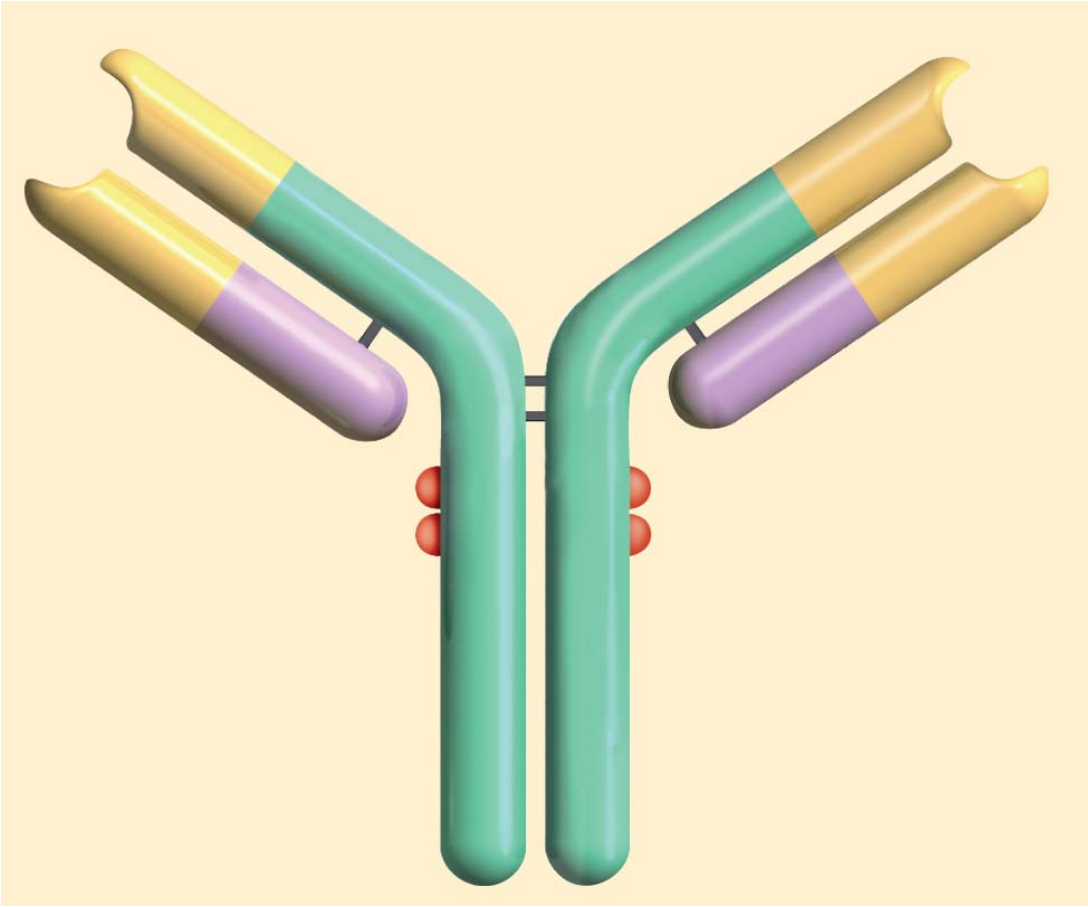
The Third Line of Defense

"Acquired Immunity"



What is Immunity?

- *Immunity protects us against internal and external threats. /// two forms - Innate Immunity VS Acquired Immunity*
- *Innate immunity exists at time of birth // Relies on numerous factors including phagocytes // characterized as "non-specific"*
- *Acquired immunity does not exist at birth /// Develops after birth*
- *Acquired immunity is only activated after contact with a specific pathogen /// referred to as adaptive immunity. // characterized as having specificity and "memory"*
- *Acquired immunity requires a group of widely distributed "wandering" cells" /// these are different types of WBC*
- *Immunity requires WBC to work "collectively" /// WBC use cytokines to communicate /// there is also integration of action between innate and adaptive immunity also mediated by cytokines*

What is Acquired Immunity?

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

- *WBCs called B cells (when activated become plasma cells) provide "humoral acquired immunity"*

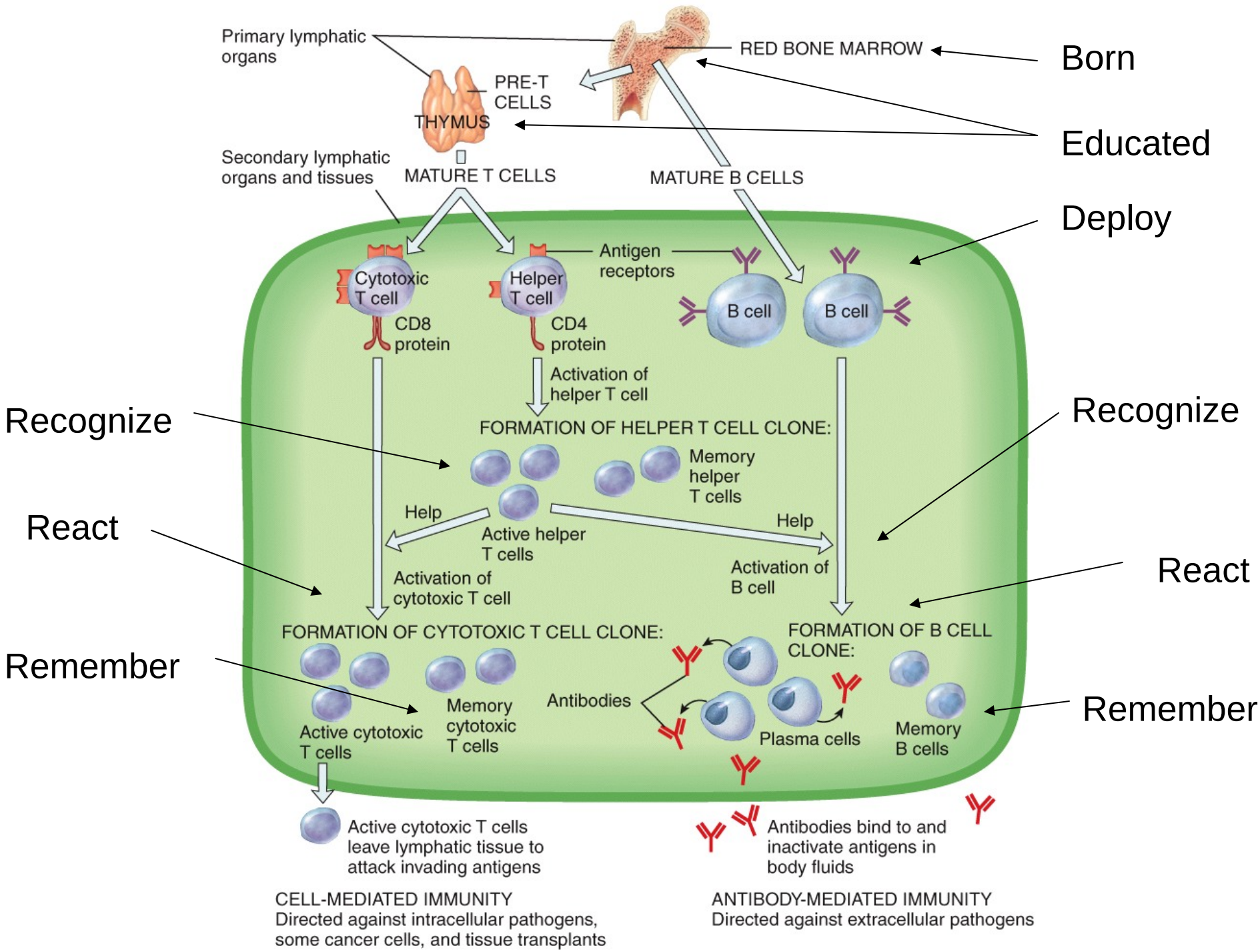
- *B cells morph into plasma cells which produce antibodies /// antibodies render pathogens* harmless and tag them for destruction.

- *B cells protect us from bacteria, virus, worms, and toxins when these objects are in our tissue fluids (not inside our cells).*

- *After threat is removed --- T and B cells produce "memory cells" //// memory cells stored in lymph nodes and other tissues /// respond immediately to a second exposure to similar pathogen. /// first exposure vs second exposure*

What makes “Acquired Immunity” so special?

- Two key characteristics (used to distinguish innate immunity or 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 antigens are the stimulus to “activate” acquired immunity*.


Primary lymphatic organs
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PRE-T CELLS
THYMUS
Educated
Secondary lymphatic organs and tissues
MATURE T CELLS
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Directed against intracellular pathogens, some cancer cells, and tissue transplants
ANTIBODY-MEDIATED IMMUNITY
Directed against extracellular pathogens

What is an Antigen ?

