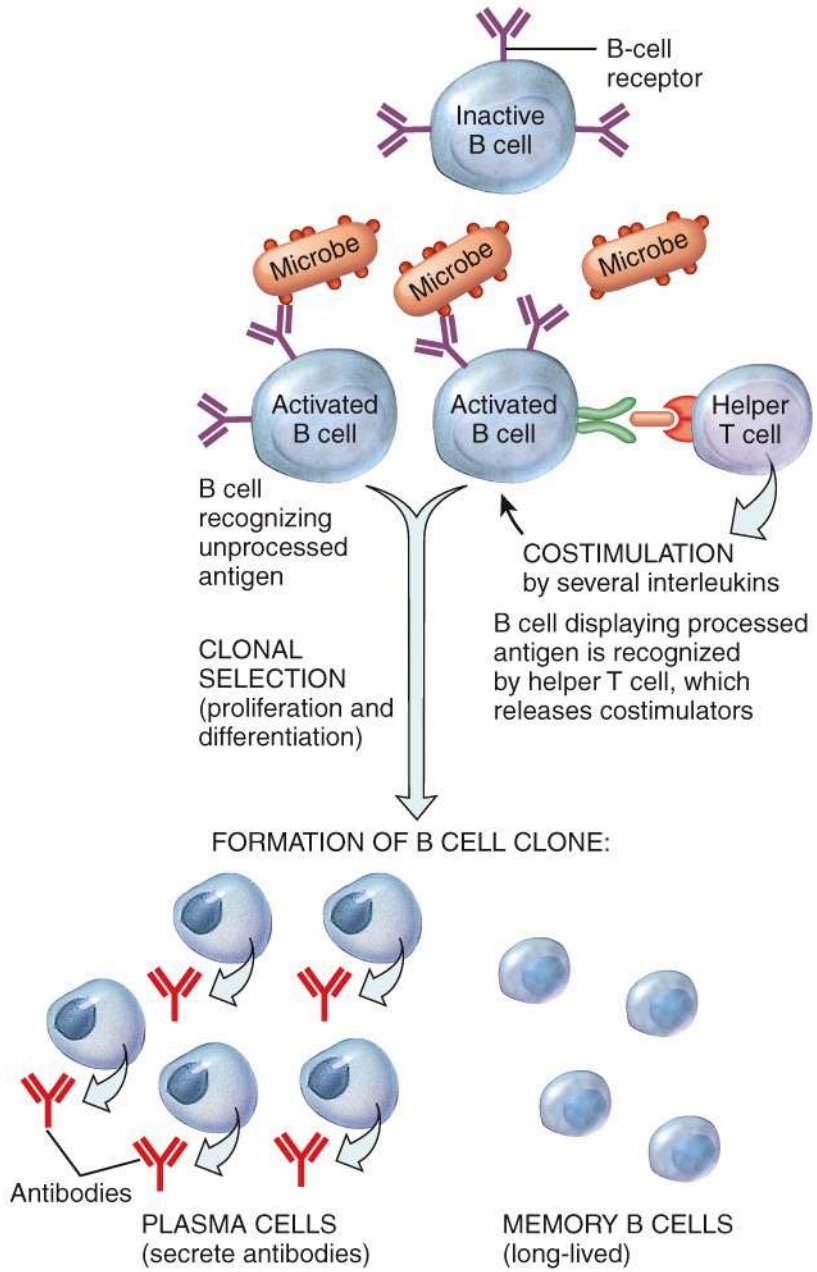
Activation of B Cells

The B cell recognition process is different than the Tc process.

Naïve immunocompetent B cells have two distinct activation methods // T_H cell dependent and T_H 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 and 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 and memory B Cells formed.



Activation of B Cells

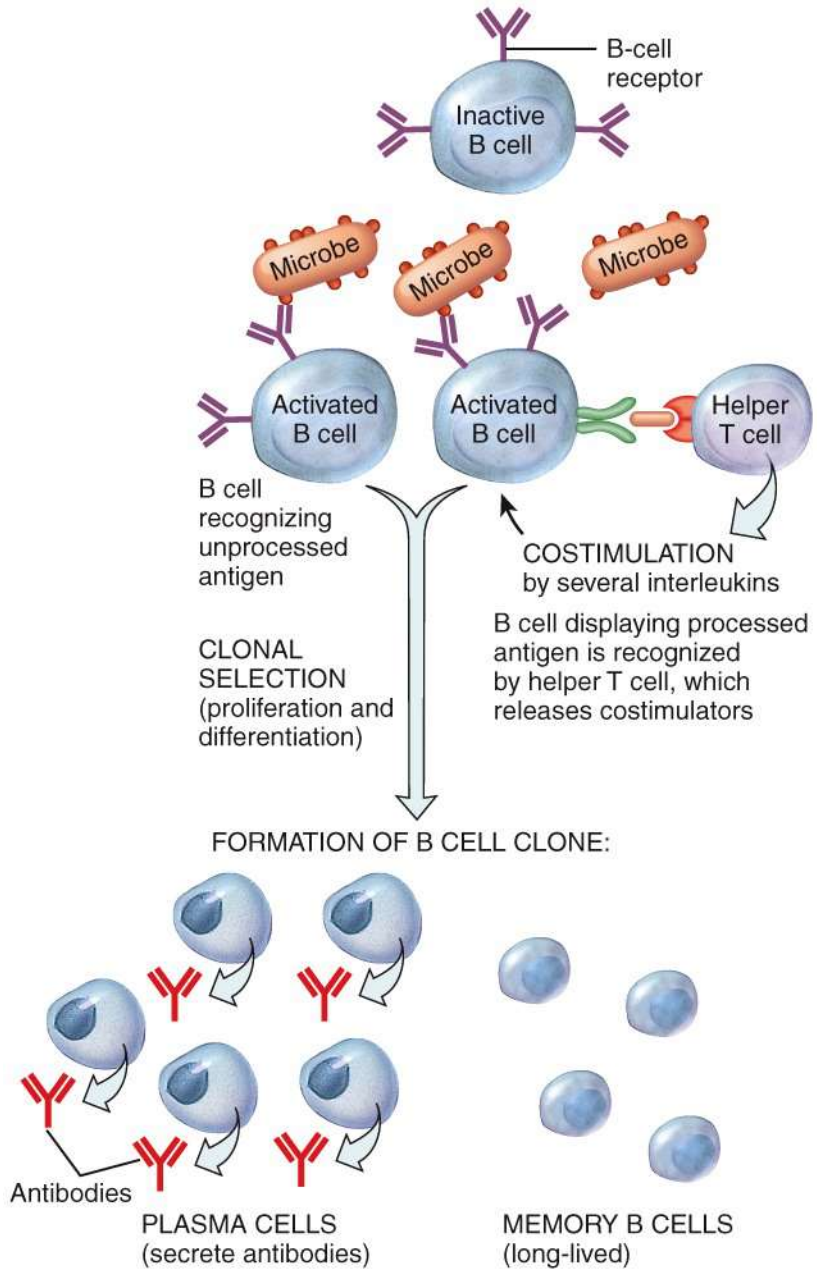
First step in “recognition” (activation) is pathogen binds to a B cell receptor.

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

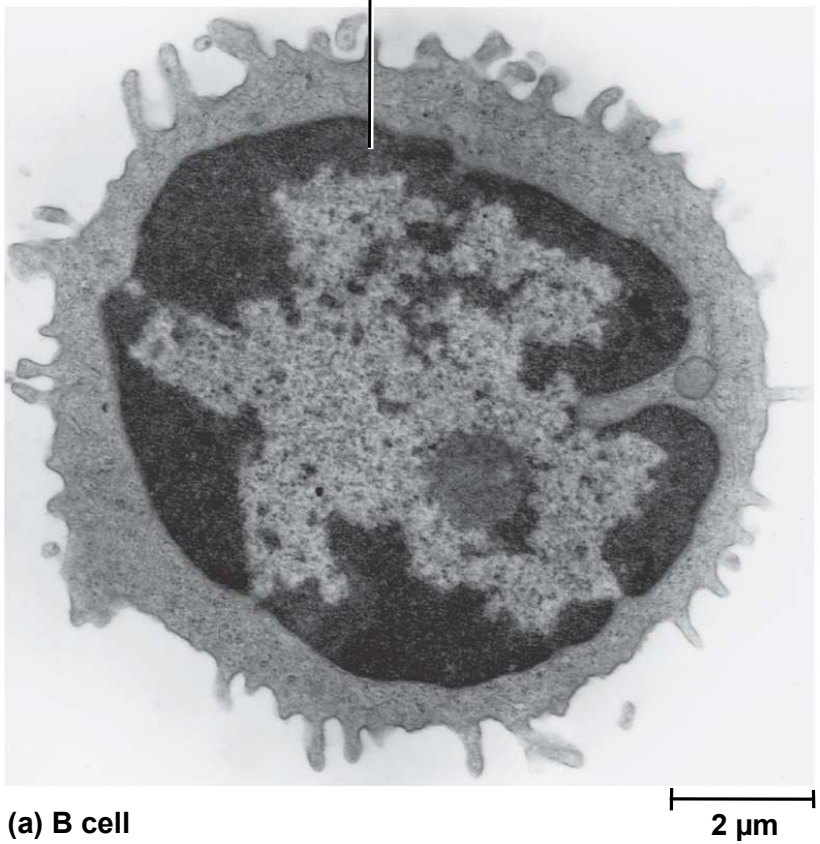
Previously activated Helper T cell to similar pathogen now binds with MHCP-II-epitope complex (second step)

Helper T cell costimlates B cell to initiate clonal selection.

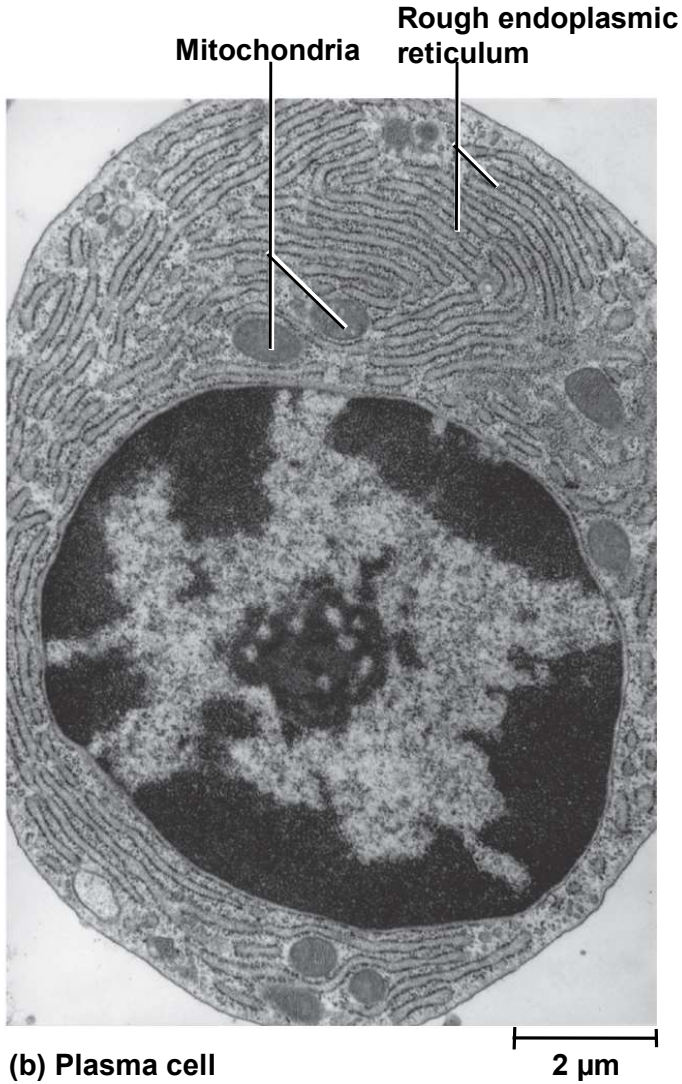
Plasma cells and memory B cells formed // Plasma cells make 2,000 antibodies per second per cell for 7 days.



B cells to Plasma cells

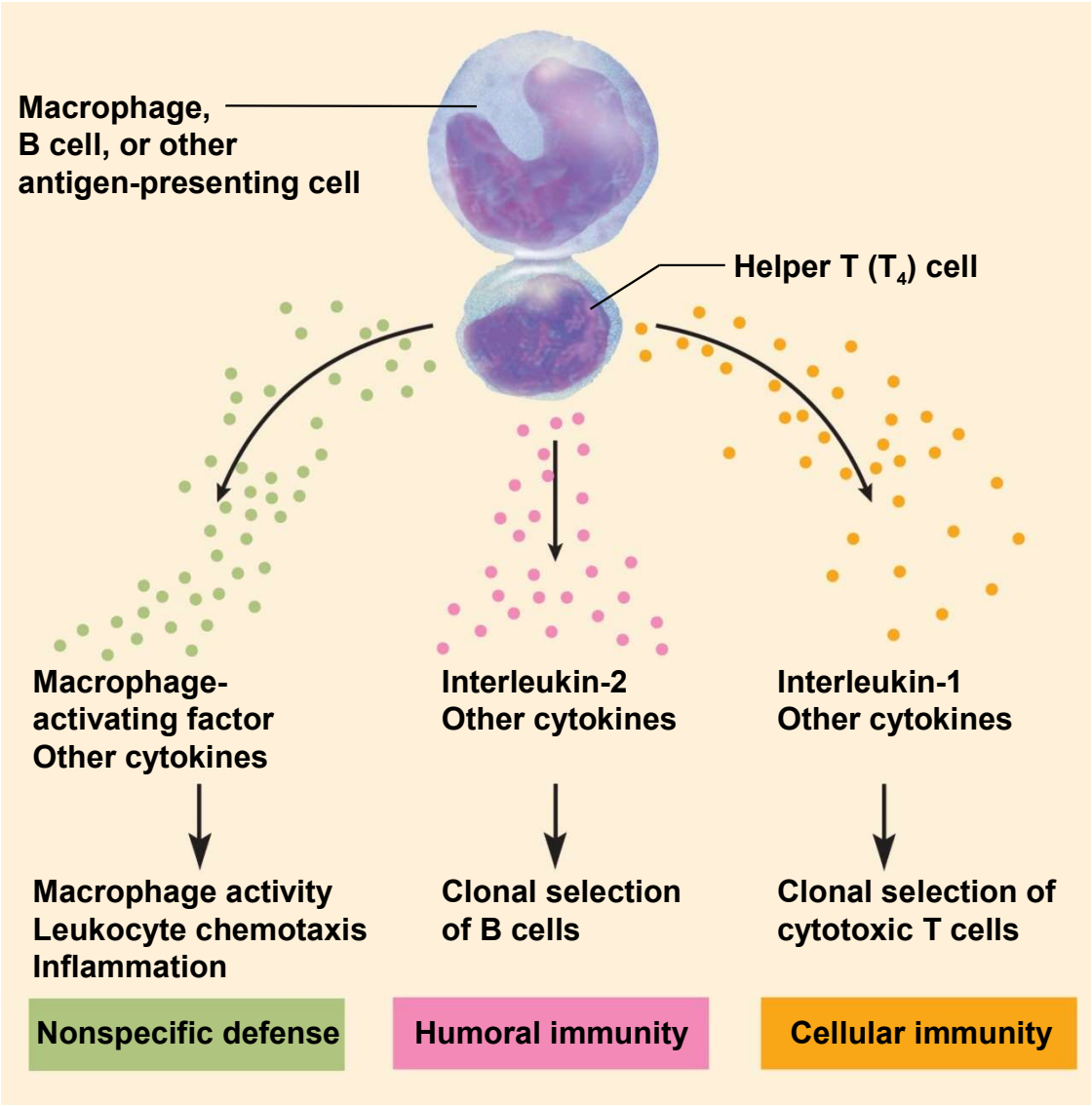


(a) B cell



(b) Plasma cell

Helper T Cell's
Pivotal Role in 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 have no 2nd or 3rd line defenses against pathogens!

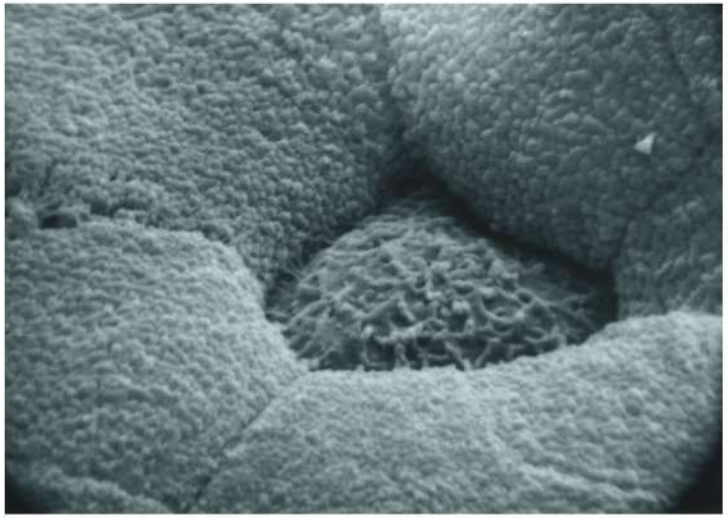
M Cells

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.