- An antigen is a molecule // protein or large polysaccharides
- Distinguish self antigen vs foreign antigen // self VS non-self
- Non-self antigen is any molecule that triggers an immune response
  - Normally large molecular weight - over 10,000 amu
  - Pathogen's transmembrane molecule /// foreign cell or virus (e.g. pathogen)
  - May be an environmental molecule or toxin made by microbe
  - Many different antigens can be on the surface of any one 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

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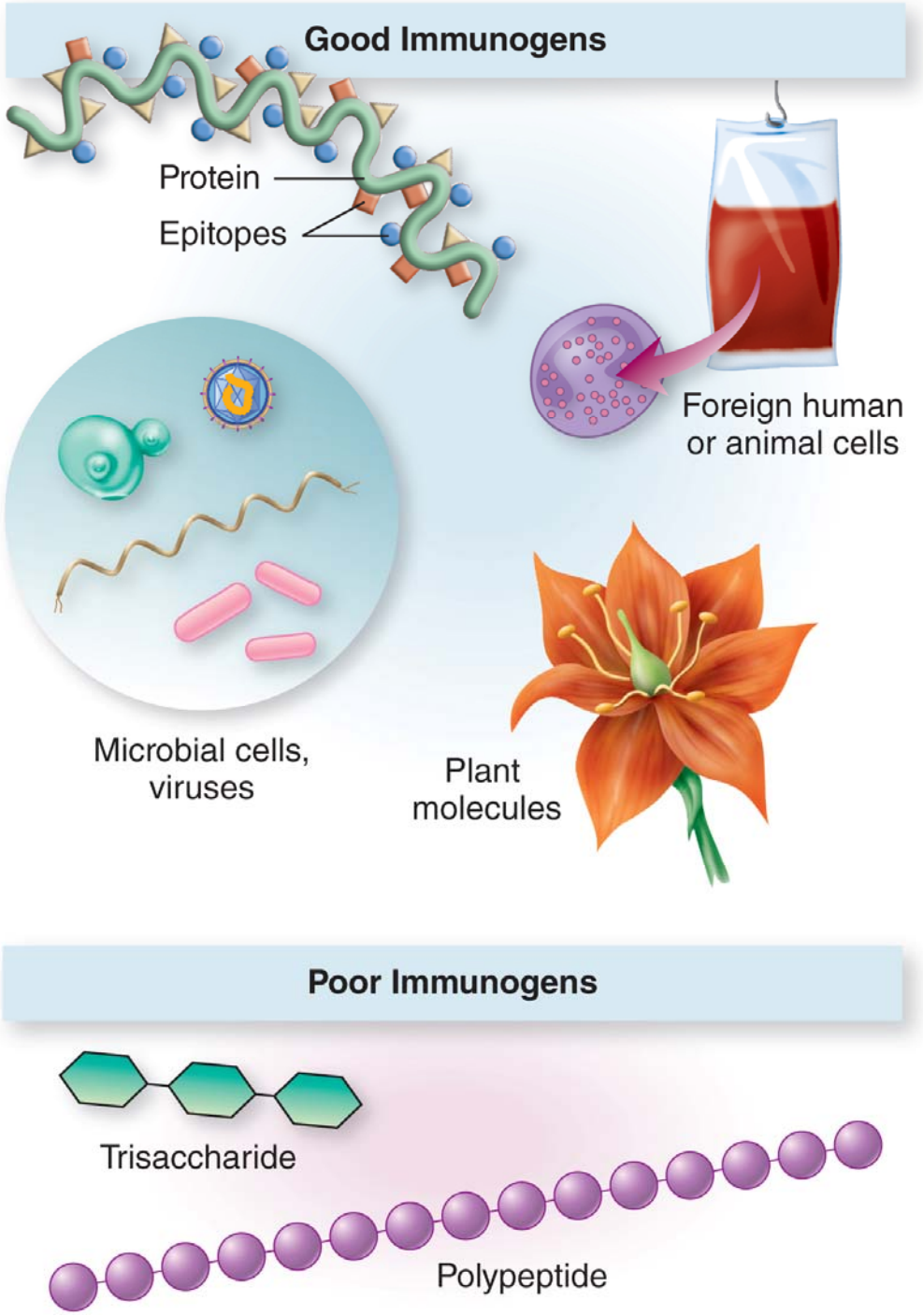


Foreign antigens (i.e. the non-self antigens) are also known as immunogens!

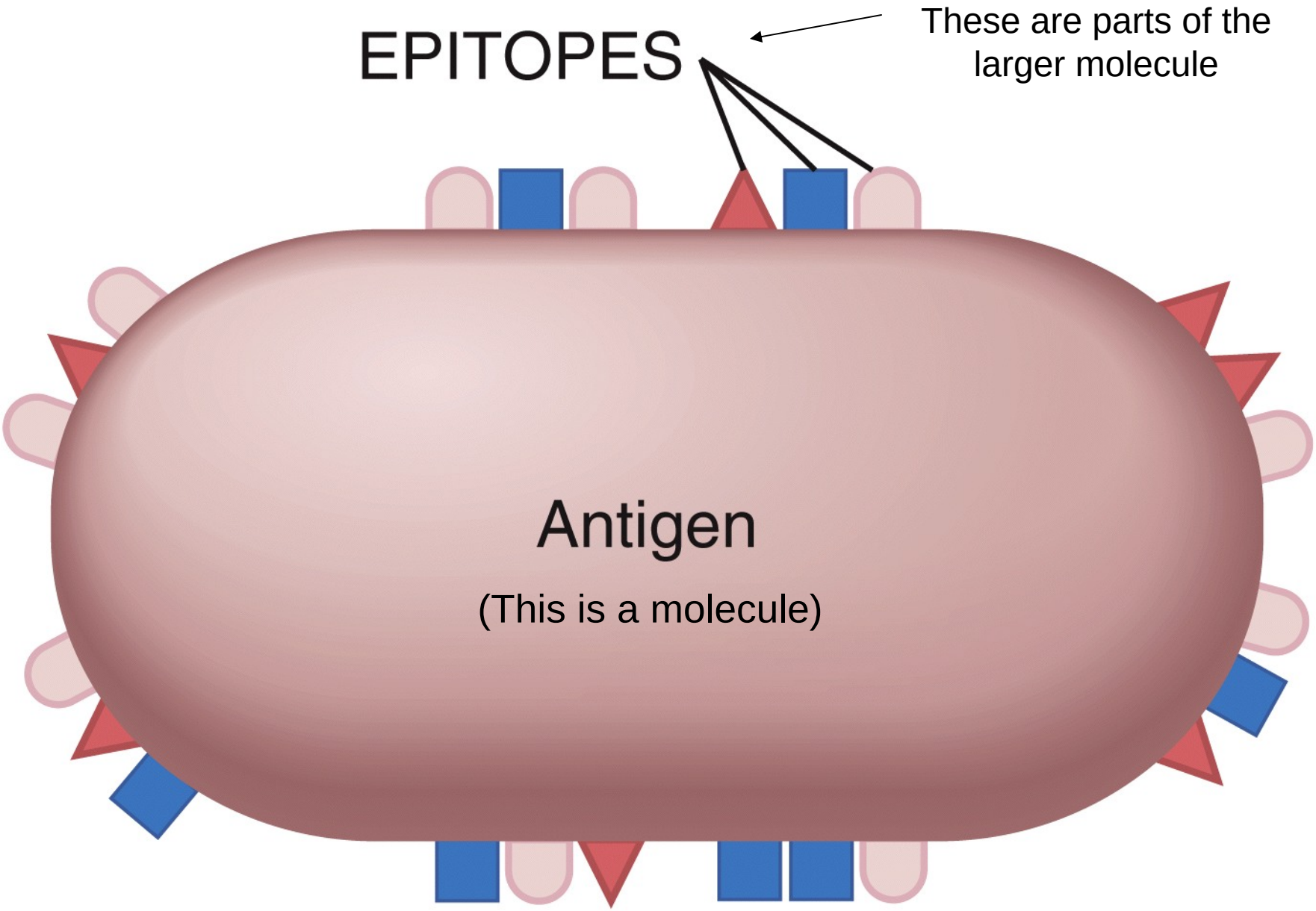
What is a self antigen?

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 an identical twin 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 <u>destroys or render harmless foreign cells (or toxins) that exhibit non-self antigens</u> // note: also basis of tissue rejection

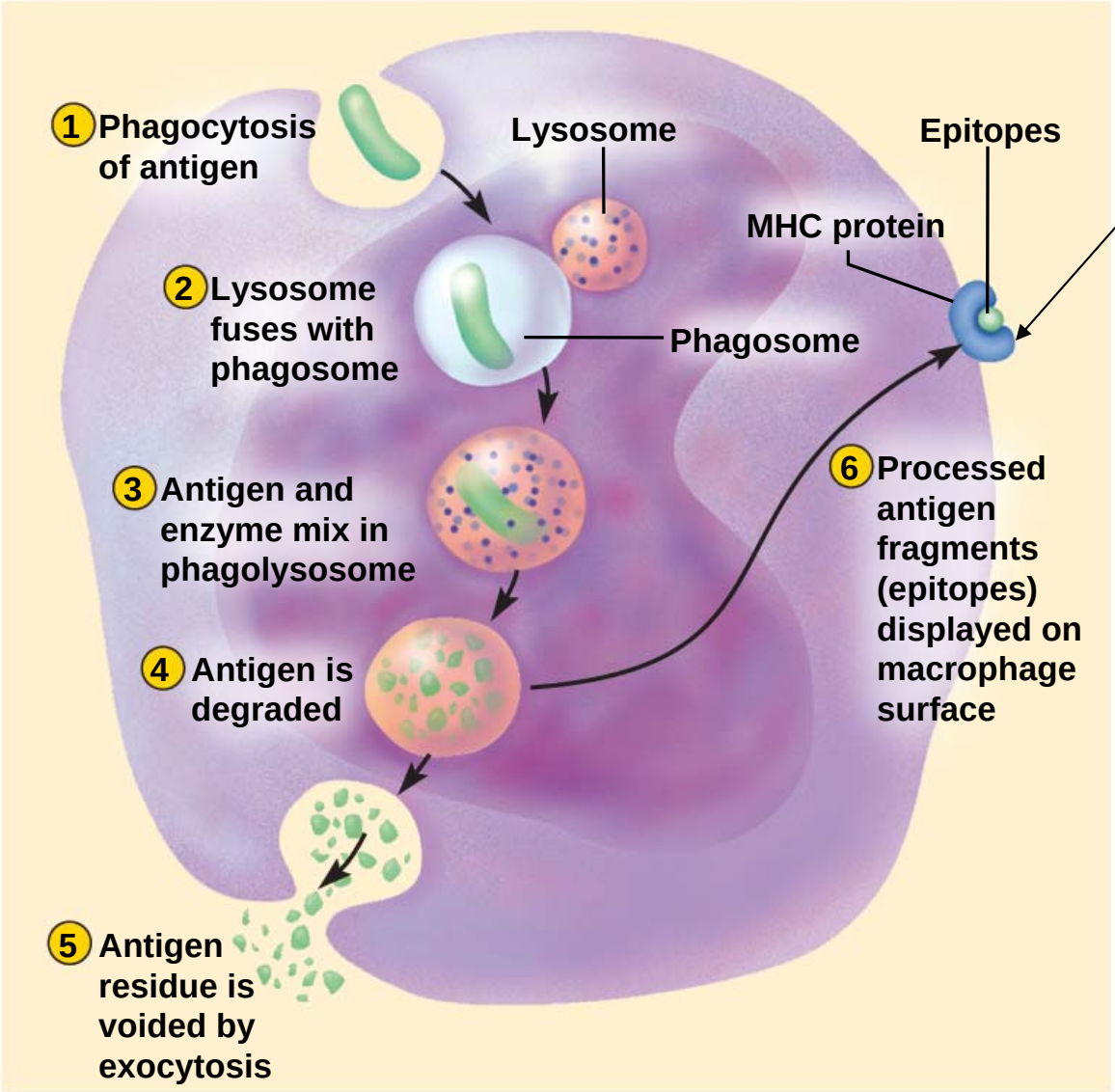
How are epitopes different than antigens?

- 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)

Antigen Processing

The first step to initiate an acquired immunity response.



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 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

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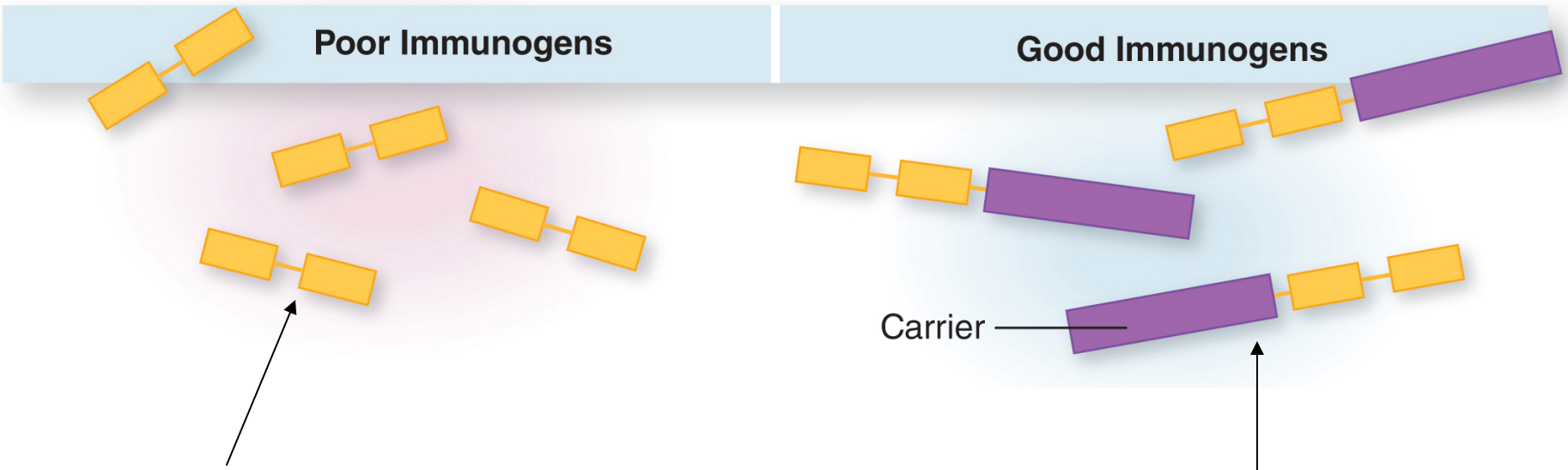


Haptens are too small to act as an antigen.

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

What Cells 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 able to identify foreign antigen on APCs which display antigen in MHCP II

- Helper T Cells then initiates clonal selection to make the following T cells

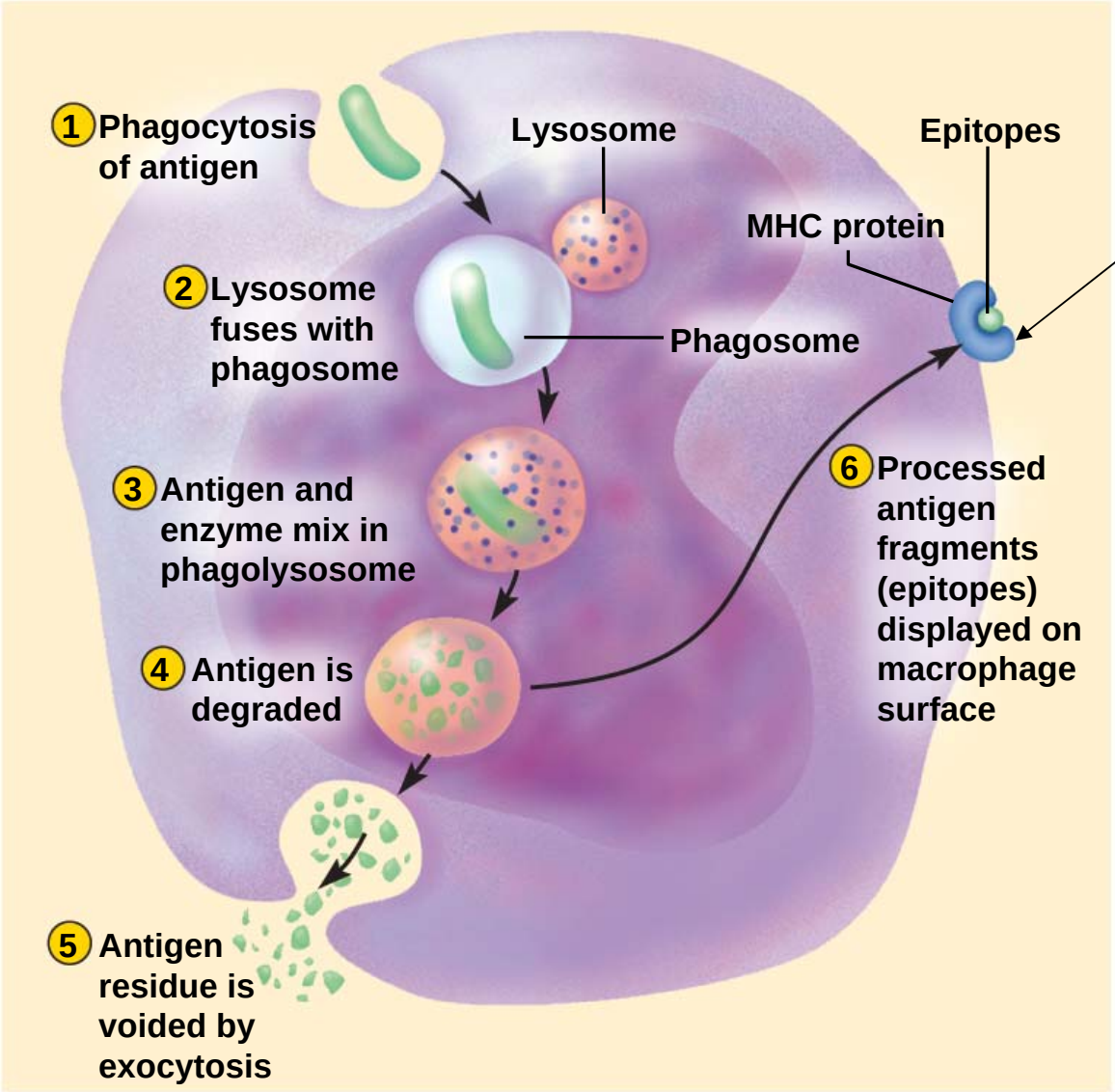
  - cytotoxic T cells – kills infected cells with MHC-I
  - memory T cells – saved for future use
  - regulatory T cells – controls immune response

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

- T Helper cells at this time will also initiate non-specific defenses / stimulate macrophage and inflammation!

Antigen Processing

The first step to initiate an acquired immunity response.



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

Why do we need two forms of immunity?