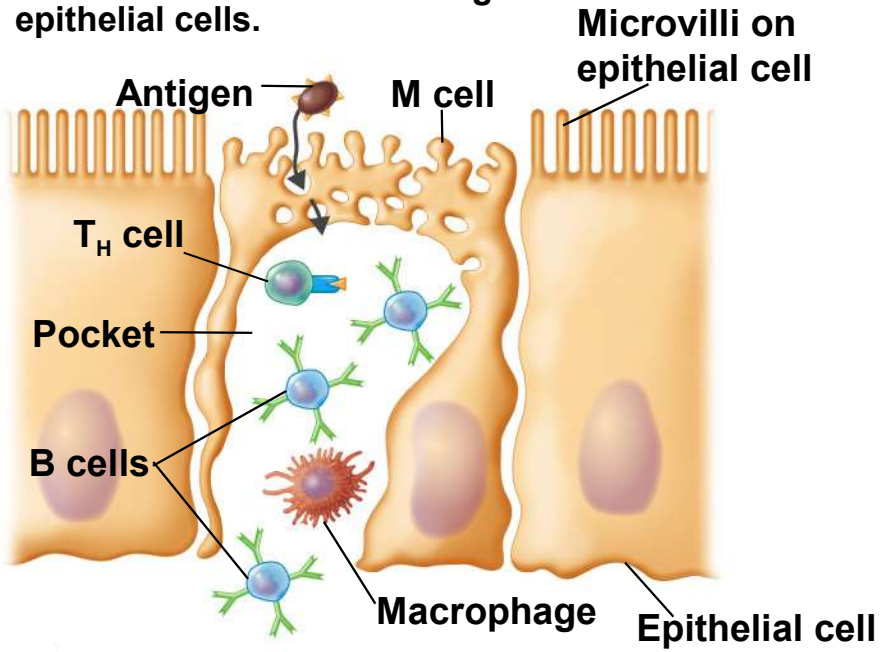
Immune system recognize bacteria even before it is in our bodies

Immune system starts to prepare defenses against bacteria.

Tonsils have 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.

We now have a general understanding about how the immune system works.

Your next step is to look at the underlying mechanisms of adaptive immunity.

This will allow you to better understand the function of immune cells and how these cells “recognize, react, and remember” unique pathogens.

Much of the information presented in the following slides, as important as it may be, will not be included as “testable” information!

However, there are a few slides in the next section that contain information which has already been covered and is considered “testable information”.

What cells are required for Adaptive Immunity? Where are they found?

- Lymphocytes / macrophages / dendritic cells / reticular cells
- These cells are concentrated in strategic places throughout the body
- Locations of high concentrations:
  - Lymph
  - Blood
  - Lymphatic organs
  - Skin / epidermis
  - Beneath mucous membranes
  - *Reticuloendothelial system (i.e. connective tissues throughout body)*
- *Note: reticular cells are in thymus /// they secrete messenger molecules which regulate development of T cells*

What lymphocytes are required for immunity?

- Lymphocytes (three types /// primary function)
  - T lymphocytes (T cells) – cellular immunity
  - B lymphocytes (B cells) – humoral immunity
  - *Natural killer cells (NK cells) – do not play role in "acquired immunity"*
    - *NK cells provide immune surveillance // non-specific // kill cells infected with cancer or virus // NK cells do not need to be activated by helper T cells!*

More information about …….

1. T Cells - Cellular Immunity
2. B Cells - Humoral Immunity

Cellular Immunity
T Cell Types (Structure and Function)

– Four Different T Cells Types

- Helper T Cells
- Cytotoxic T Cells
- Memory T Cells
- Regulatory T Cells

  – Key Ideas

  – Only Tc cells can kill host cells containing which reside inside human cells

  – *Helper T cells are required to activate resting Tc cells*

Cellular Immunity
Cytotoxic T Cells = Tc (Structure and Function)

- also known as T8, CD8, or CD8+ (CD = cluster of differentiation proteins embedded in plasma membrane)
- CD8 term often used to describe Tc before they become activated
- Tc are only T cell able to kill infected cells
- Only Tc lymphocytes directly attack and destroy foreign cells (e.g. tissue transplanted) or diseased host cells
- These are the 'effectors' of cellular immunity
- Attack cells infected with exogenous antigen
- Dock to infected cell and use perforin and/or granzymes to kill cells

Cellular Immunity
Helper T Cell = T_H (Structure and Function)

- also known as T4, CD4, CD4+
- CD4 term often used to describe TH before they become activated
- activated help T cells requred to activate T_C cell and B cell (the T cell dependent B cells)
- TH secrete cytokines that also stimulate components of the nonspecific resistance (i.e. activate and bring macrophage and neutrophils into the infected area, prevent macrophage from leaving the area)

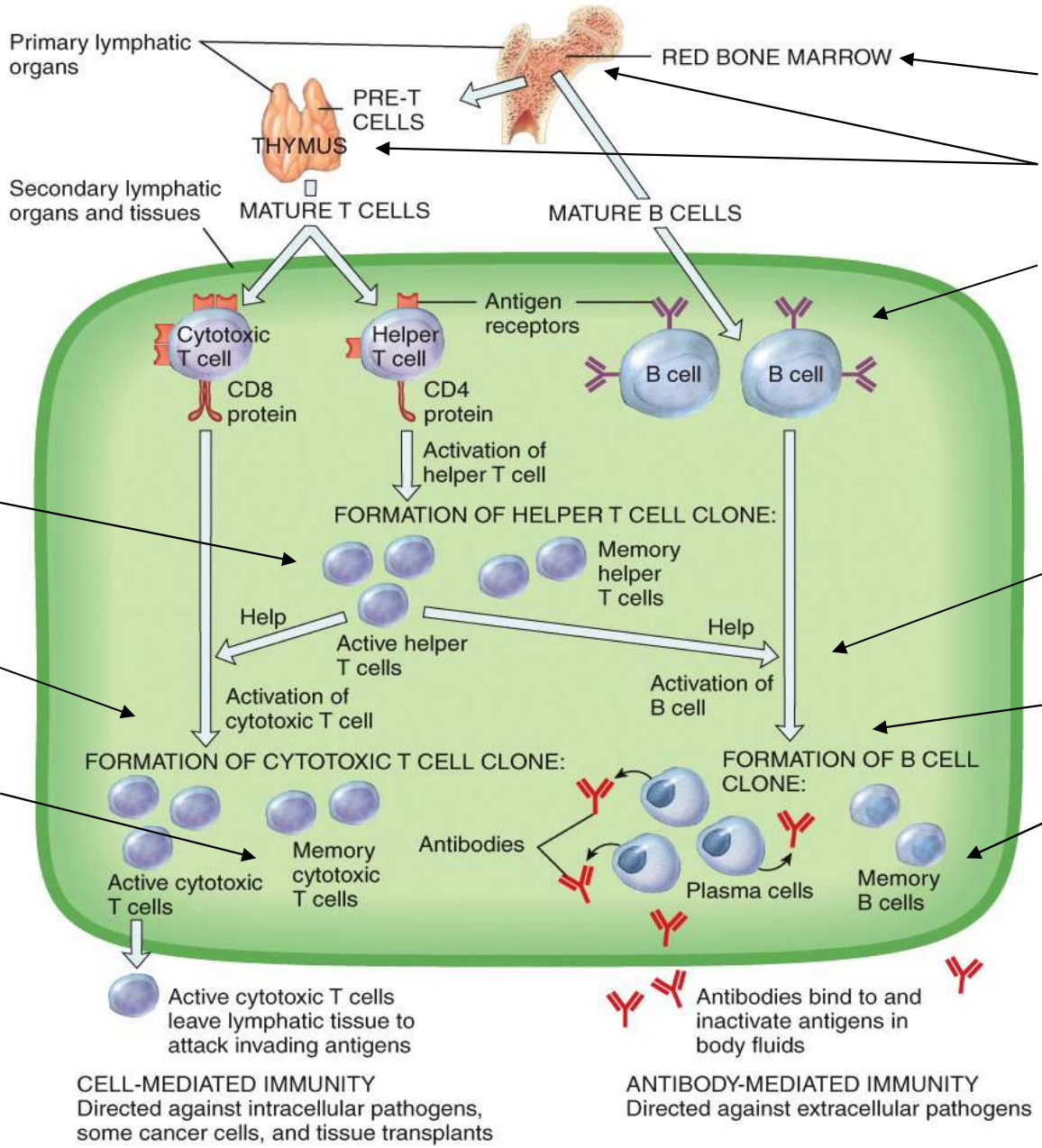
Cellular Immunity
Regulatory T Cell = T_R (Structure and Function)

- T_R cells – T-regs
- Least understood
- inhibit multiplication and cytokine secretion by other T cells
- limit immune response // <u>its believed that when TR cells fail it then results in autoimmune disease</u>

Cellular Immunity
Memory T Cell = Tm (Structure and Function)

- descend from same cytotoxic T cell line (same receptor type)
- During clonal selection Tm cells produced along with other T cell types
- After pathogen defeated only Tm cells against the specific pathogen persist in the lymph nodes and other lymphatic tissues
- On a second exposure the Tm cells immediately reintroduce clonal selection /// defeats pathogen even before you can develop a fever!
- responsible for the “memory” in cellular immunity
- note: most cells die after pathogen defeated via apoptosis but memory cells remain for decades!

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

React

Remember

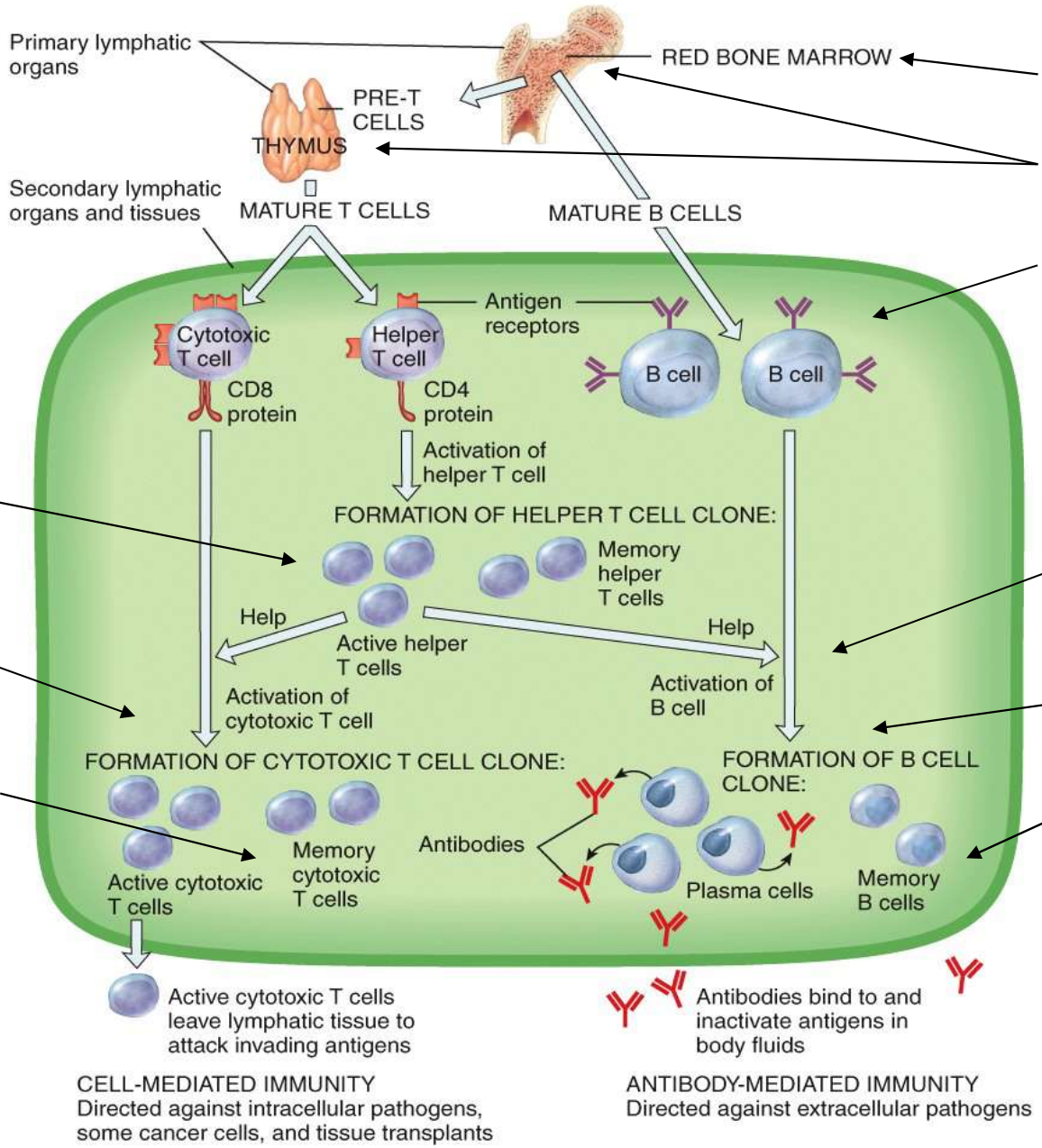
T Cell Developmental Stages
Cellular Immunity

Born

Educated

Deployment

This is an overview of adaptive immunity.



Born

Educated

Deployed as

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Recognize

React

Remember

Recognize

React

Remember

T Cells - Stage One = Born

- Born in the red bone marrow // descendant of the pluripotent stem cells (PPSCs)

- released into the blood as still-undifferentiated stem cells that colonize the thymus

T Cells - Stage Two = Education

- Educated in thymus // thymosins stimulate maturing T cells to develop surface antigen receptors
  - with receptors in place, the T cells are now naive immunocompatent
  - receptors capable of recognizing epitope presented to them by APCs
  - reticuloendothelial cells in the thymus test T cells by presenting 'self antigens' to them
  - educational process continued on next 3 slides

T Cells - Stage Two = Education

- Two ways to fail their education / two tests:
  - inability to recognize the RE cells self antigen
    - » especially their MHC protein (self-antigens)
    - » *would be incapable of recognizing a foreign attack on the body (MHC carries the epitope!)*
  - reacting to self antigen
    - » *T cells would attack one's own tissues*

T Cells - Stage Two = Education

- negative selection - T cells that fail either test must be eliminated
  - two forms of negative selection
    - » clonal deletion – self-reactive T cells die and macrophages phagocytize them
    - » anergy – self-reactive T cells remain alive but unresponsive
  - *negative selection leaves the body in a state of* self-tolerance

T Cells - Stage Two = Education

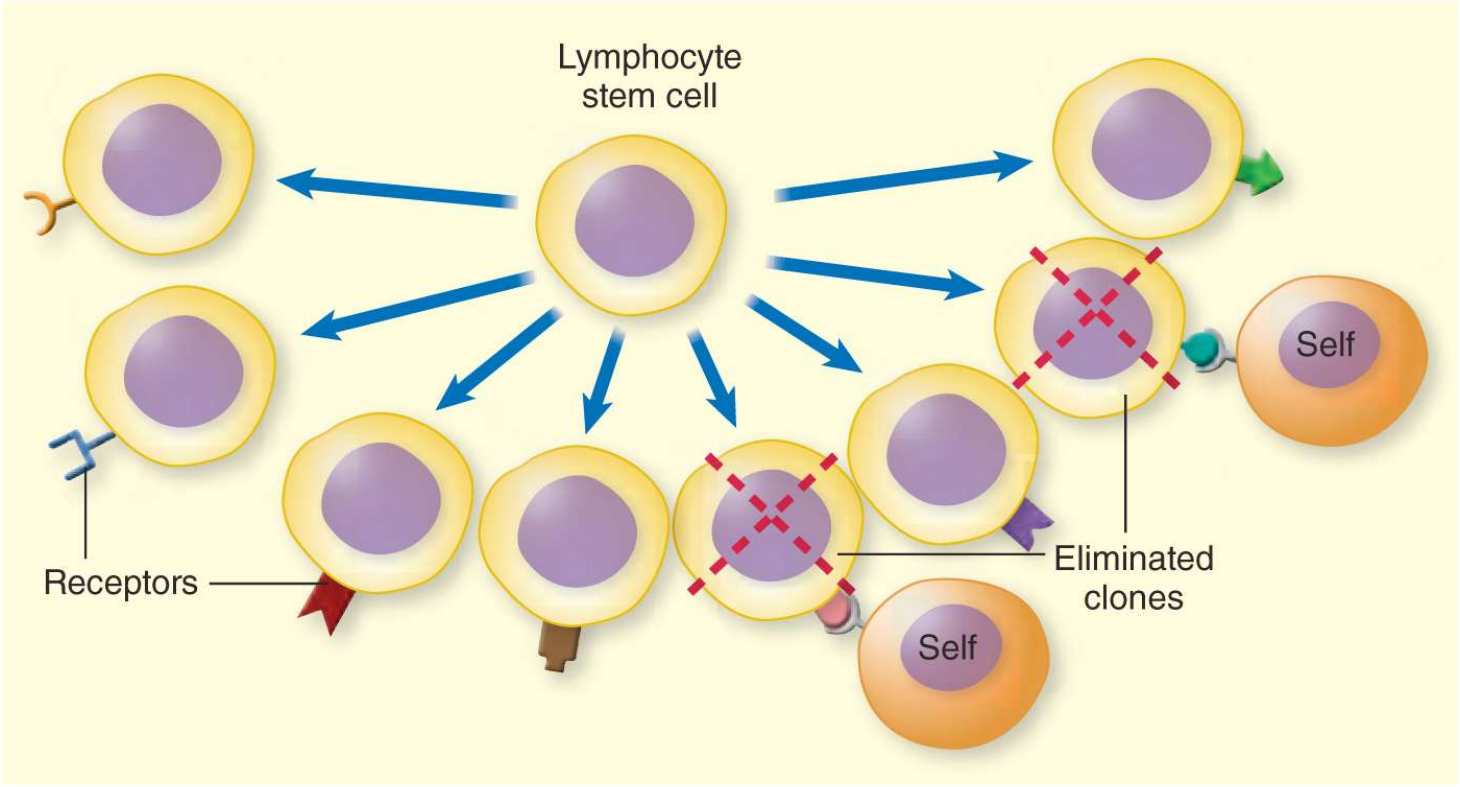
- Self-tolerant CD8 & CD4 cells move to medulla of the thymus and undergo positive selection
  - multiply and form clones of identical CD8 & CD4 cells programmed to respond to a specific antigen
- These cells become the naïve immunocompatent T lymphocytes
  - immunocompetent cells (have receptors for specific antigen in their membrane)
  - have not yet encountered the foreign antigens = naive
  - CD4 (future Helper T Cells)
  - CD8 (future Cytotoxic T Cells)
- These cells are now ready to be deployed!!!