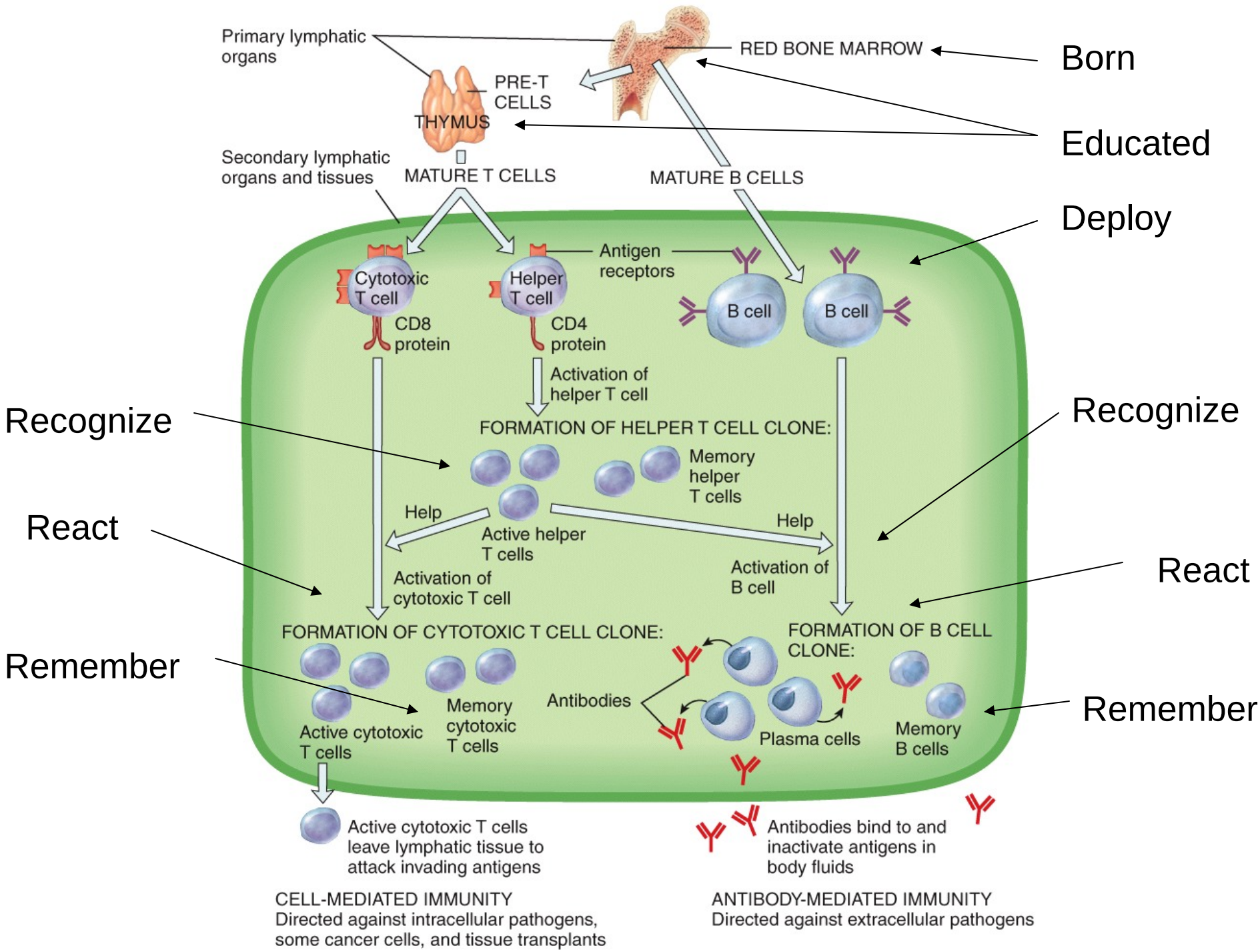
- ***Because a pathogen can be either outside or inside our cells.***
- *Humoral Immunity: Action of B cell which when stimulated morph into plasma cells // plasma cells make antibodies /// antibodies only attack antigens when they are outside our cells.*
- *Cellular Immunity: T cells (i.e. cellular immunity) can only recognize foreign antigen if 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.*

What Is Cellular Immunity?

- *Cellular Immunity = action of four different types of 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 system that kill infected host cells*
  - *NK cells (also a lymphocyte) able to kill infected host cells but not specifically // response as "immune surveillance.*

What Is Humoral Immunity?

- *Humoral Immunity = action of B cells*
  - *Different classes of B cells (plasma cells, memory B cells, regulatory B cells)*
  - *Each class has a special function*
  - *Plasma cells make antibodies // each plasma cell makes 2,000 antibodies per second for approximately 7 days*
  - *Antibodies attach directly to foreign antigen /// render them harmless and tag pathogen for destruction*
  - *Note: antibodies don't directly kill anything /// must use complement to kill pathogen*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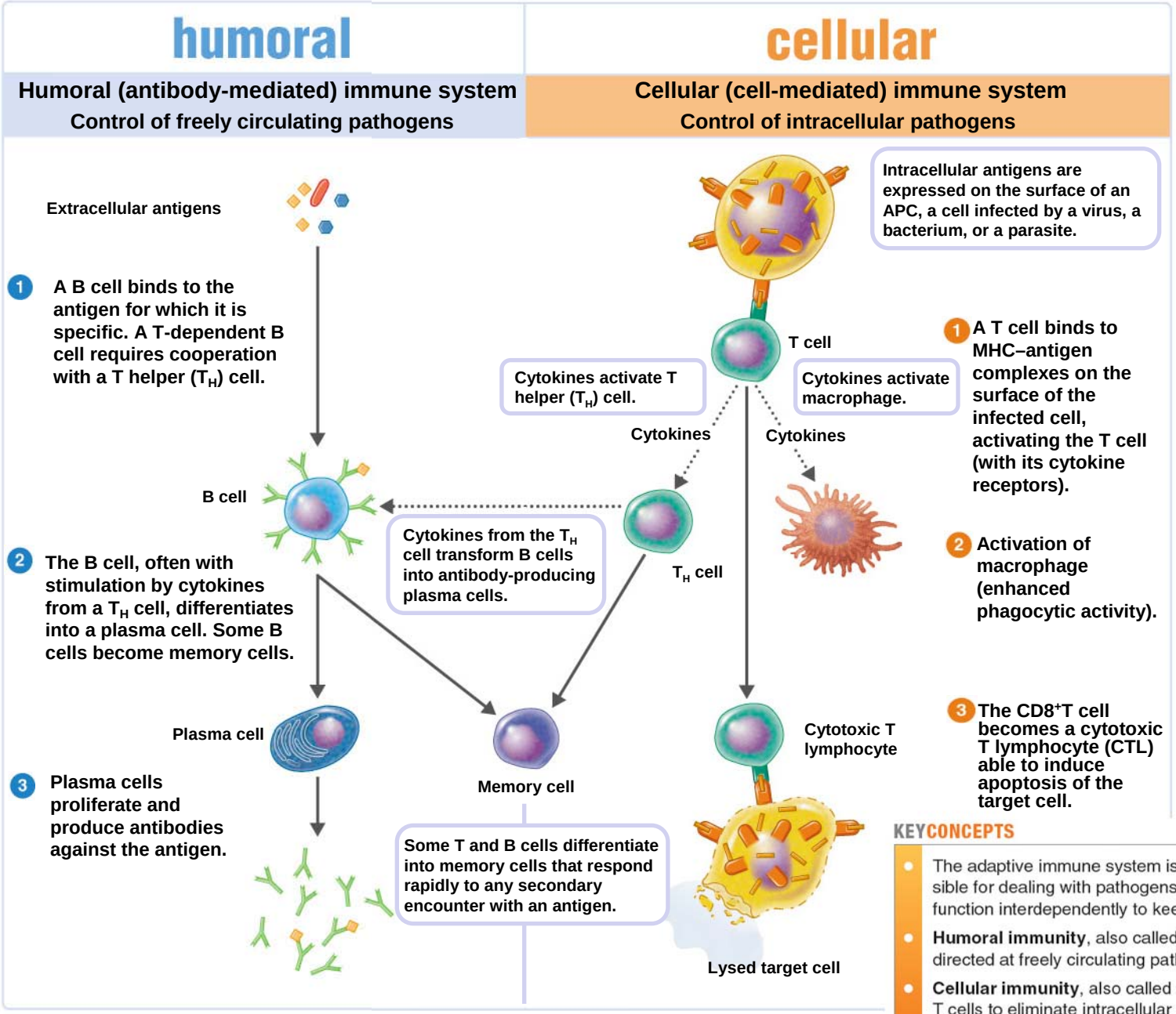
The dual nature of the adaptive immune system.



KEYCONCEPTS

- 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.

Key Questions You Need
To Ask if You Want to Understand Acquired Immunity

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

Key Questions You Need To Ask if You Want to Understand Acquired Immunity

- How are educated deployed immune cells *(now called naive immunocompatent T and B cells)* "activated"? *(Note: These cells are the cells now 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
  - 2) react
  - 3) remember

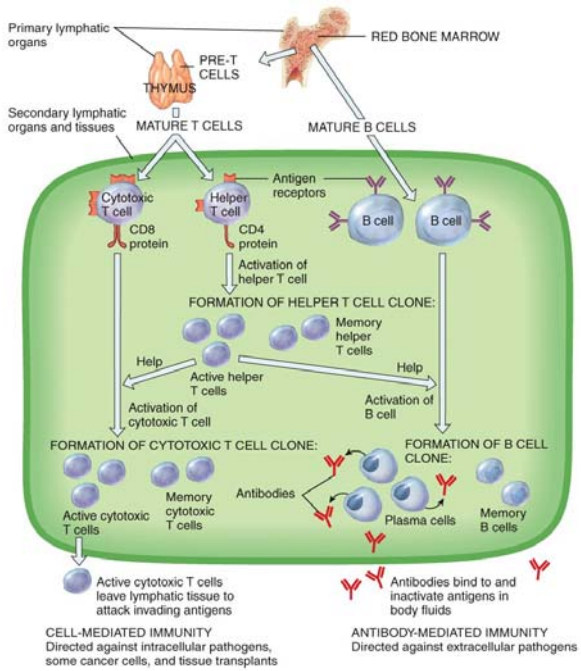
- What will happen to activated immune cells after the pathogen is defeated?