T Cells - Stage Three = Deployment

- Deployment
  - naive immunocompatent CD8 (cytotoxic T cell) and CD4 (helper T cell) leave the thymus
  - Only 2% of the T cells that enter the thymus will leave as immunocompetent T cells
  - naive T cells leave thymus and colonize lymphatic tissues, organs, and are free to wander around the body looking for foreign antigen
  - When activated by foreign antigen
    - CD8 cells may become cytotoxic T cells
    - CD4 cells may become helper T cells

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

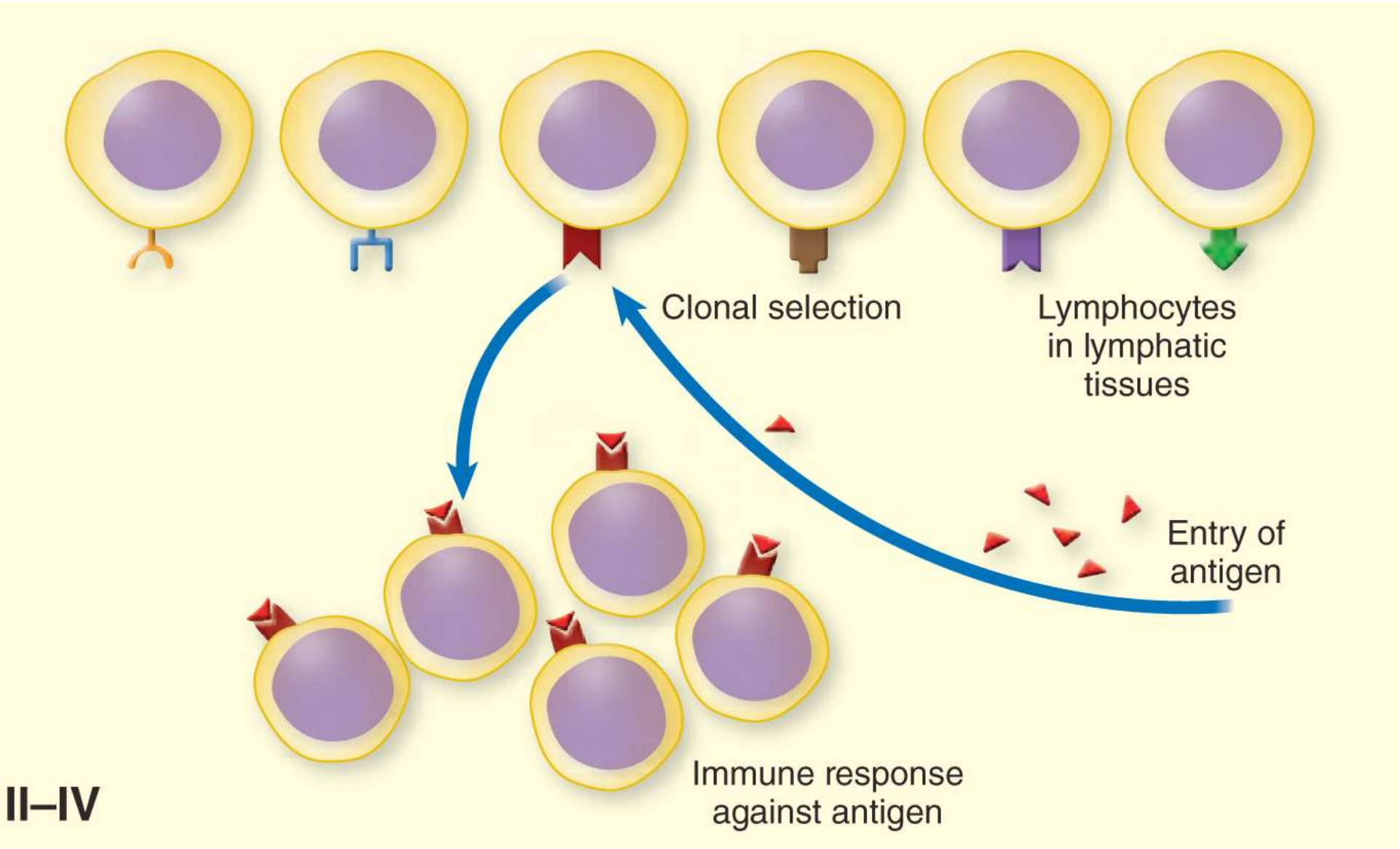
Deployed as “Naïve Immunocompatent” T Lymphocytes (helpers and cytotoxic)



Repertoire of lymphocyte clones, each with unique receptor display

Naïve Immunocompatent T Cells Activated by

Unique Antigen (epitope) That Then Initiates Clonal Selection



More information about …….

B Cells - Humoral Immunity

Structure, Function, and Developmental Stages

Humoral Immunity
B Cell Types (Structure and Function)

– Humoral immunity (antibody-mediated)

- Immunocompatent naïve B cells need to be activated before they "morph" into plasma cells
- These plasma cells are pre-programmed to make antibodies to matched a specific foreign antigen // i.e. have unique receptor matched to specific foreign antigen
- antibodies never directly kills a pathogen but render them harmless and tag them for destruction
- can only work against the infectious microorganisms when the pathogen is outside of the cells (in the interstitial or vascular space)

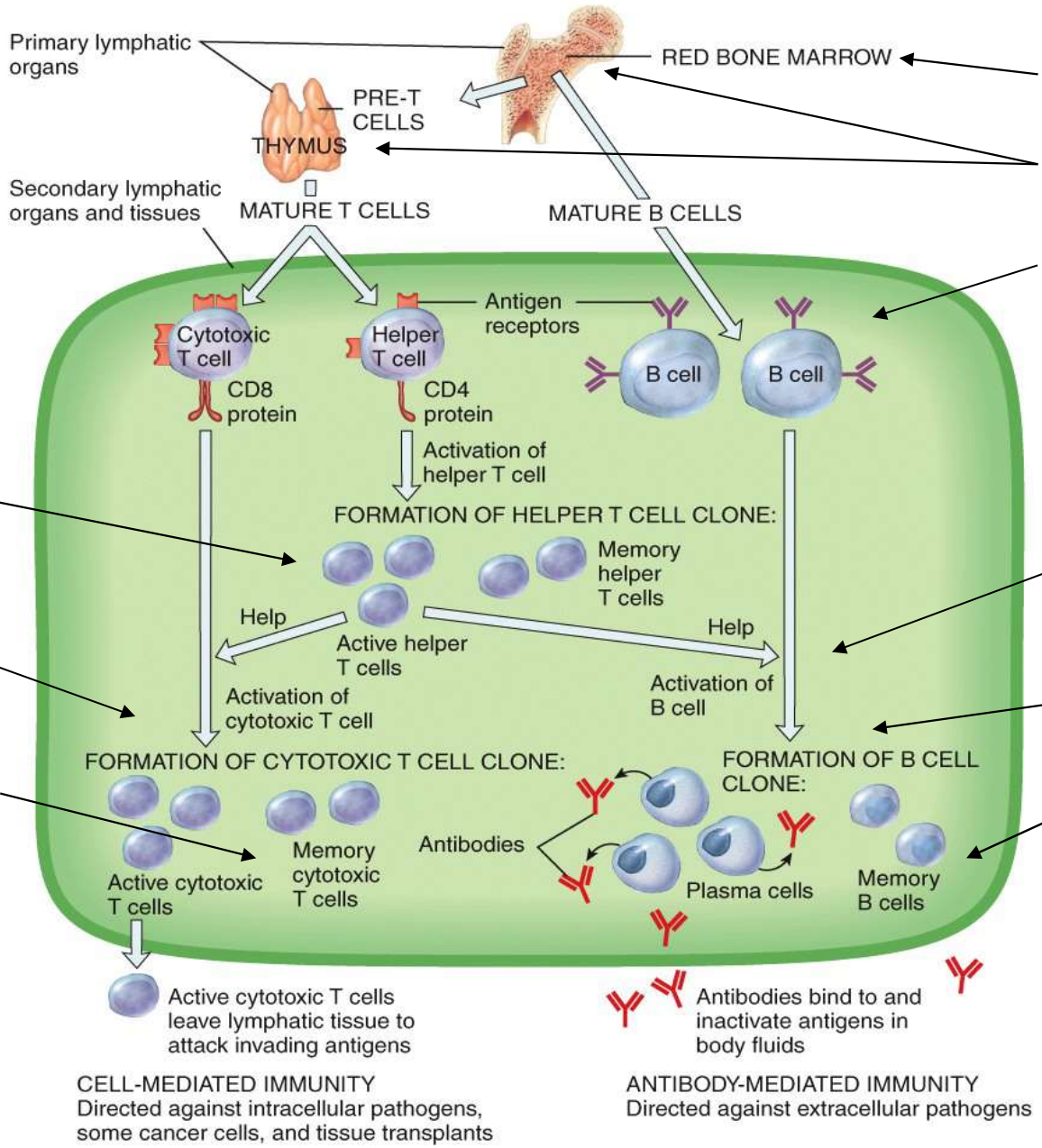
B Cell Developmental Stages
Humoral Immunity

Born

Educated

Deploy

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

React

Remember

B Cell Stage One = Born

- B cells born in bone marrow
  - site of multiplication, development & maturation
  - Develop from fetal stem cells that remain in **bone marrow**

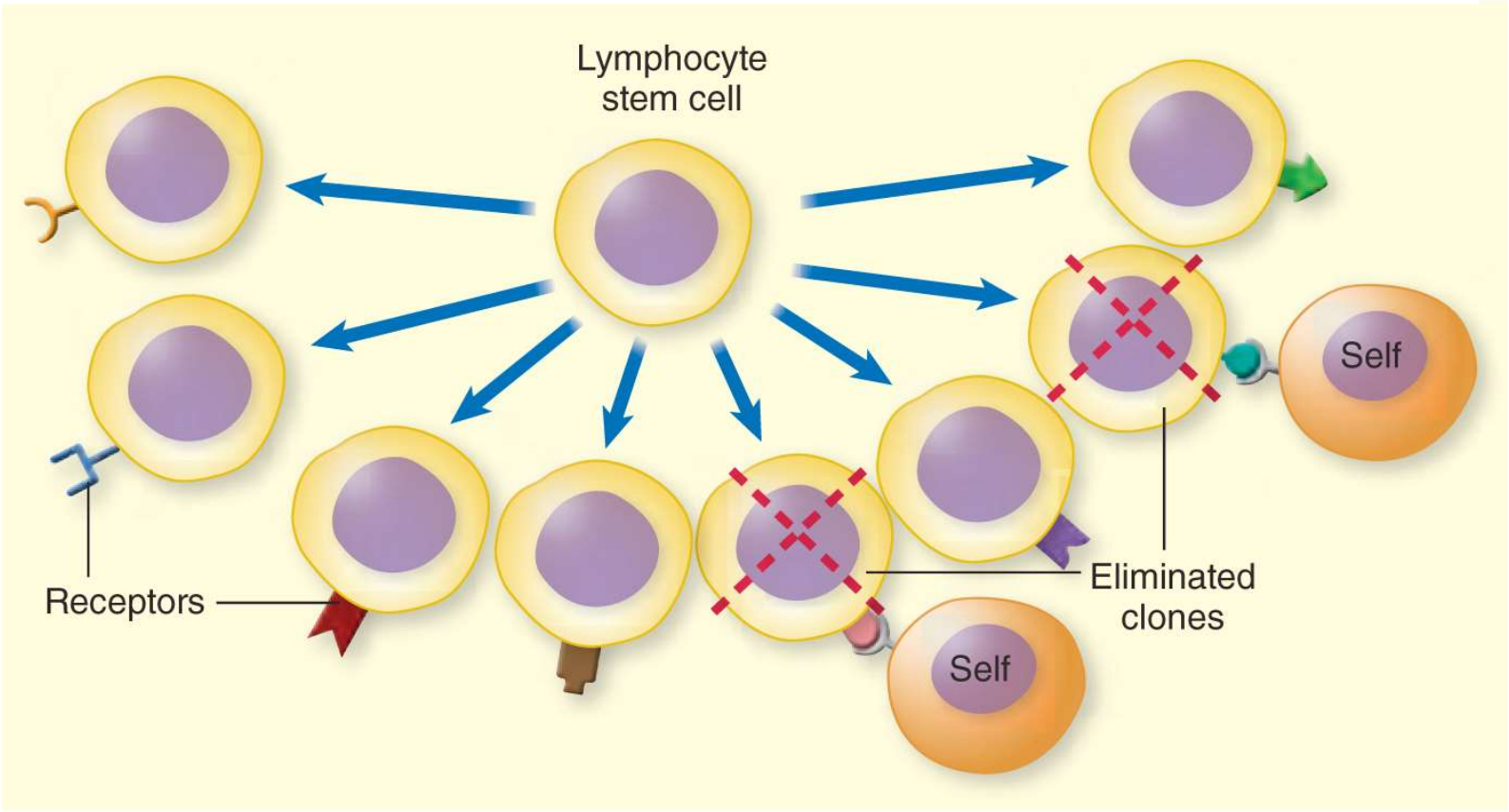
B Cell Stage Two = Education

- Educated in bone marrow /// Similar process as seen with T cells
  - B cells that react to self antigens undergo either anergy or clonal deletion
  - self-tolerant B cells /// synthesize antigen surface receptors to foreign antigen // receptors are IgD class antibodies embedded into membrane
    - divide rapidly / positive selection
    - produce immunocompetent clones (these cells have receptors for foreign antigen in their membrane)
    - B cells are naïve and ready for deployment

B Cell Stage Three = Deployment

- Immunocompatent naive B cells leave bone marrow and colonize lymphatic tissues, organs, and are free to wander around the body looking for foreign antigen
- When activated by foreign antigen
  - B cells morph into plasma cells and are able to make different classes of antibodies specific to the epitope (antigen)
  - Note: B cells may serve as their own Antigen Presenting Cell
  - After antigen binds to surface receptor it is internalized inside B cell where it is processed and displayed in an MHCII complex on its membrane
  - T cell dependant B cells complex with helper T cell then change into active plasma cell