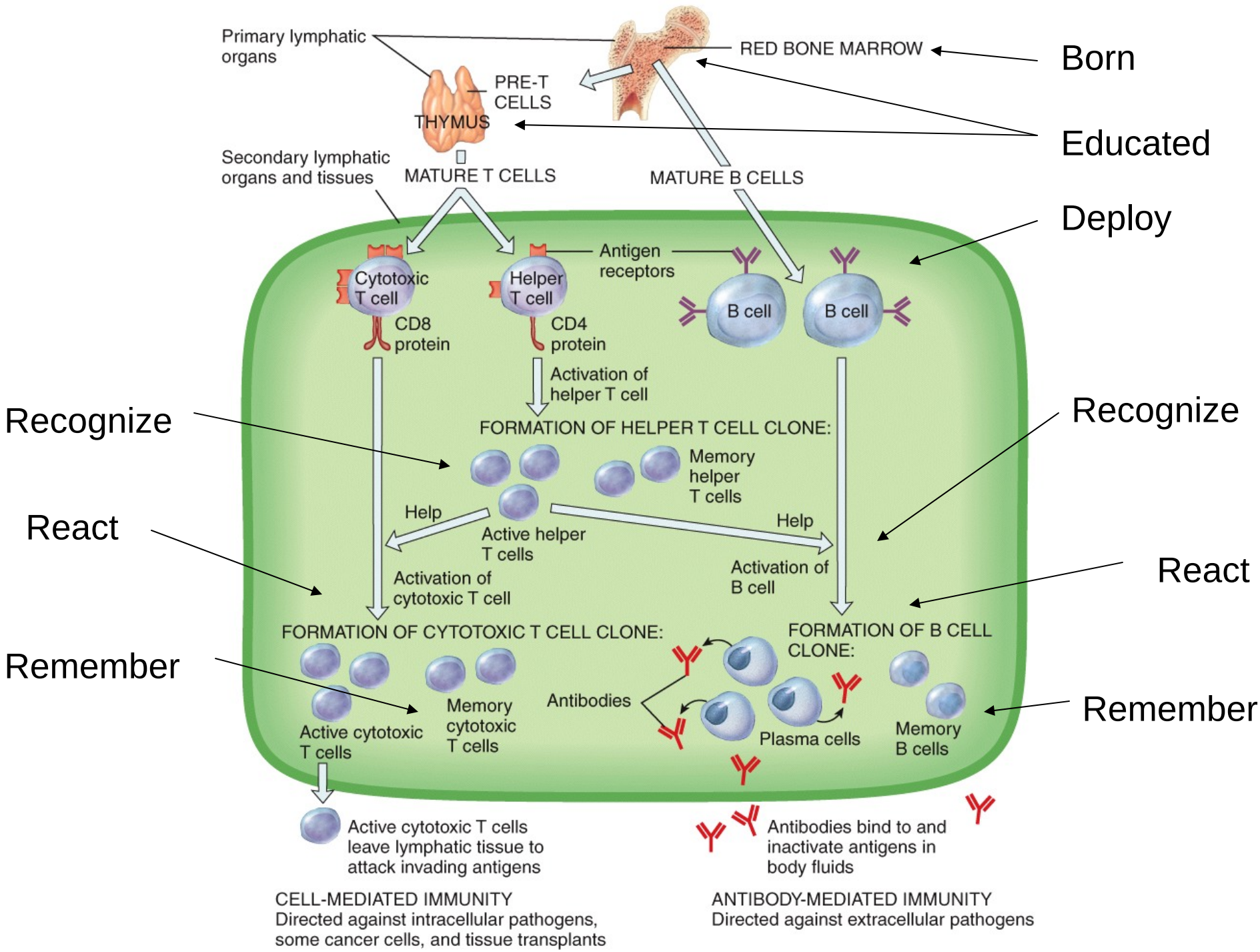
The **immune system** is complex and difficult to understand on the first pass.

It helps to visualize the overall process first before you try to learn the individual steps responsible for the functions of the immune system.

After you grasp the overall process, then you can drill down for greater understanding of the overall process of adaptive immunity.

This graphic is an overview of how the immune system works. You need to memorize this summary as your first step to understanding the immune system. (see next slide)

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Directed against intracellular pathogens, some cancer cells, and tissue transplants
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Directed against extracellular pathogens

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

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

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

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 Adaptive 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 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 <u>directly attack and destroy foreign cells</u> (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)

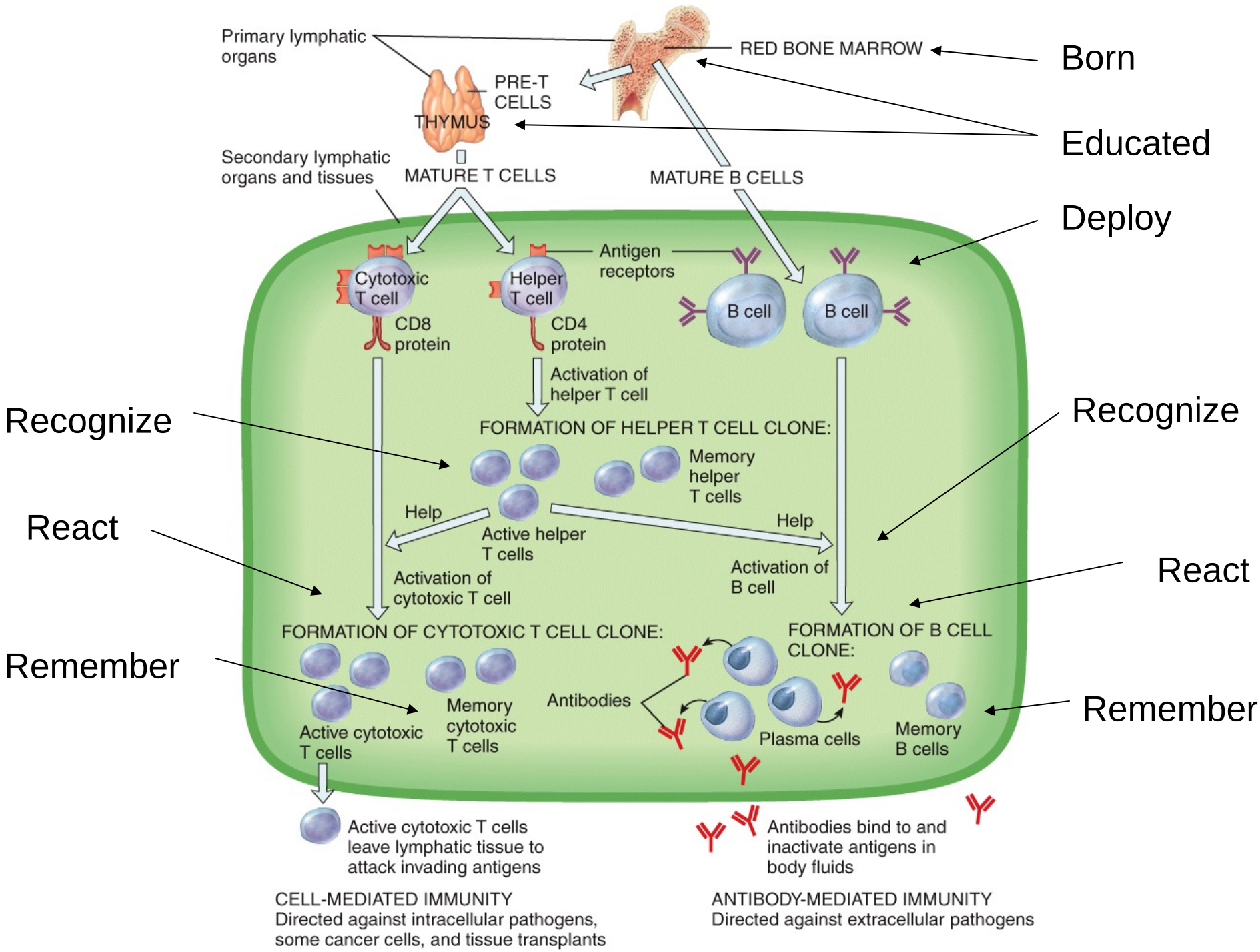
- also known as T4, CD4, CD4+
- CD4 term often used to describe TH before they become activated
- activated help T cells requred to activate T_C cell and B cell (the T cell dependent B cells)
- TH secrete cytokines that also stimulate components of the nonspecific resistance (i.e. activate and bring 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
- <u>note: most cells die after pathogen defeated via apoptosis but memory cells remain for decades!</u>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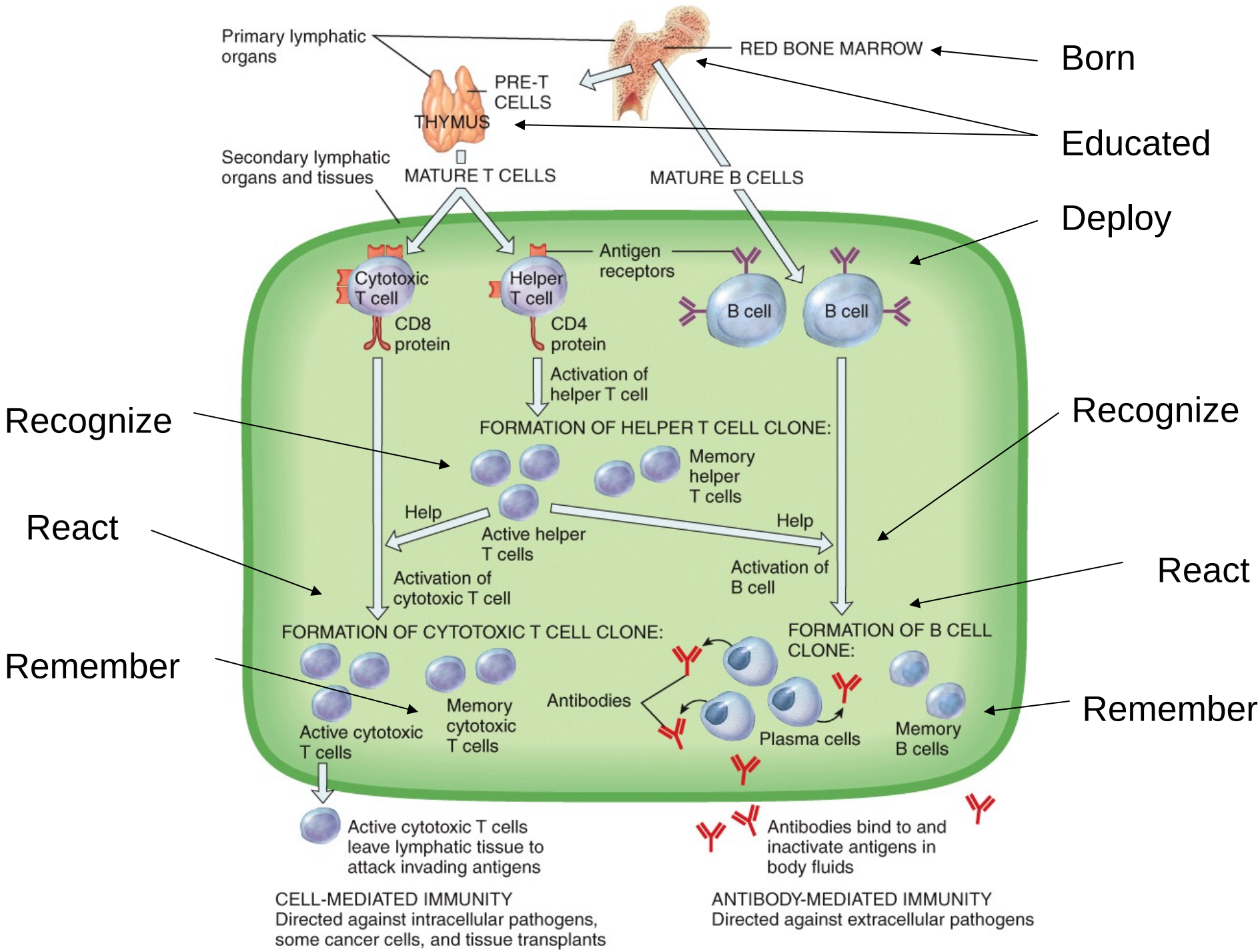
T Cell Developmental Stages
Cellular Immunity