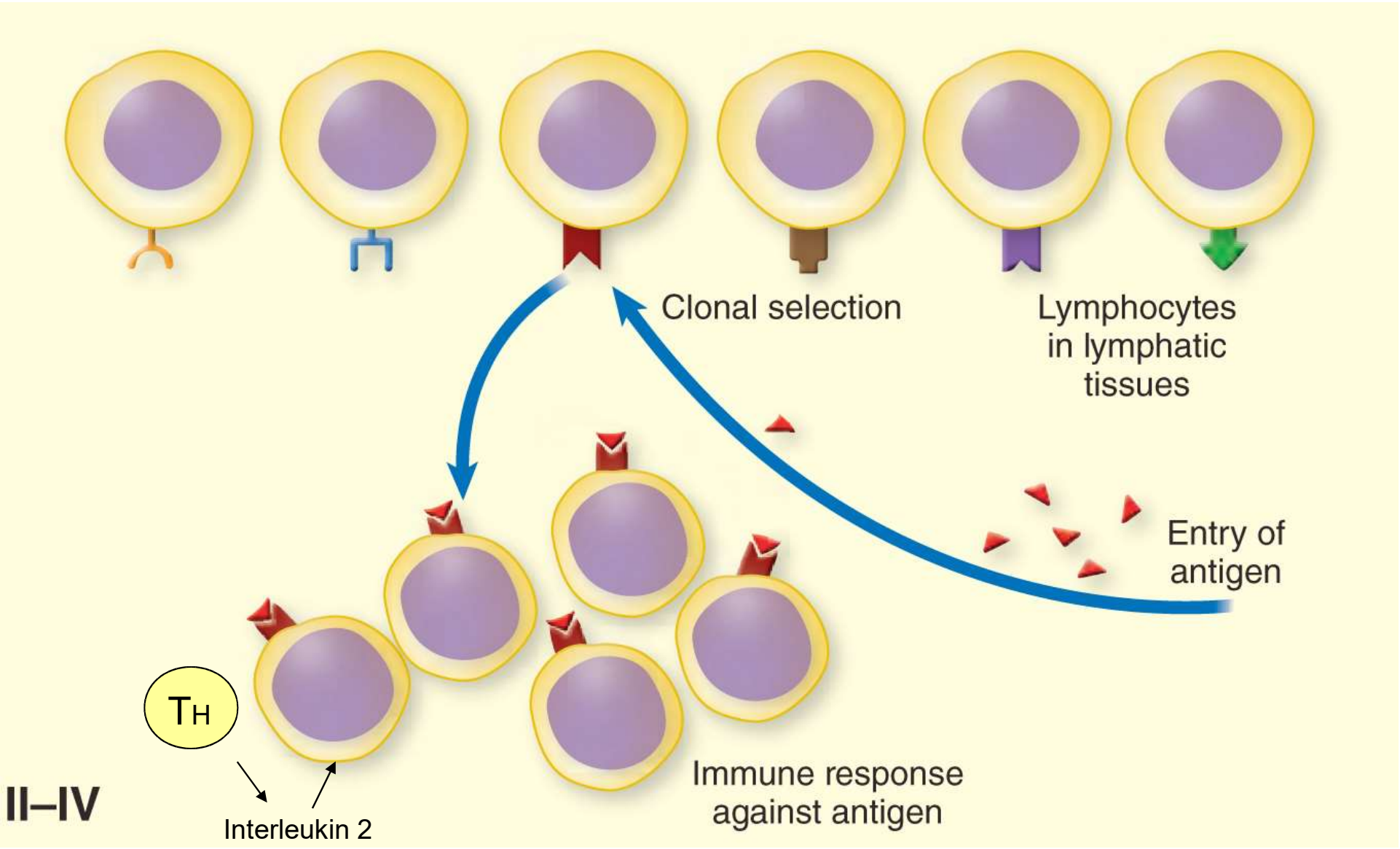
B Lymphocytes are “Educated” Then Become “Naïve Immunocompatent”



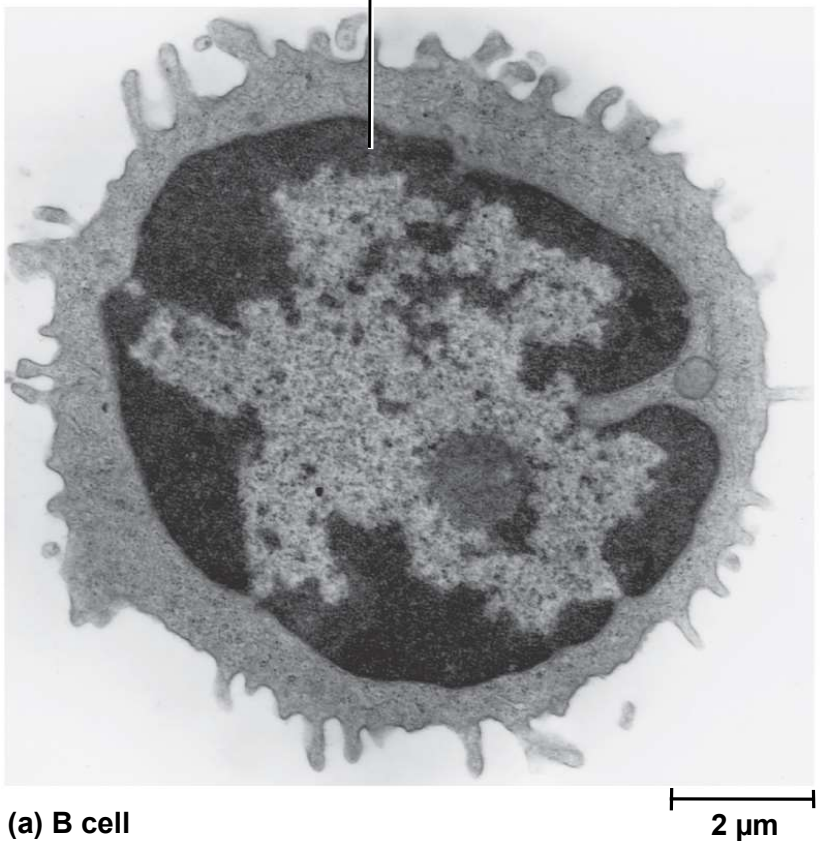
Repertoire of lymphocyte clones, each with unique receptor display

Naïve Immunocompatent B Cells Activated by Unique Antigen (epitope)

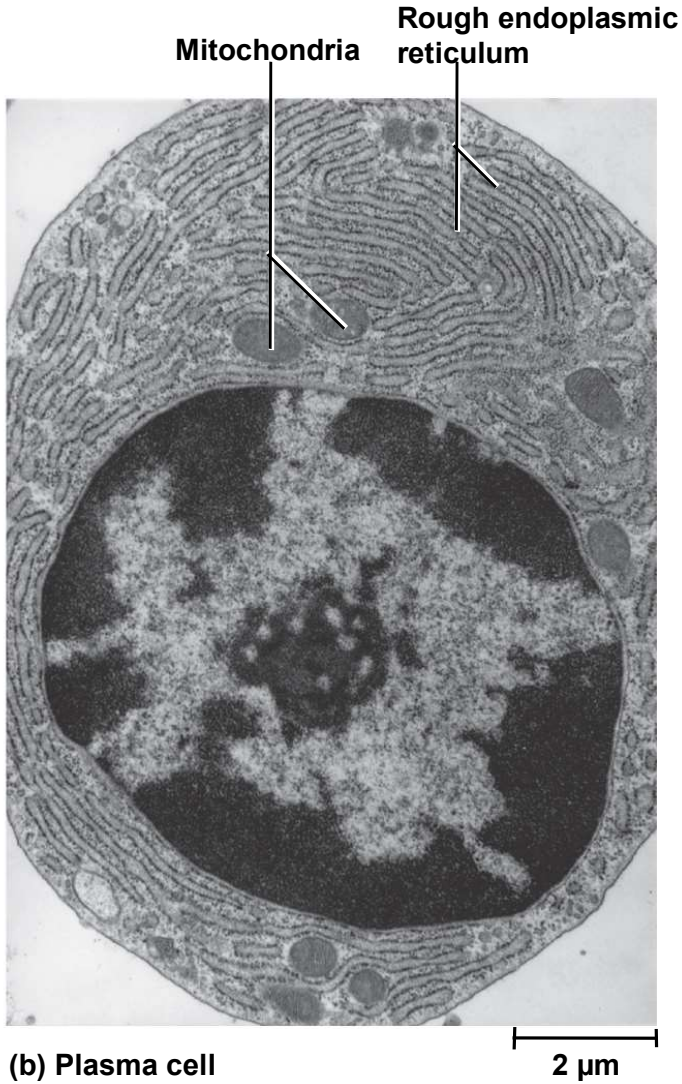
With co-stimulation by Helper T Cells Which Initiates Clonal Selection



B cells to Plasma cells



(a) B cell



(b) Plasma cell

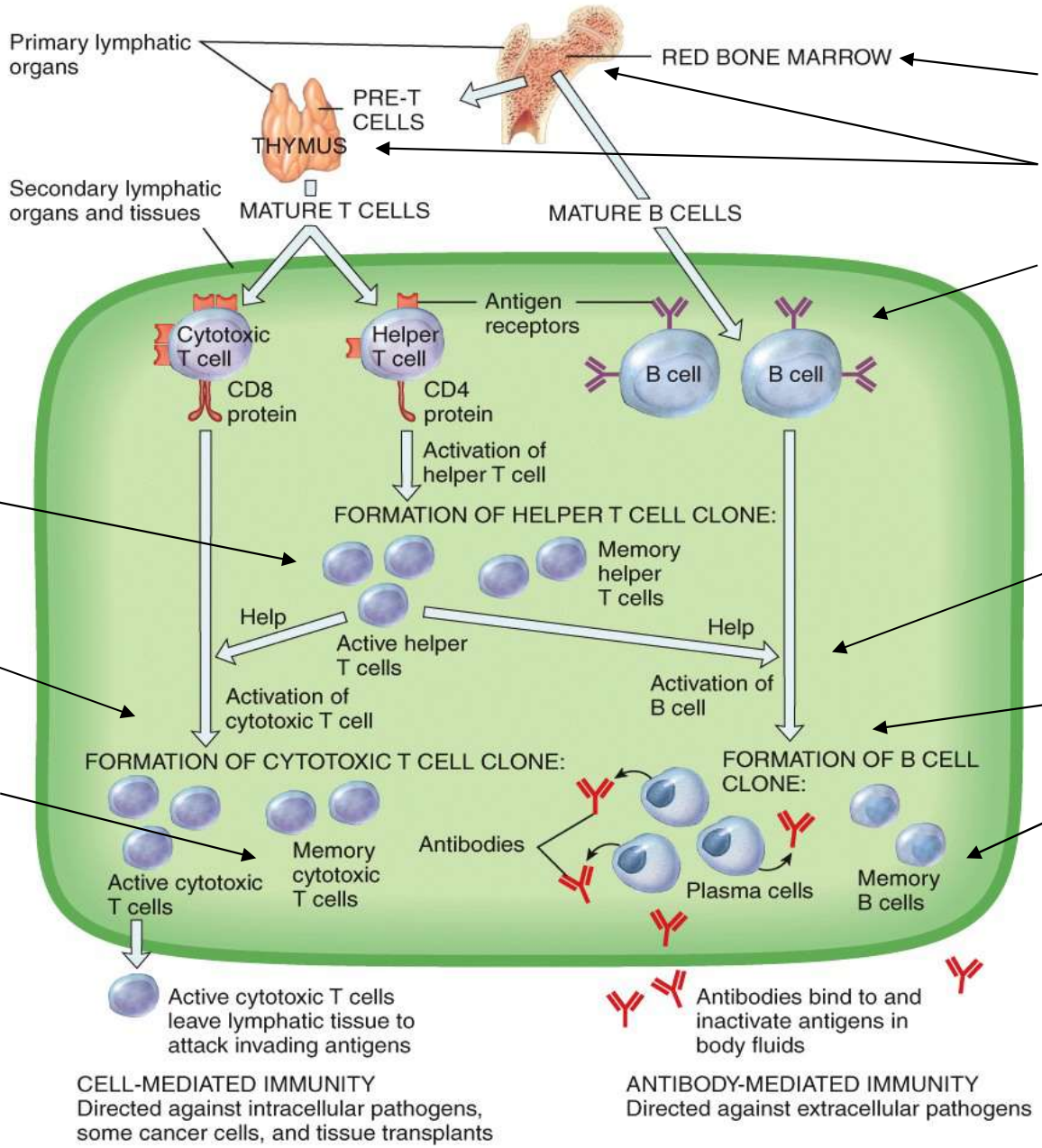
After Naïve Immunocompatent T_C (CD8) and T_H (CD4) Cells Are Deployed Throughout Our Tissues ….

How do these naïve immunocopatent cells recognize a pathogen when the pathogen enters the body?

How do T cells and B cells react in order to destroy the pathogens?

Following Deployment – The Three Rs

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

React

Remember

How Are Deployed Naïve Immunocompetent T and B Cells Activated? (recognize pathogen)

---

1. Your cells routinely display different types of cytoplasmic proteins in their plasma membrane (e.g. normal VS cancerous proteins).

1. Deployed immunocompetent Tc and B cells are not able to directly recognize or respond to antigen that is embedded in our cells. Foreign antigen must be “presented” to educated Tc and B Cells.

1. Some WBC are able to internalize (i.e. phagocytosis) pathogens, WBCs digest those pathogens, and then display segments of the pathogen’s protein in the WBC’s plasma membrane (antigen presentation).

1. This is why the immune system need Antigen Presenting Cells

How Are Deployed Naïve Immunocompetent T and B Cells Activated? (recognize pathogen)

5. After antigen is processed by APCs the immune system uses the "captured epitopes" to activate Tc cells and B cells

6. The activation steps for Cytotoxic T cells and B cells are different but both are dependent on the functions of the Helper T Cells

6. The activation process is a positive feedback system which results in "clonal selection and cell differentiation.

6. After Tc cells and B cells are activated then acquired immunity progresses in three stages

   * The three "R" = recognize / react / remember (see next slide)

Three Key Events of Activation That Follows Deployment of T and B Cell

- Both T and B cells follow these three stages
- Known as the "three R's" of immunity
  - **Recognize (activation)**
  - **React (attack)**
  - **Remember (memory)**

Three Key Events of Activation That Follows Deployment of T and B Cell

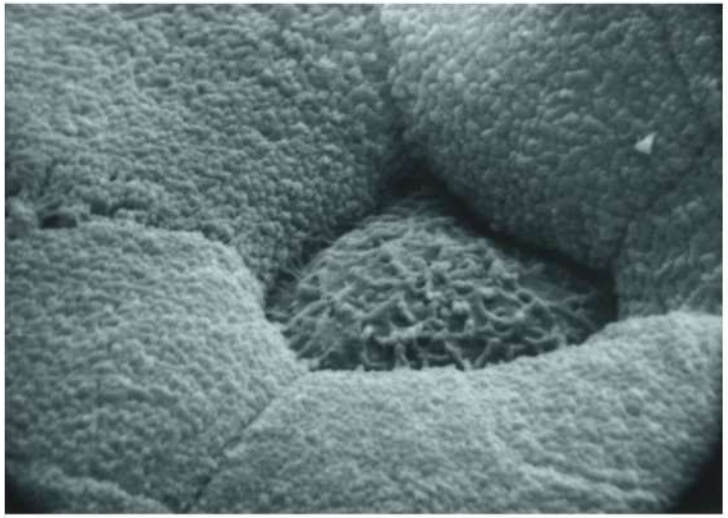
- Note: the “recognition step” relies on interaction between the MHCP and matched receptors on T cell and B cell
- receptors on both T cells and B cells are matched to the same antigen
- Therefore --- we activate both T and B cells at the same time against the same pathogen
- Why?

M Cells

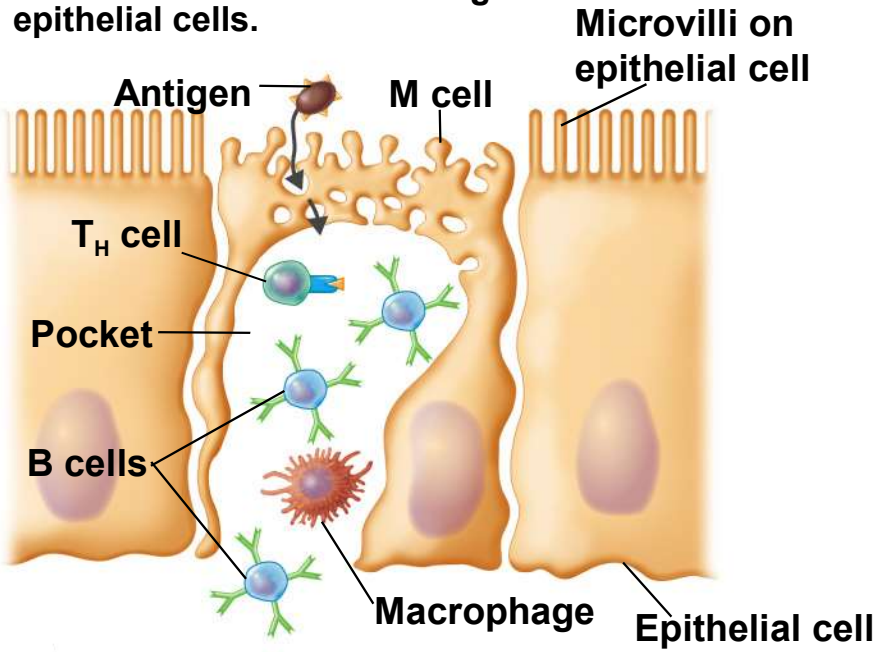
This is how immune cells try to find out (i.e. recognize) what type of pathogens may “break into” the sterile compartments of your body.