Born

Educated

Deployment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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:
  - <u>inability to recognize the RE cells self antigen</u>
    - » especially their MHC protein (self-antigens)
    - » *would be incapable of recognizing a foreign attack on the body (MHC carries the epitope!)*
  - <u>reacting to self antigen</u>
    - » *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

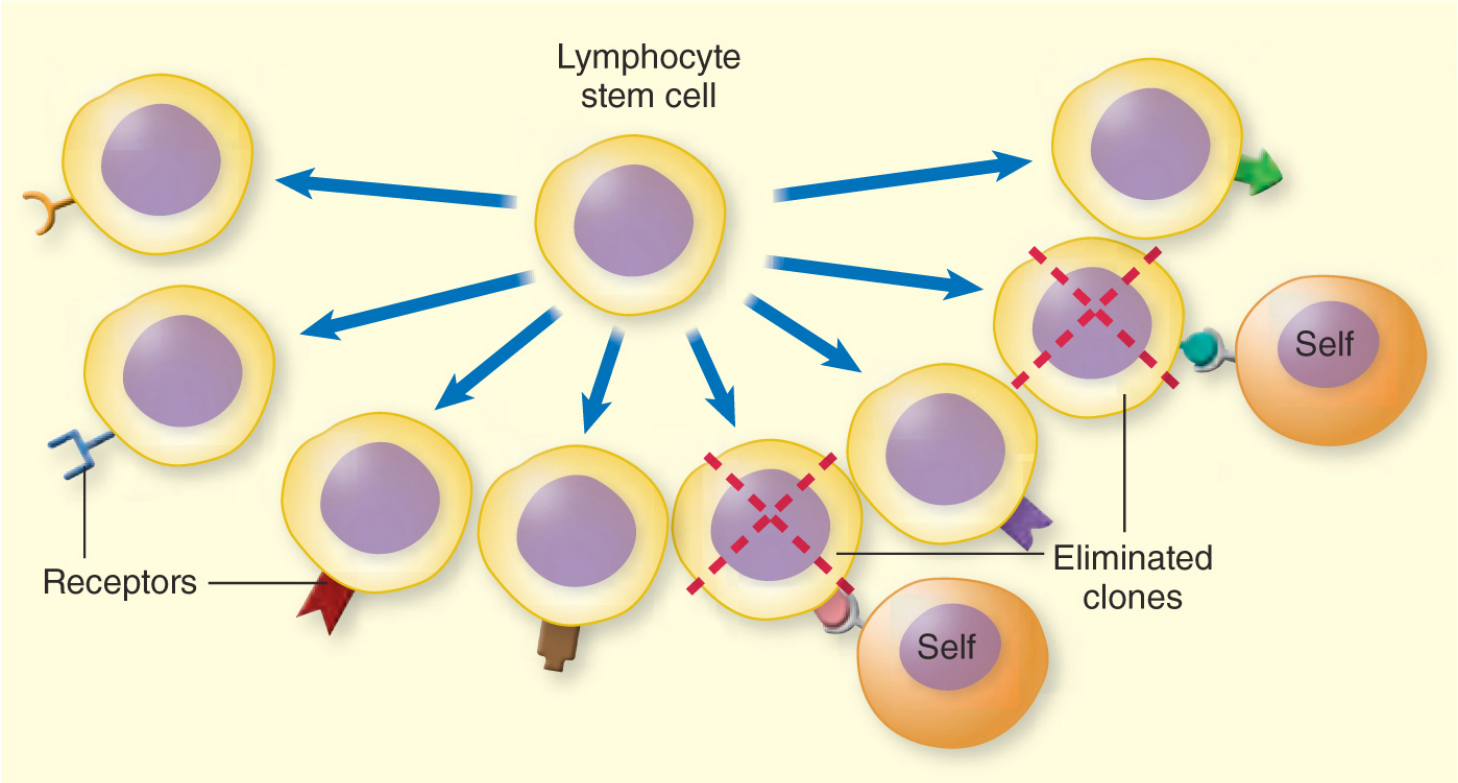
- Self-tolerant CD8 & CD4 cells move to medulla of the thymus and undergo positive selection
  - multiply and form clones of identical CD8 & CD4 cells programmed to respond to a specific antigen
- These cells become the naïve immunocompatent T lymphocytes
  - immunocompetent cells (have receptors for 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

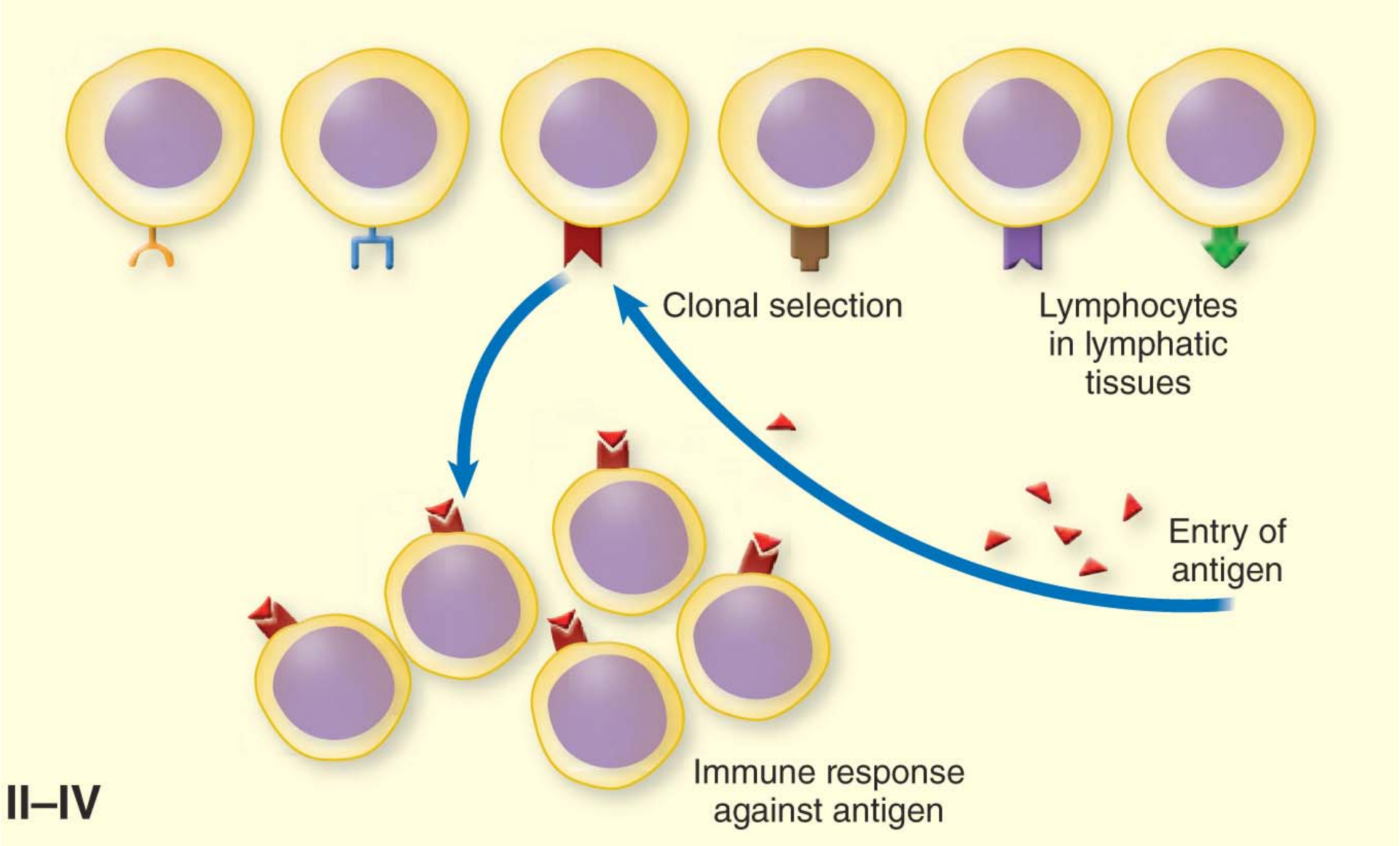
Deployed as “Naïve Immunocompatent” T Lymphocytes (helpers and cytotoxic)



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)

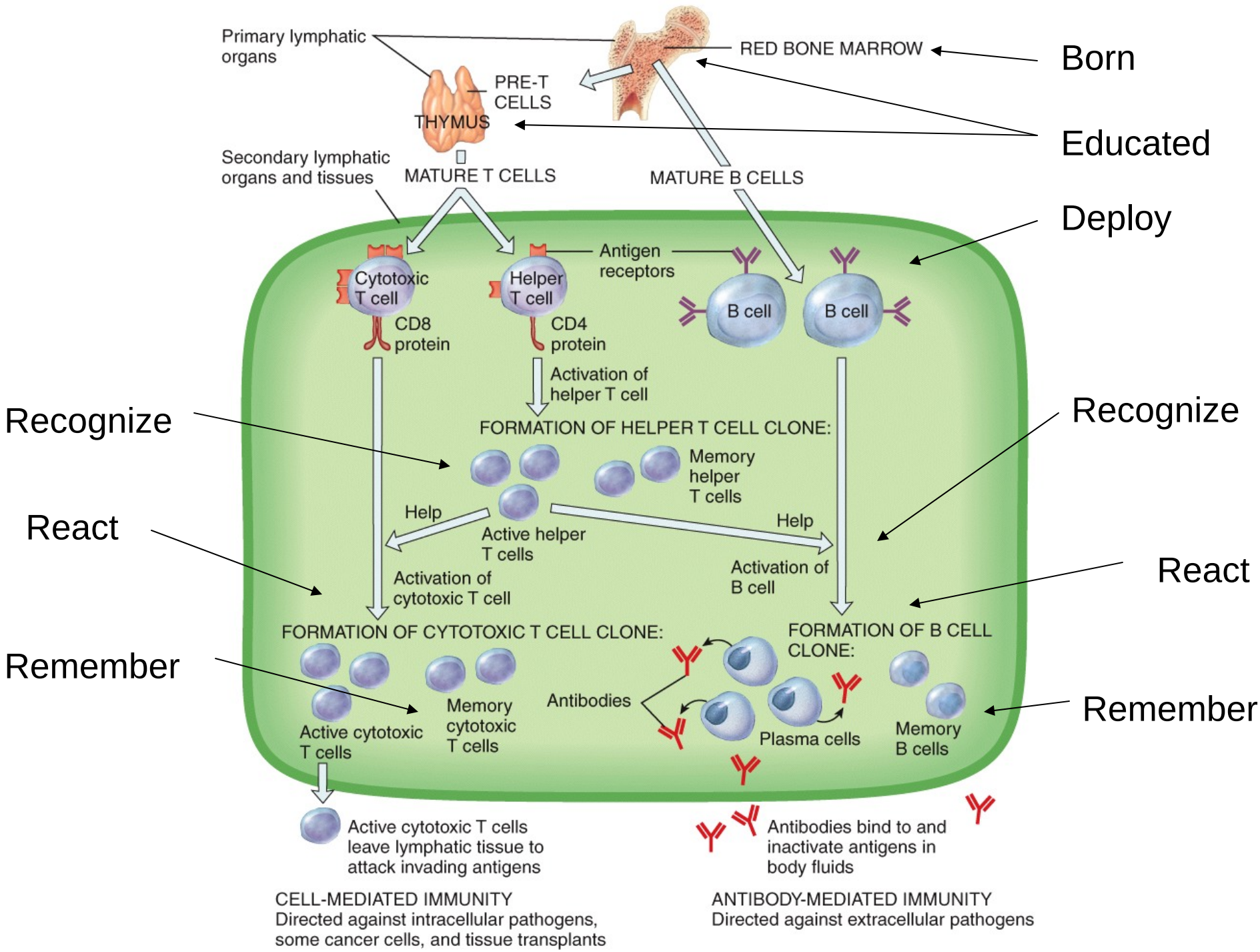
- Immunocompatent naïve B cells need to be activated before they "morph" into plasma cells
- These plasma cells are pre-programmed to make antibodies to matched a specific foreign antigen // i.e. have unique receptor matched to specific foreign antigen
- antibodies never directly kills a pathogen but 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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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**