Immune system recognize bacteria even before it is in our bodies

Immune system starts to prepare defenses against bacteria.



(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.

How Do Major Histocompatibility Complex Proteins (MHCP) Display Cytoplasmic Proteins in The Membrane?

- Two type = MHCP-I and MHCP-II

- These molecules are cytoplasmic proteins /// constantly being made in the endoplasmic reticulum then migrating from the cytoplasm to the plasma membrane where they are inserted into the plasma membrane

- They are shaped like “hot dog buns” and they carry self and non-self epitopes // the epitopes are the “hot dogs” inside the buns in this model

How Do Major Histocompatibility Complex Proteins (MHCP) Display Cytoplasmic Proteins in The Membrane?

- MHCP-I are associated with all nucleated cells of body (except RBC)
- MHCP-II are only associated with antigen presenting cells
  - Macrophage
  - Dendritic cells
  - B cells
  - B cells activate themselves to become plasma cells
  - macrophage and dendritic cells present epitopes to CD4 and CD8 cells

How Do Major Histocompatibility Complex Proteins (MHCP) Display Cytoplasmic Proteins in The Membrane?

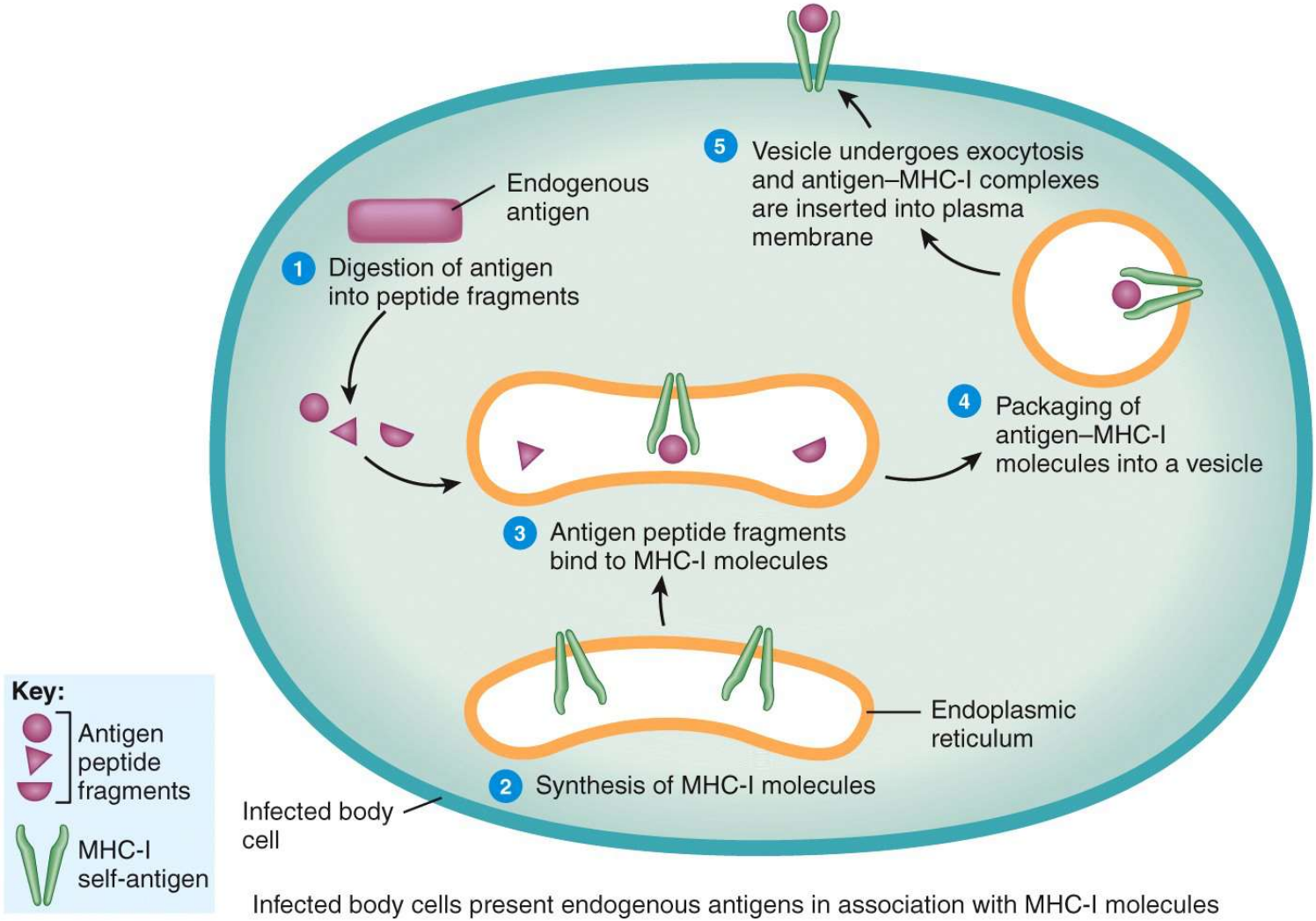
- Inside MHCP-I cells “non normal proteins” (i.e. cancerous) or foreign antigen, (e.g. virus and bacterial antigens) are partially digested
- Their “epitopes” are placed inside a MHC “place holder”
- The MHC-epitope is then inserted into the plasma membrane
- Active cytotoxic Tc can identify the MHC-epitope on the surface of the cell /// this is how Tc cells know what is inside the cell

How Do Major Histocompatibility Complex Proteins (MHCP) Display Cytoplasmic Proteins in The Membrane?

- Infected cells can now be killed by Tc cells
- Note: natural killer cells can also recognize cancerous and viral infected cells /// non-specific // NK cells do not undergo clonal selection like T and B cells
  - T-Cytotoxic cells respond only to MHC – I proteins
  - T-Helper cells respond only to MHC – II proteins

Endogenous Antigens Processed by Host Cells Using MHC-I

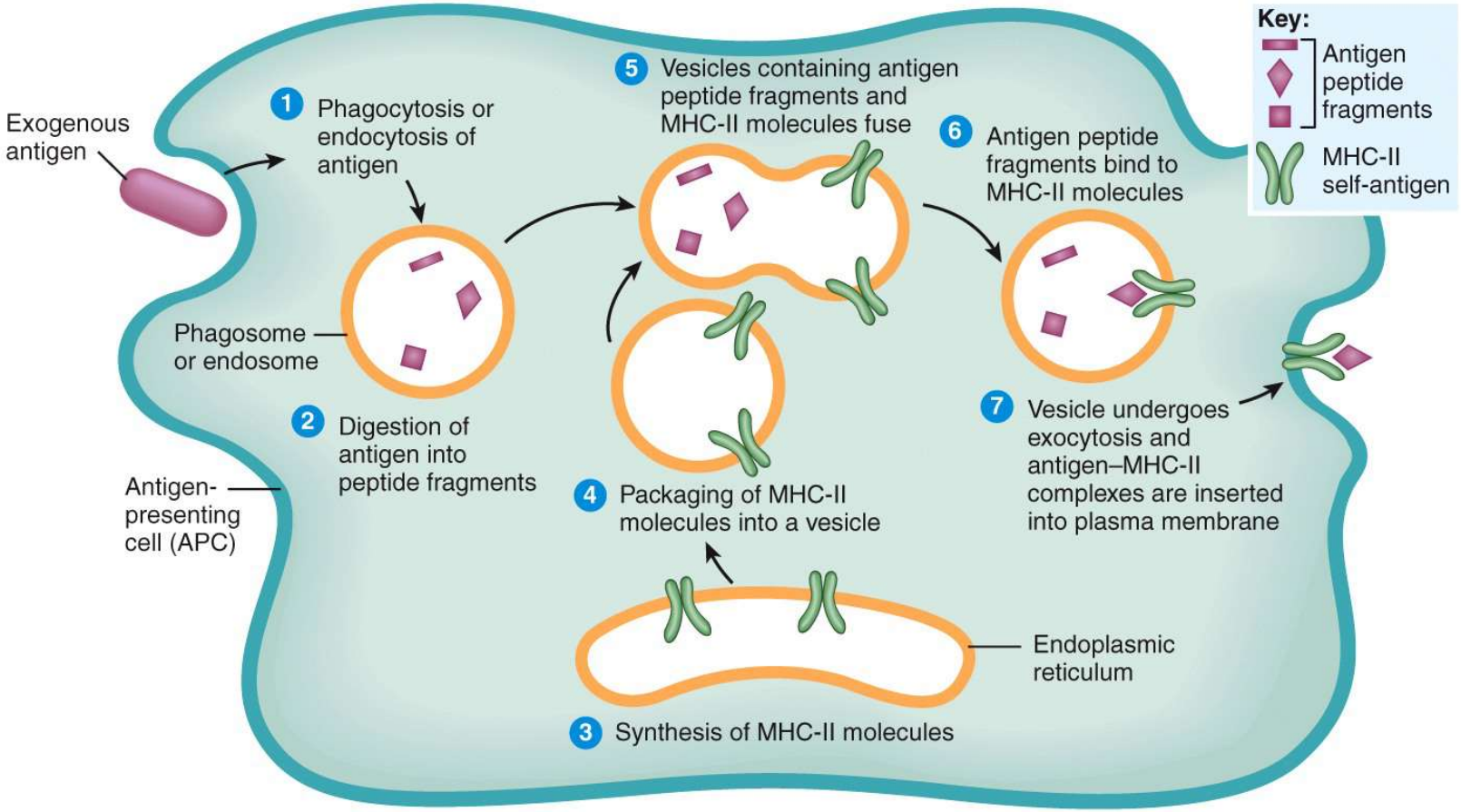
(Note: This is used as the first step to activate a CD8. Activation requires costimulation by activated Helper T cell to turn CD8 into active cytotoxic T cell. Cytotoxic T cells use similar epitope-MHCP-I complexes to initiate cell destruction.)



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

Exogenous Antigens Processed by APCs Using MHC-II

(Note: this is how a naïve immunocompetent CD4 cells – the Helper T Cell - becomes aware that there is a foreign antigen present in the host)



APCs present exogenous antigens in association with MHC-II molecules

Activation of Helper T Cells

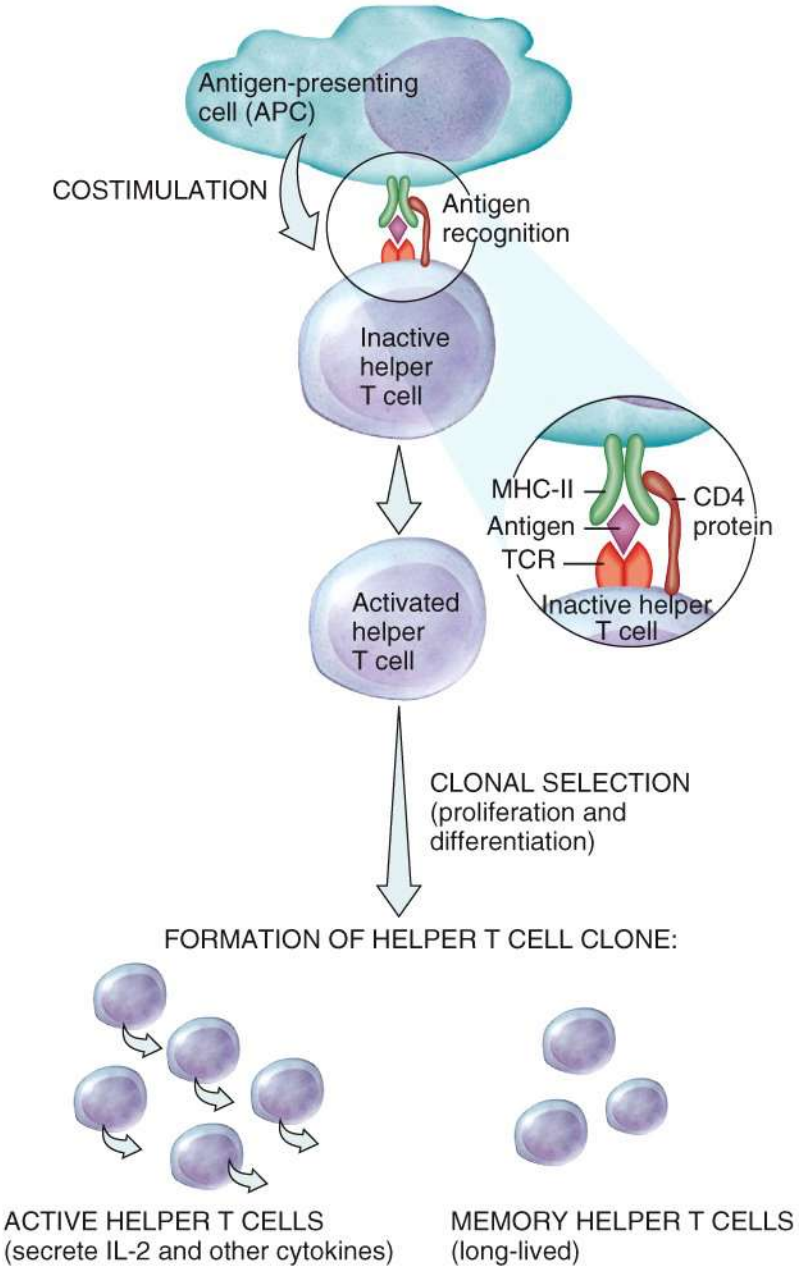
This is the recognition phase.

Immune system must first activate helper T cells

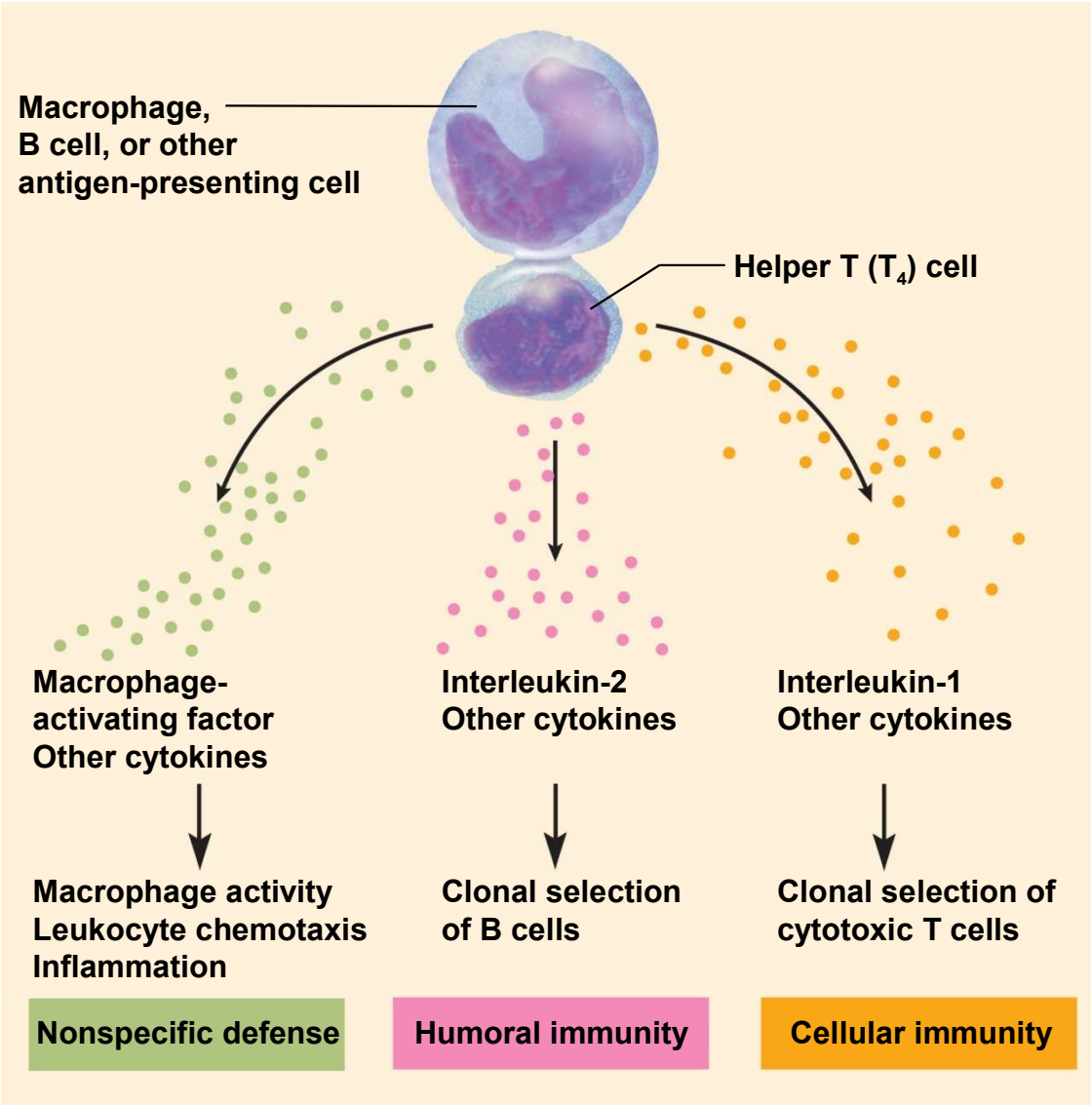
Helper T cell then able to activate both naïve immunocompetent cytotoxic T cells and B cells,

Helper T cells will also enhance macrophage activity and the events associated with inflammation

Note: the CD4 protein on helper T Cell function as a costimulatory or a second check to insure helper T Cell will activate the appropriate cytotoxic T cells and B cells



Helper T Cell's
Pivotal Role in Immunology



T_H Cells are required to activate both humoral and cellular immunity

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

Without T_H Cells you have no defenses against pathogens!

Helper T Cell Activation

- begins when T_H cell binds to a MHCP-II complex displaying an epitope that the T_H cell is programmed to recognize
- note: only Antigen Presenting Cells have MHCP II (e.g. macrophage or dendretic cell
- T_H cell must also receive another signal molecule (interleukin) from the "docked" APC // this confirms T_H in presence of foreign antigen
- This is known as costimulation // results in activation of TH and clonal selection
  - helps insure the immune system does not launch an attack in the absence of a pathogen
  - reduces chance immune cells would turn against one's own body and injury our tissues

Helper T Cell Activation

- Helper T cell are necessary for an immune responses
- First Step /// helper T cell bind to APC (e.g. macrophage) forming the Ag-MHCP II complex
- Second Step /// Macrophage secretes interleuken I // this then stimulate helper T cells to secrete interleukin II
  - *The interleukin II then exerts three effects:*
    - *attract neutrophils and NK cells*
    - *attract more macrophages, stimulate their phagocytic activity, and inhibit them from leaving the area*
    - *stimulate more T and B cell // more mitosis and maturation / more clonal selection*

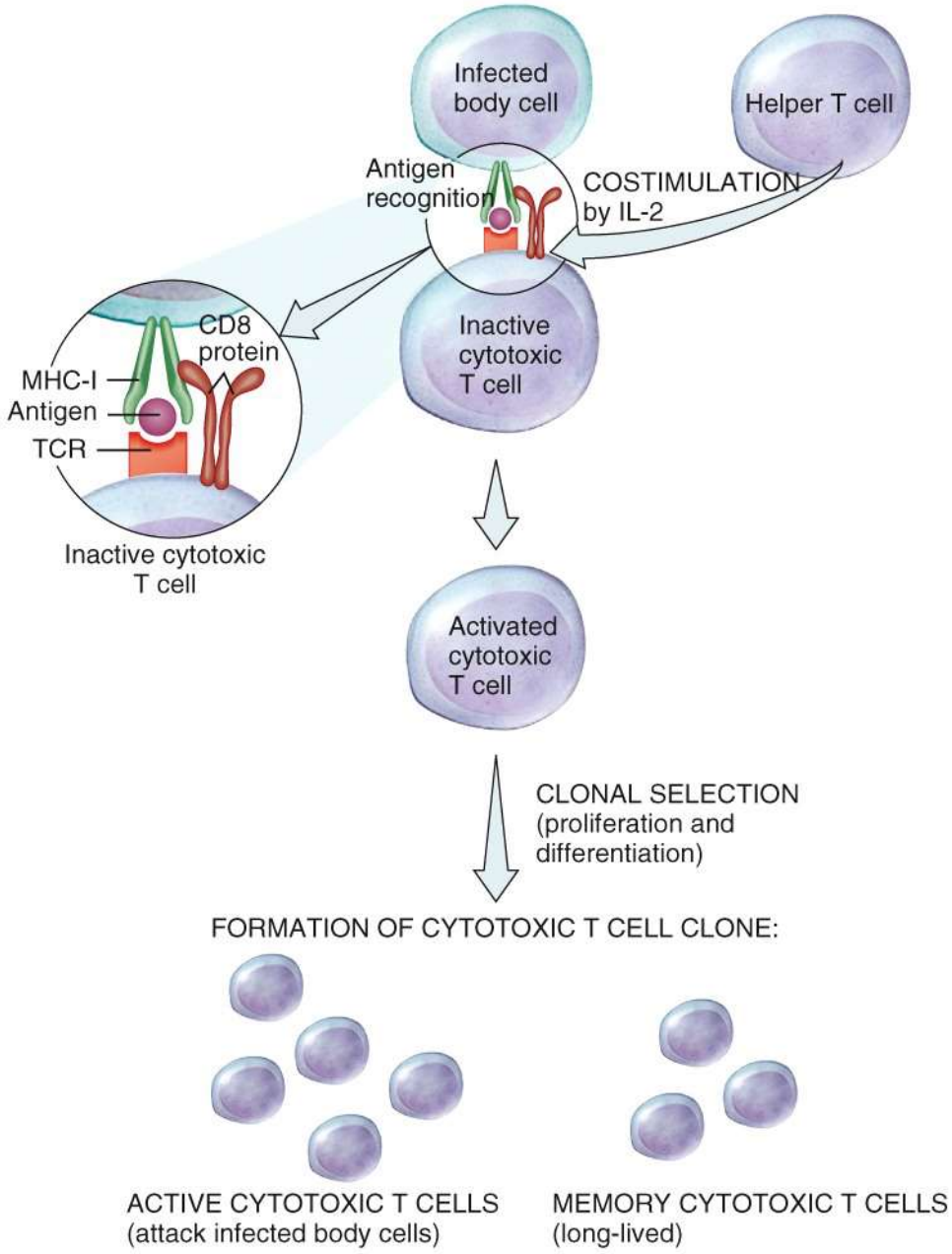
Activation of Cytotoxic T Cells

The first step (recognize step) occurs when an activated helper T Cell encounters an inactive cytotoxic T cell

Recognition followed by Helper T Cell costimulation – note CD8 protein is the costimulator

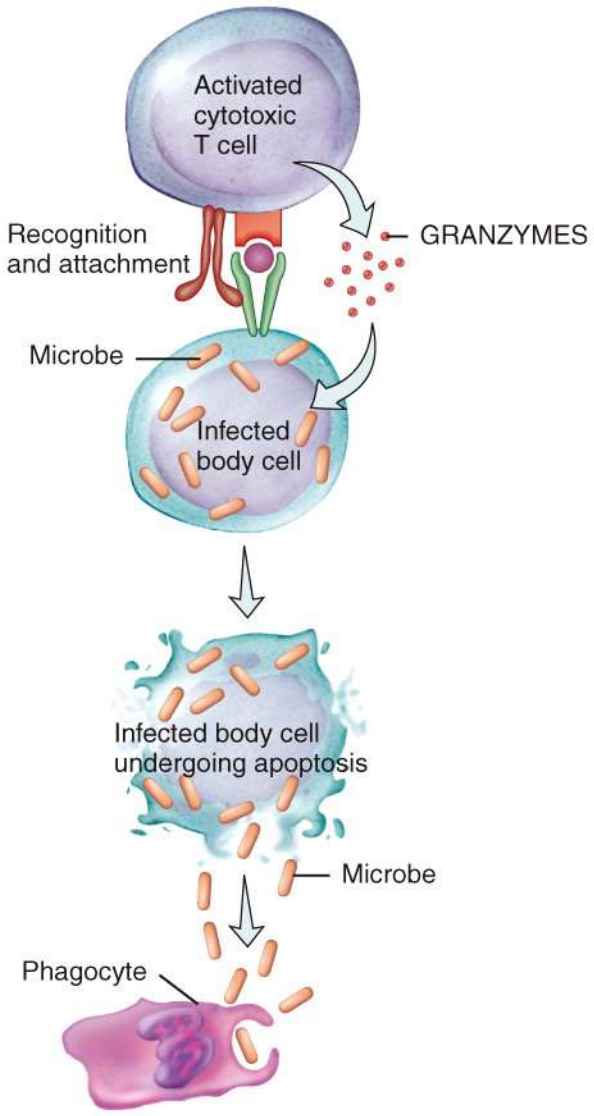
Following complex formation and costimulation // Clonal selection occurs producing many similar activated cytotoxic T cells

After Tc activated they circulate throughout body and may dock and kill any cell displaying MHCP-I foreign epitopes

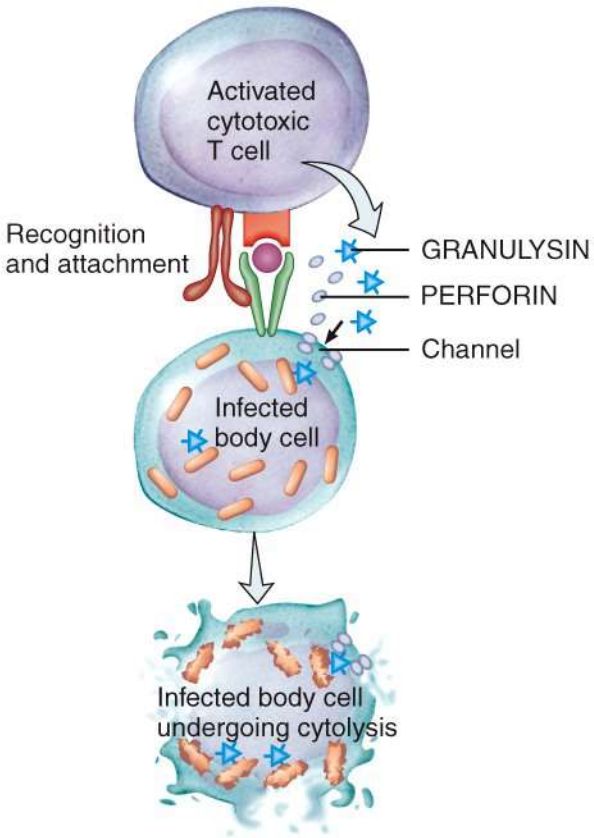


React Stage of Cytotoxic T Cells

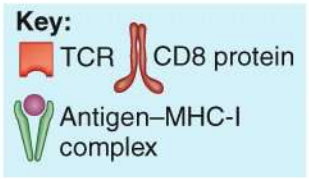
Note two different methods to destroy infected cells with exogenous antigen



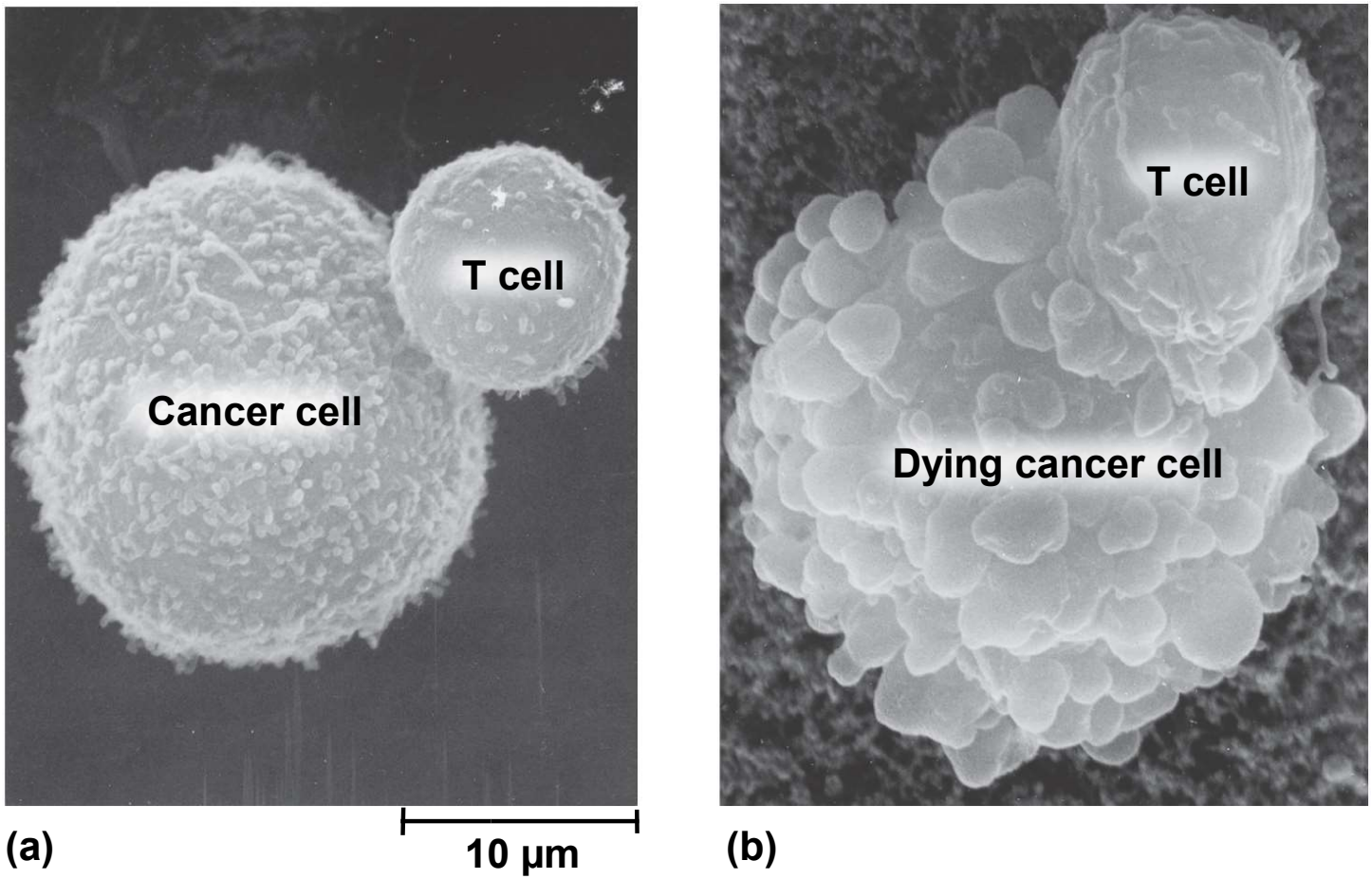
(a) Cytotoxic T cell destruction of infected cell by release of granzymes that cause apoptosis; released microbes are destroyed by phagocyte



(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

Tc React Stage

- only T cells can directly attack and kill infected cells /// when activated T_C cell recognizes epitope and MHC – I protein on an infected cell (virus or cancer cell) cytotoxic then T cell 'docks' to cell
- delivers a lethal hit of toxic chemicals
  - Granzymes – enzyme which inters infected cell causing apoptosis
  - perforin and granulysin – kill cells in the same manner as NK cells
  - interferons – inhibit viral replication /// recruit and activate macrophages
  - tumor necrosis factor (TNF) – aids in macrophage activation and kills cancer cells // also secreted by monocytes
- goes off in search of another enemy cell while the chemicals do their work
- Kills cell by apoptosis method / macrophage engulf and digest cell

How do Cytotoxic T Cells work in your body?

- Wandering activated T cells inspect membranes for epitopes displayed in MHCPs

- If cells (non-APC) displays MHCP-I with self-antigen, the T cell disregards it and does not dock to cell // cell not infected with virus or cancer

- If cells (non-APC) displays MHCP-I with non-self antigen (endogenous but not normal “looking” antigen), the T cell will initiates an immune attack to kill cell // these dying cells are engulfed by phagocytes and digested

T_M Cells - Remember Cells = T Memory Cells

- T_M cell recall response // upon re-exposure to same pathogen later in life, memory cells launch a quick attack so that no noticeable illness occurs

  - *Now this "person is immune to the disease"*
  - *This concept was realized over 1,000 years ago and early civilizations used crude vaccination methods to protect themselves against small pox*
  - *First practices in China and Middle East – from there spread to Western Civilizations*

T_M Cells - Remember Cells = T Memory Cells

- immune memory develops only after primary exposure (first exposure) to foreign antigen

- following clonal selection, some T_C and T_H cells become memory cells

  - T_M are long-lived (may live 70 years or longer) // more numerous than naïve T cells

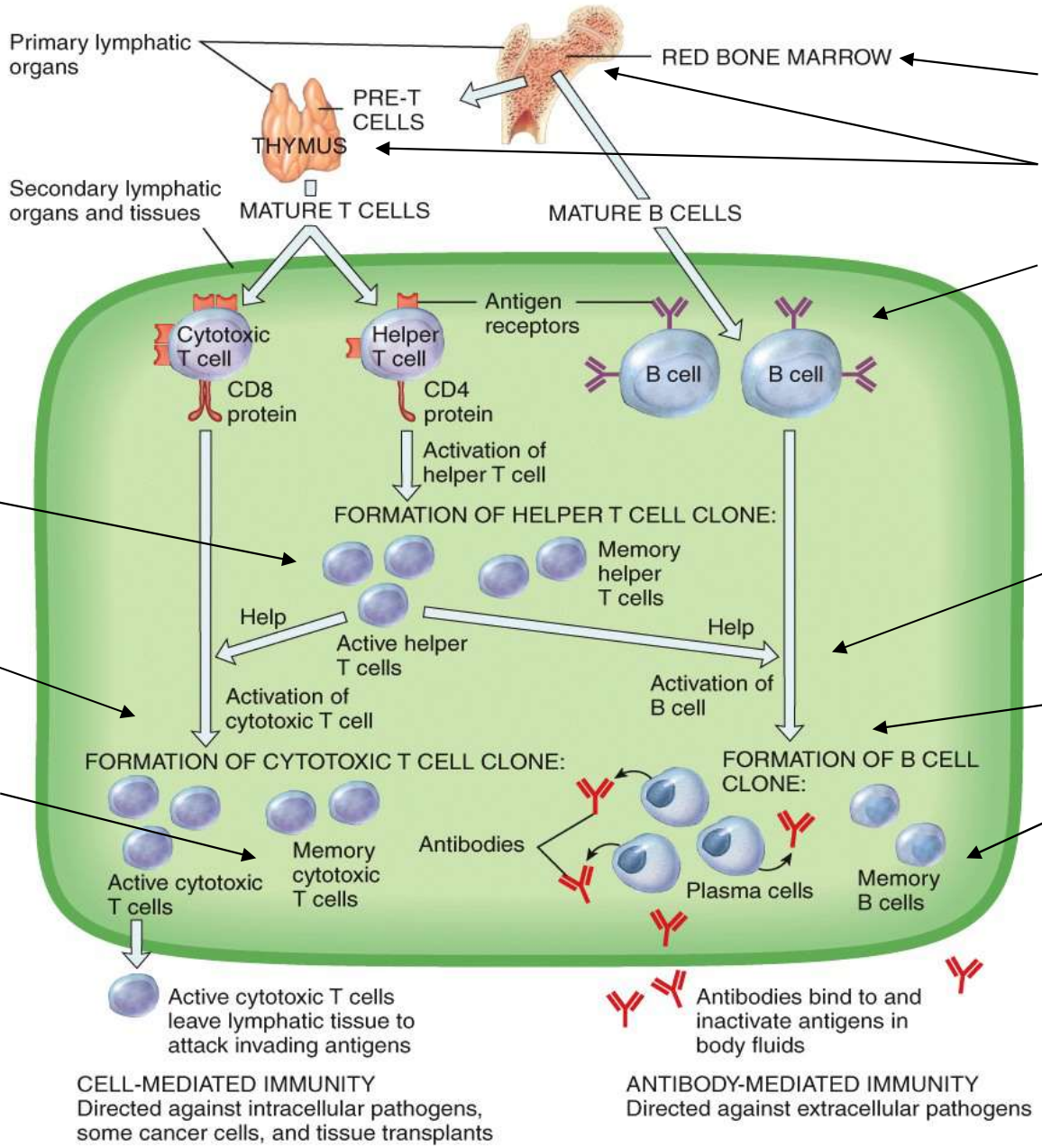
  - T_M require fewer steps to be re-activated, so they respond more rapidly then first exposure

Humoral Immunity (B Cells)

(Events Following Deployment)

The Three Rs

This is an overview of adaptive immunity.



Born

Educated

Deployed as

naive immunocompatent cells (resting cells)

Recognize

React

Remember

Recognize

React

Remember

Humoral Immunity

- A more indirect method of defense than cellular immunity
- B lymphocytes once activated become plasma cells // responsible for humoral immunity // plasma cells produce antibodies
  - Antibodies do not kill cells
  - Antibodies render antigen harmless or tag them for destruction by other mechanisms (i.e. complement proteins)
  - Note: only cellular immunity (TC) attacks and kill infected or foreign cells directly
- Humoral immunity works in three stages similar to cellular immunity
  - recognition
  - react (attack)
  - remember (memory)

Humoral Immunity - Recognition

- Naïve Immunocompetent B cell
  - thousands of surface receptors on B cell's plasma membrane for same antigen // B cell will be APC for itself!
  - activation begins when same antigen binds to several of these receptors
    - links them together /// taken into B cell by receptor-mediated endocytosis
    - Note: small molecules are not antigenic because they cannot link multiple receptors together
    - B cell processes (digests) the antigen // links epitopes to its MHC–II proteins // displays these on the cell surface
    - Helper T cell will dock with B cell to complete activation

Humoral Immunity - Recognition

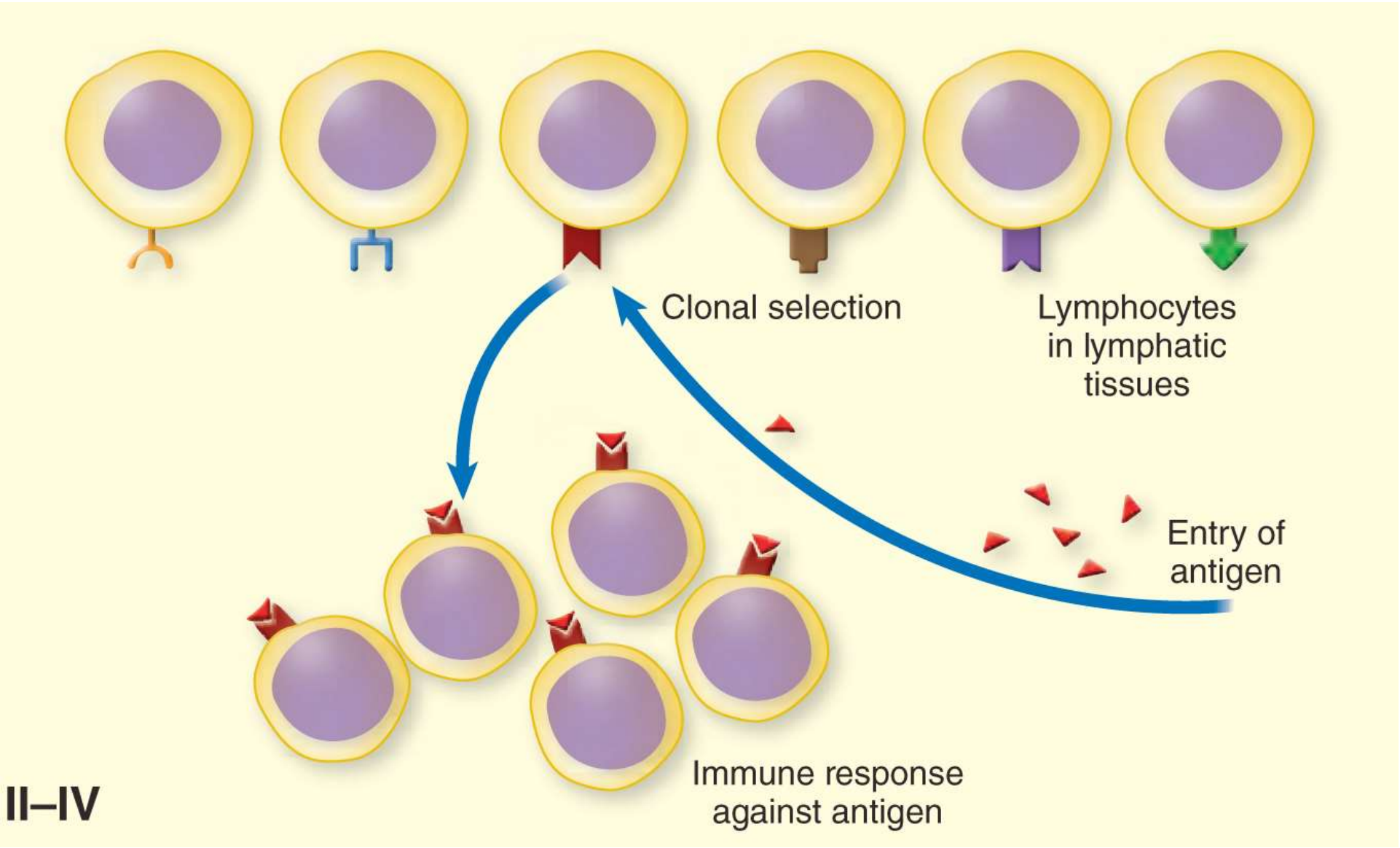
- Generally speaking - B cell response goes no further
- Requires a Helper T cell to bind to the B cell"s Antigen-MHCP complex
  - B-cell-T_H-Antigen-MHCP complex then secretes interleukins that activate B cell
  - Results in clonal selection
    - Some B cells become plasma cells / produce antibodies
    - Some B cells become Memory B cells
    - Some B cells become Regulatory B cells
  - secrete antibodies at a rate of 2,000 molecules per second during their life span of 4 to 5 days

Recognition Leads to Clonal Selection

- React (Attack) – the second “R”
  - antibodies bind to antigen
  - render toxins and antigen harmless
  - ‘tag’ cells with foreign antigen for destruction // G and M antibodies activate complement
- Remember (Memory) – the third “R” /// some B cells differentiate into memory cells

Naïve Immunocompatent B Cells Activated by

Antigen (epitope) That Then Initiates Clonal Selection



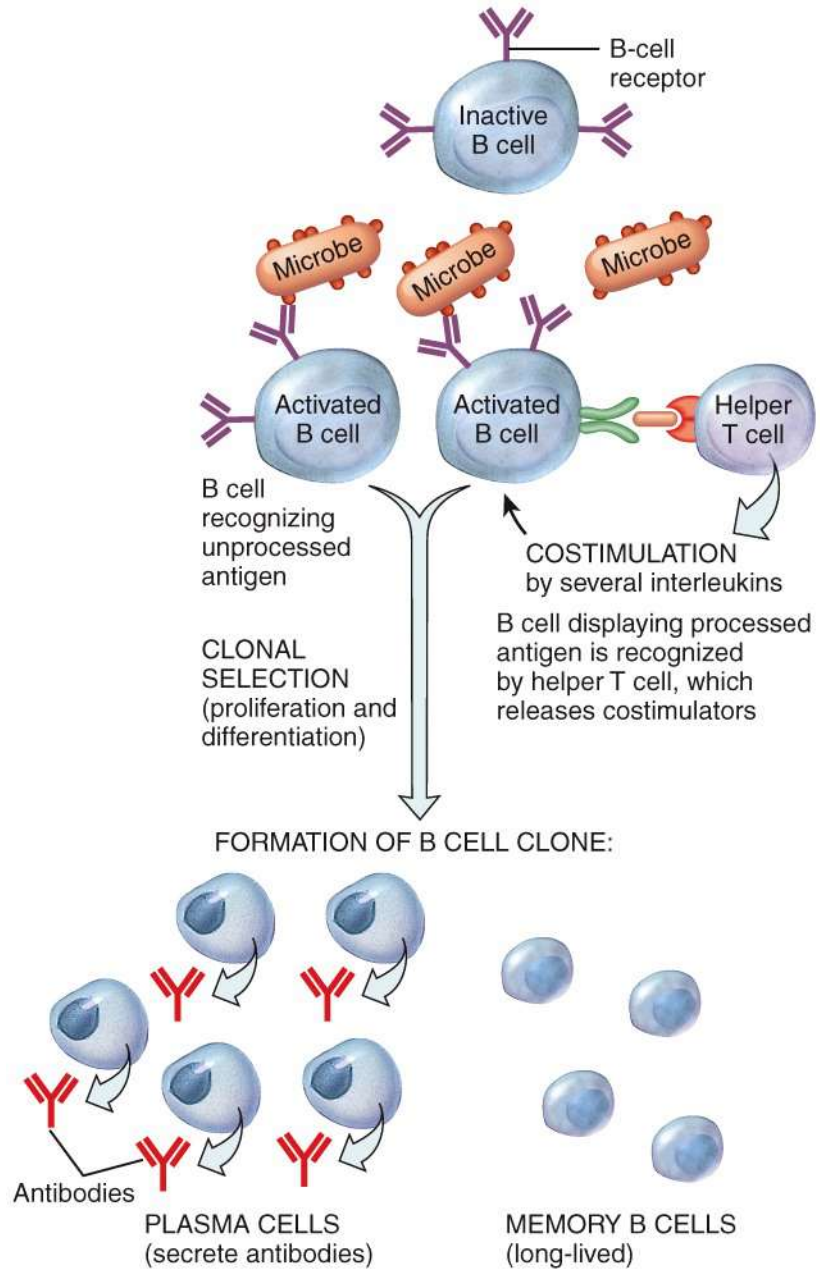
Activation of B Cells

This is the recognize phase

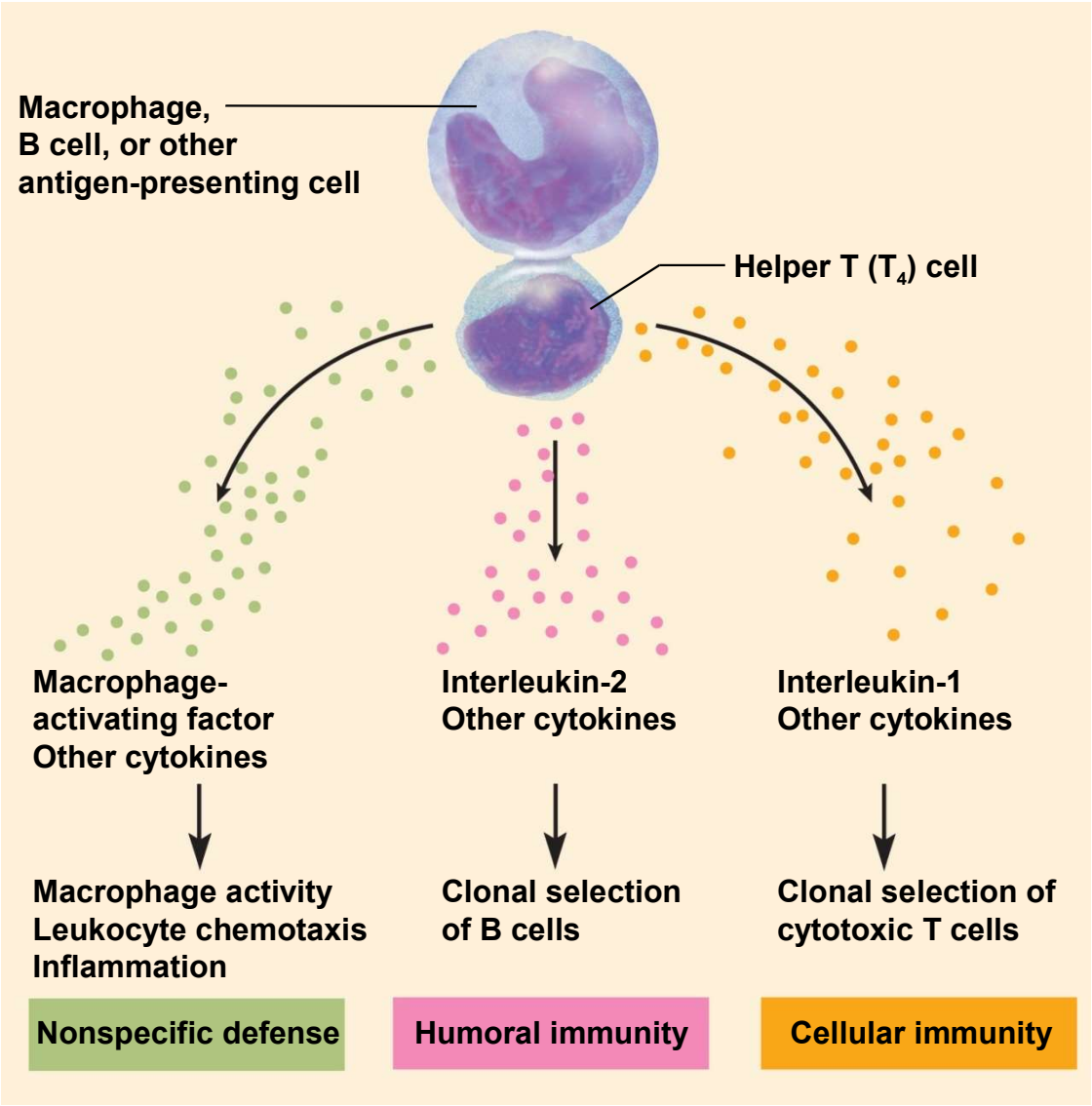
If B cells enter clonal selection without the Helper T cells (T cell independent) then…

The B cell activation is less robust and no B memory cells formed

T cell dependent uses Helper T cell with costimulation // stronger response with many more plasma cells formed and memory B Cells formed.

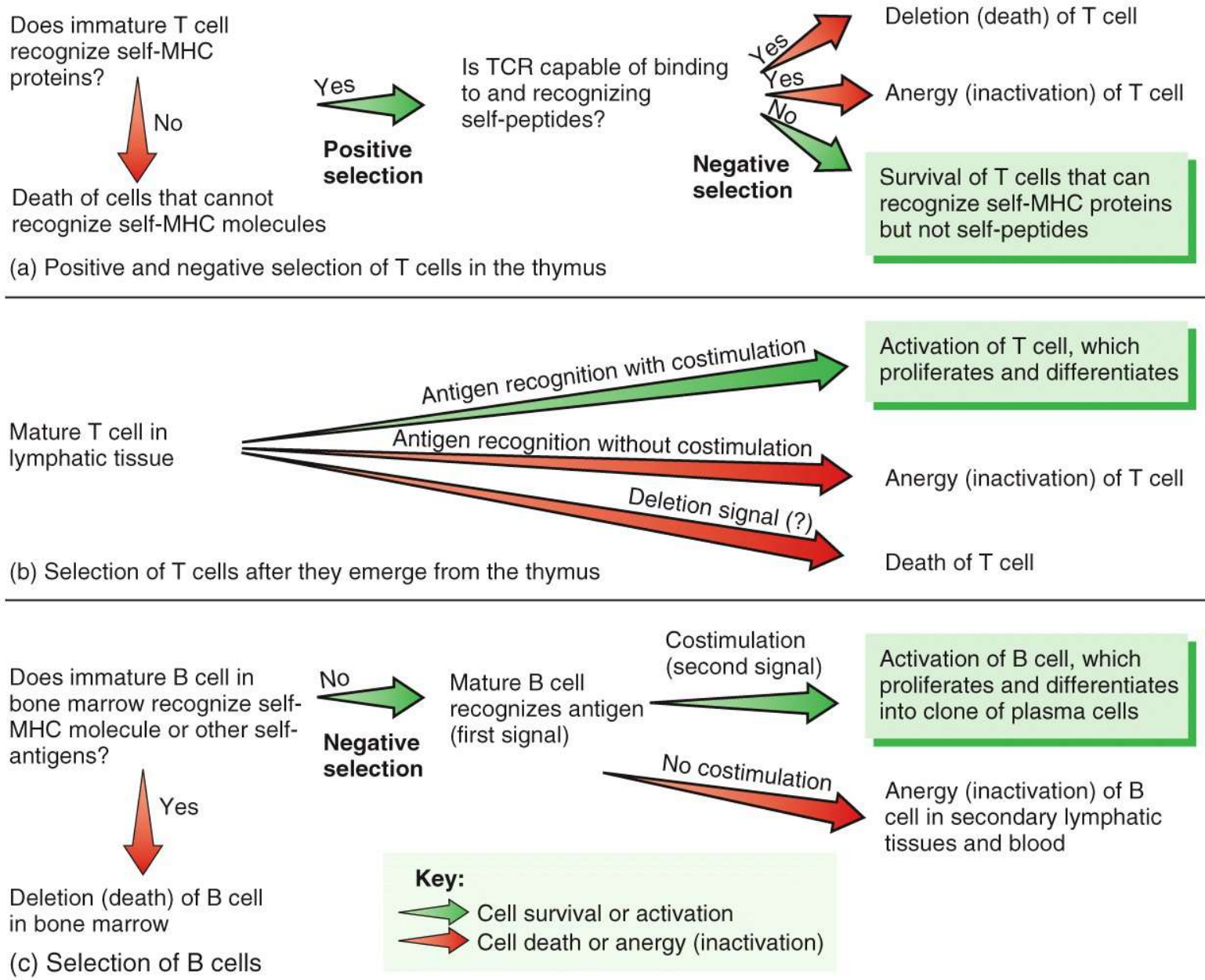


Helper T Cell's Pivotal Role in Immunology

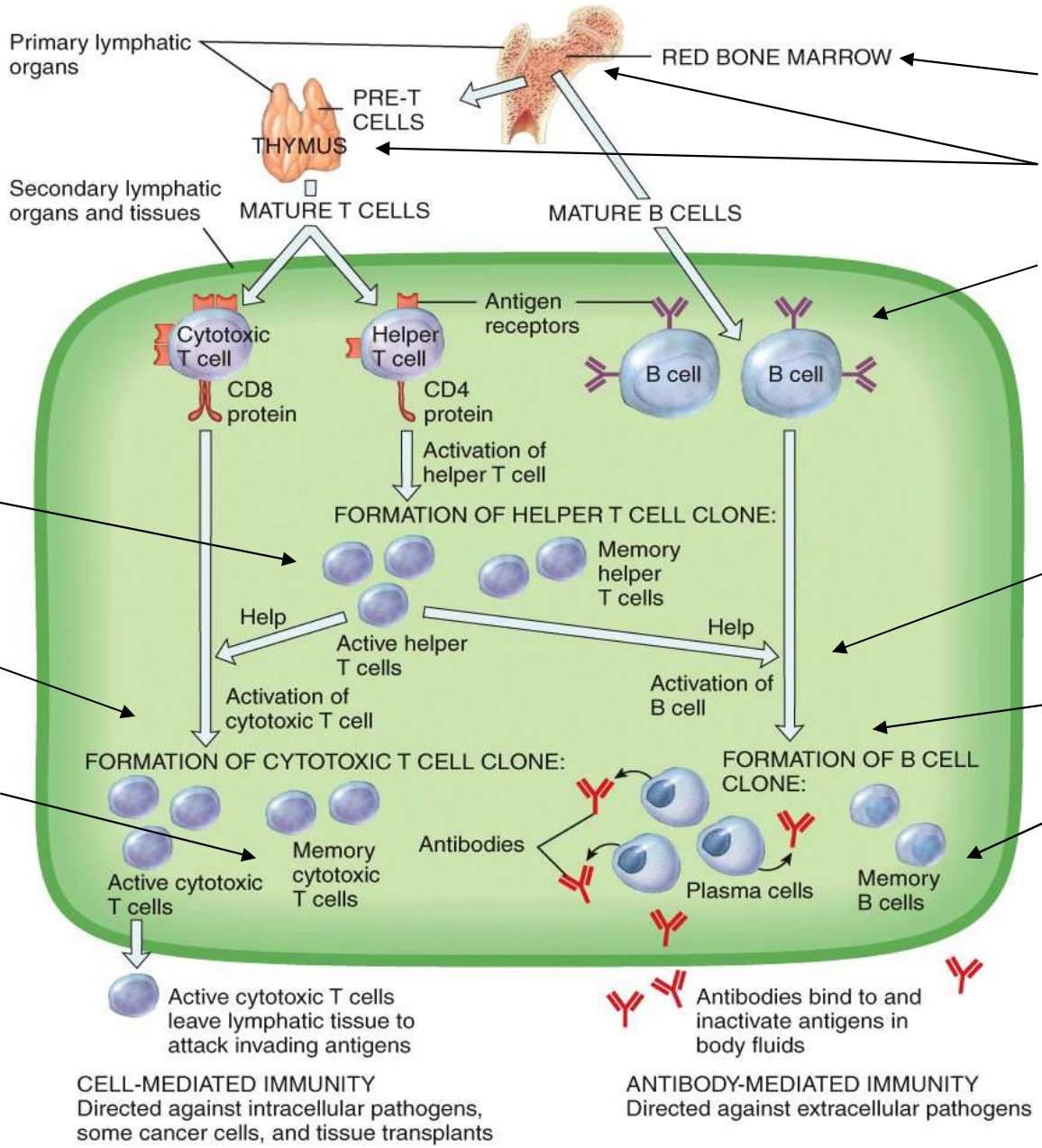


T_H Cells are required to activate both humoral and cellular immunity plus it also releases cytokines which increase the activity of macophage, leukocyte chemotaxis and inflammation. Without T_H Cells you have no defenses against pathogens!

Summary of Immunity



This is an overview of adaptive immunity.



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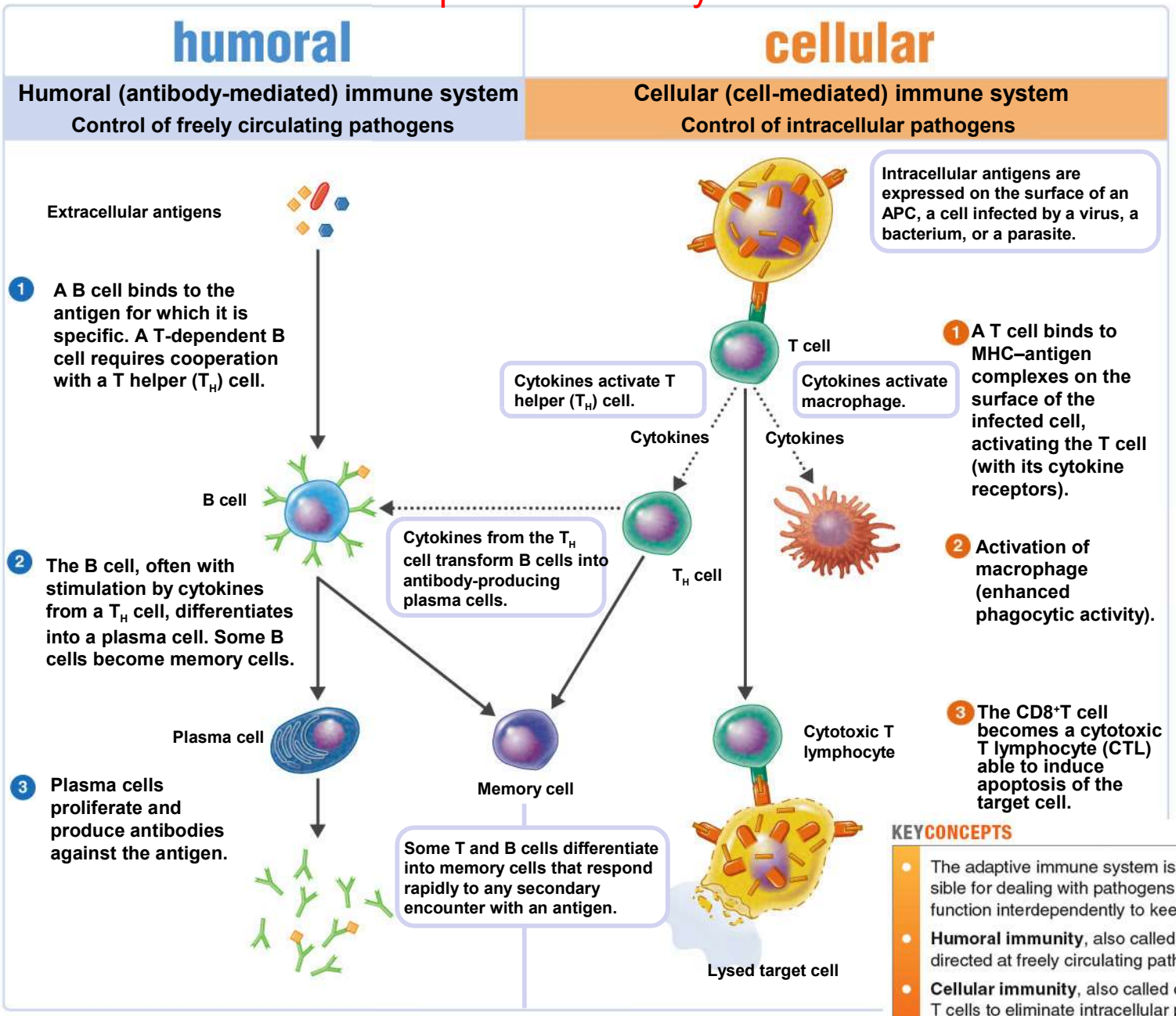
The dual nature of the adaptive immune system.



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 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 “cancer immunotherapy's” which could be used without or with the old therapies.
- Cancer immunotherapy's leverage our knowledge about the immune system to direct immune system cells against “specific types of cancer cells” or remove factors that naturally inhibit our immune cells from attacking cancerous cells.
- These new cancer immunotherapy's target only cancerous cells.
- Early “clinical trials” are truly joyous! There is now more than hope people diagnosed with certain types of cancers.
- New Therapies: Checkpoint Inhibition, Dendritic Cell Vacines, and CAR T Cells

See Next Slide

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

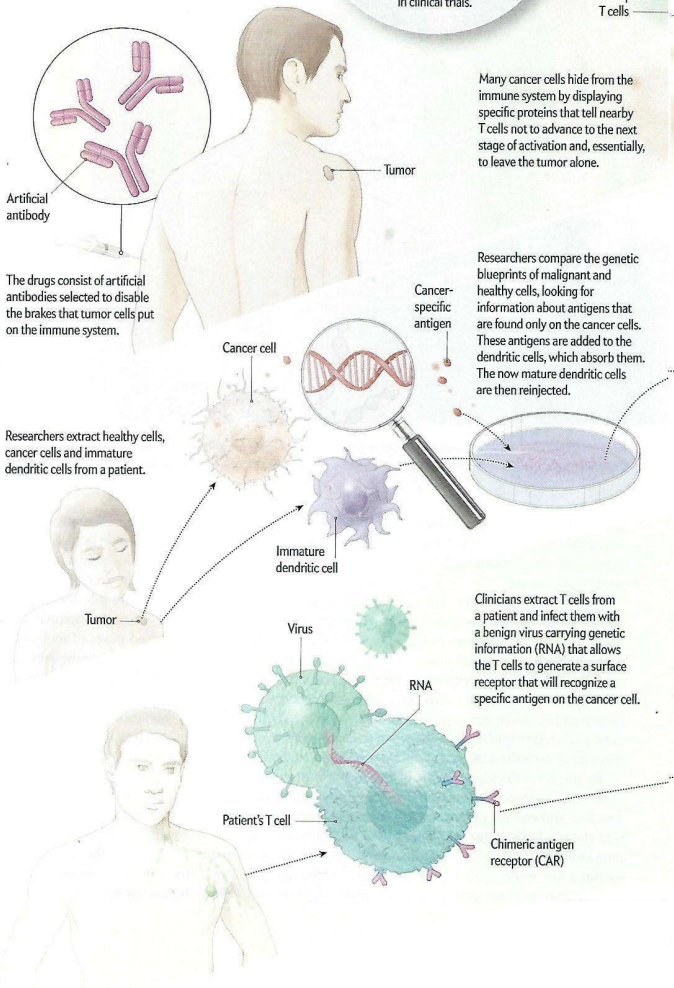
Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found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

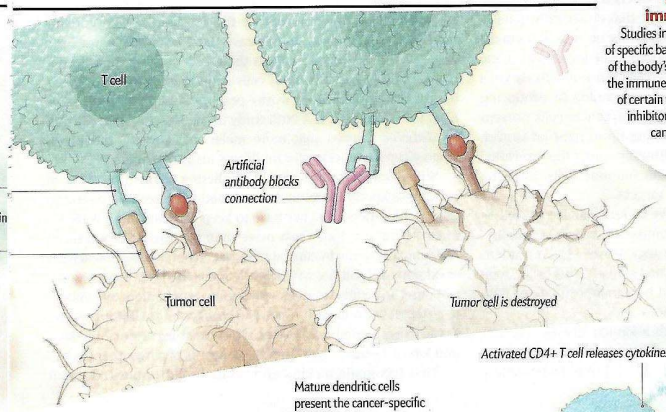
CAR-T Cells

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.

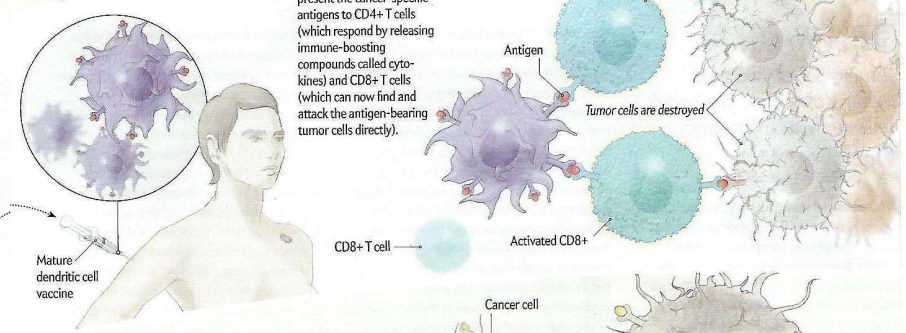


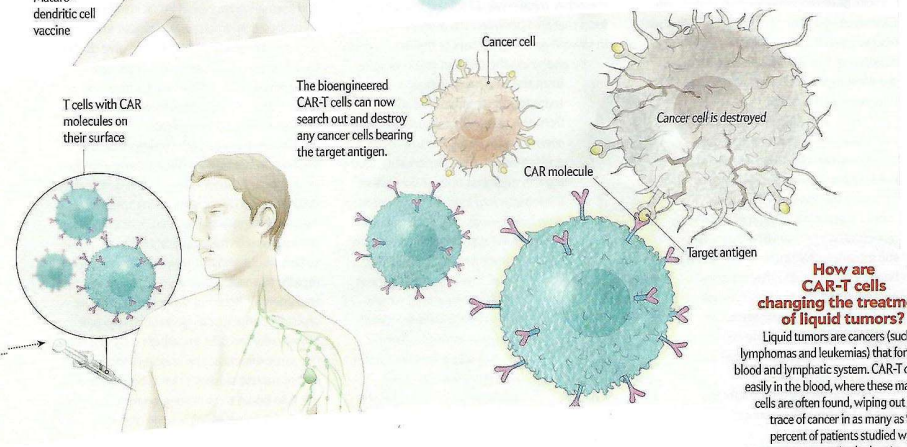


Could intestinal bacteria boost the effectiveness of immune treatments?

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

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





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 in Unit 3 Online Lecture Material