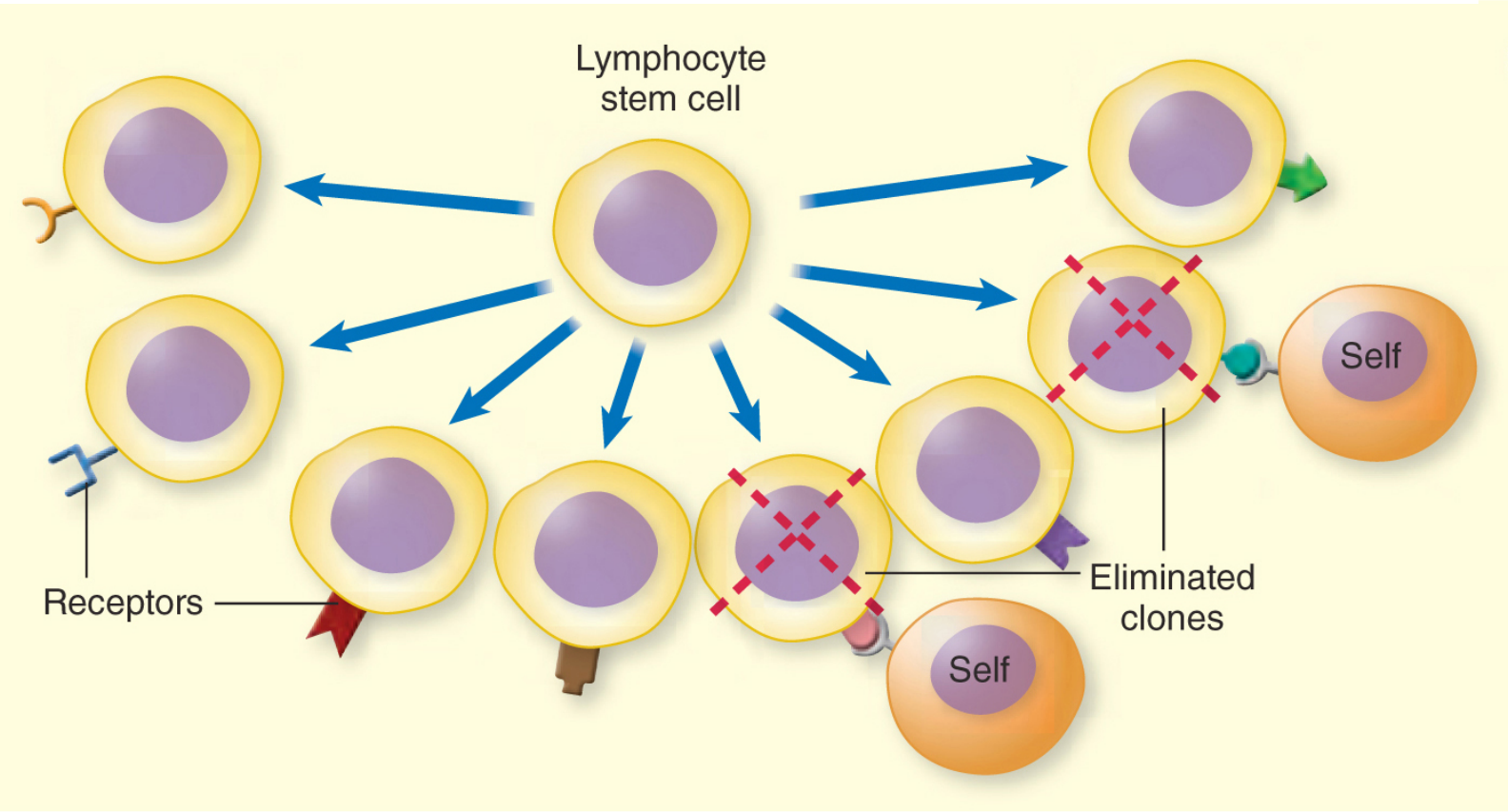
B Cell Stage Two = Education

- 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

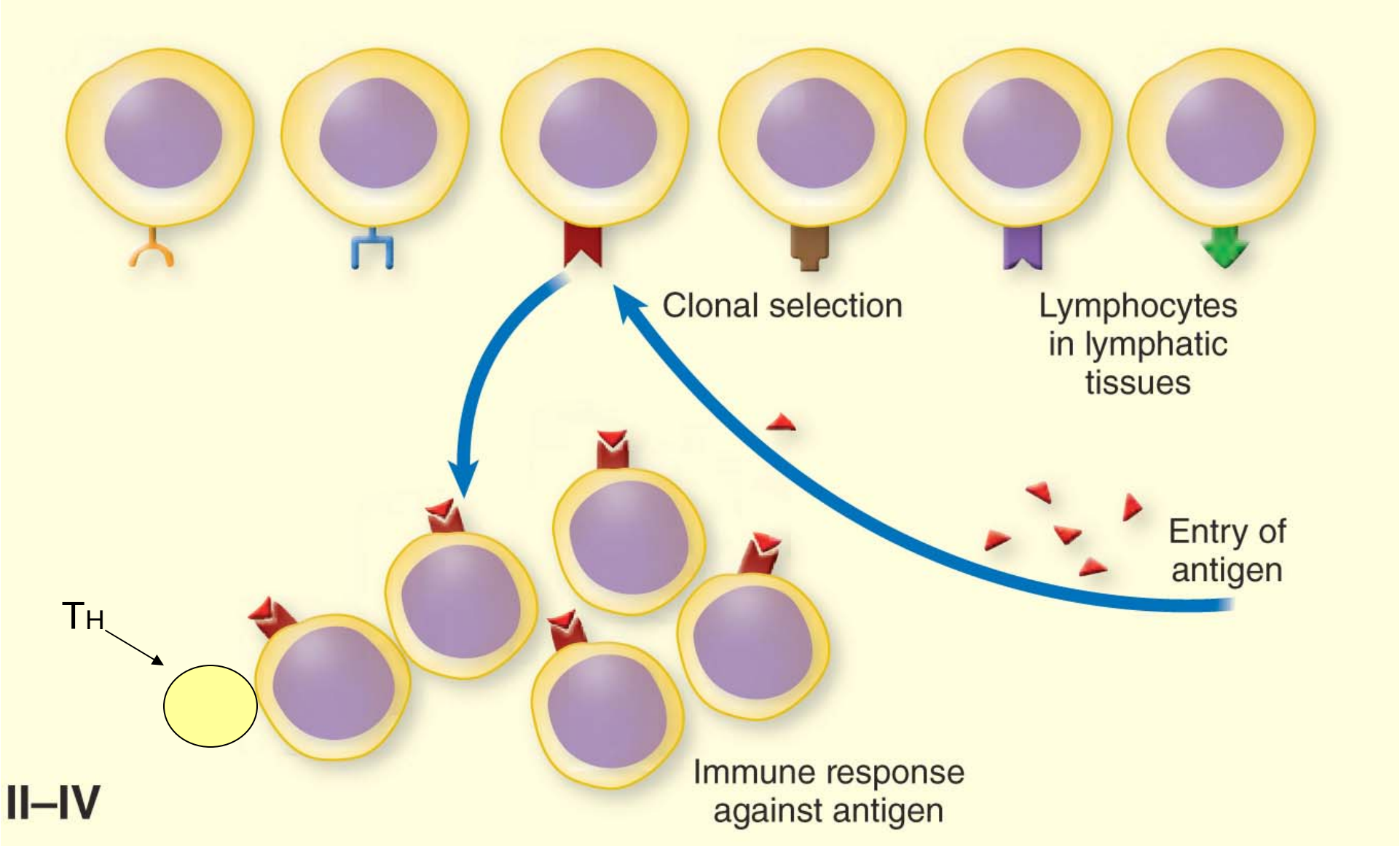
B Lymphocytes are “Educated” Then Become “Naïve Immunocompatent”



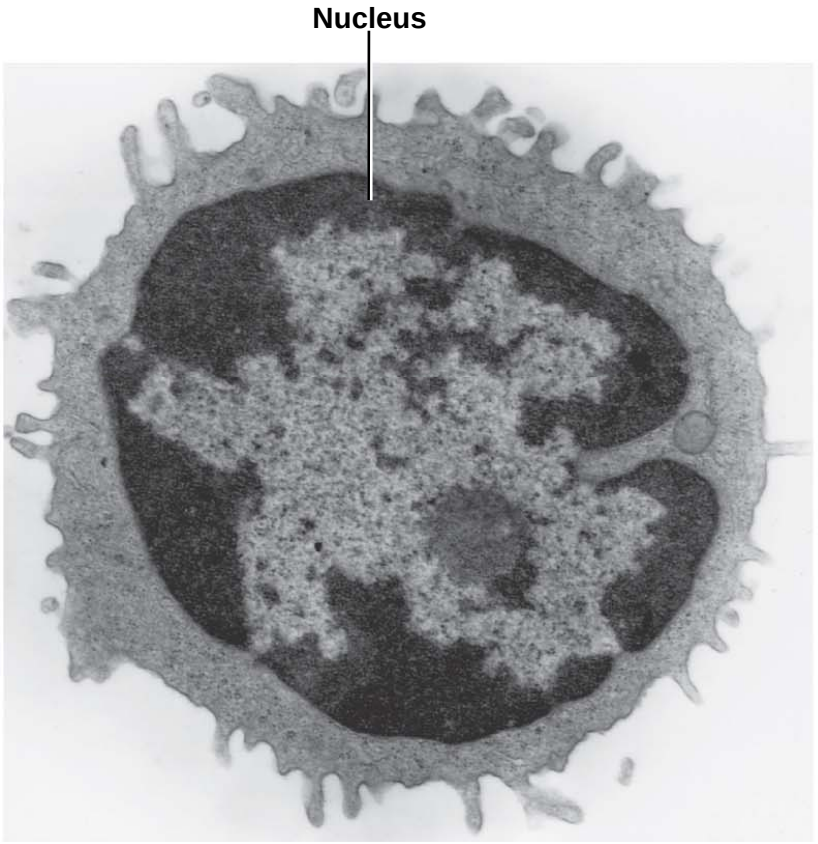
Repertoire of lymphocyte clones, each with unique receptor display

Naïve Immunocompatent B Cells Activated by Unique Antigen (epitope)

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

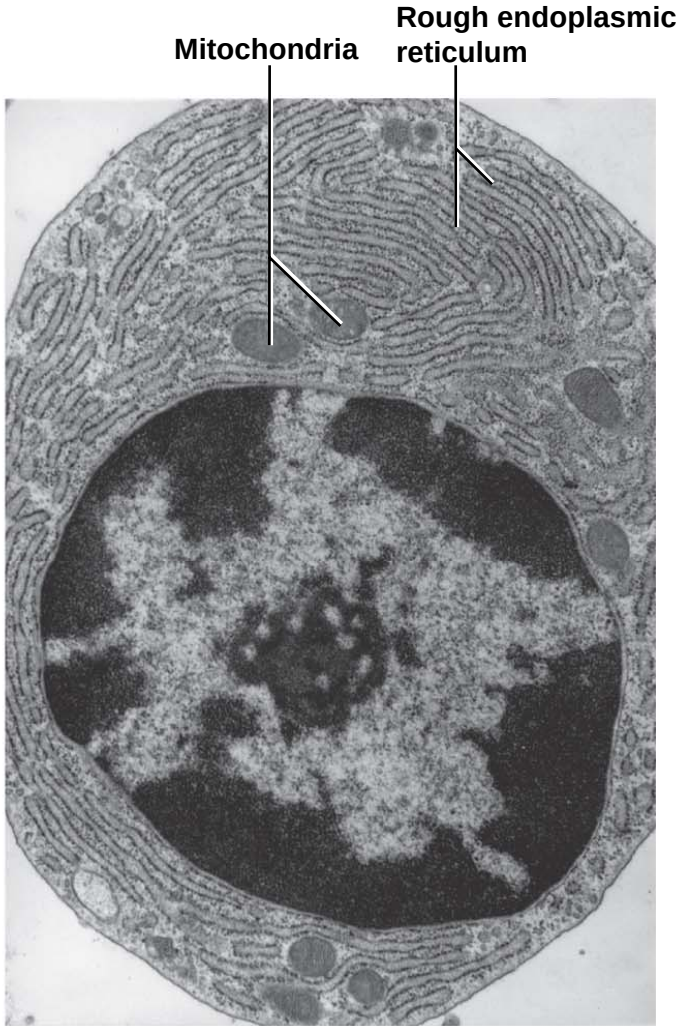


B cells to Plasma cells



(a) B cell

2 µm



(b) Plasma cell

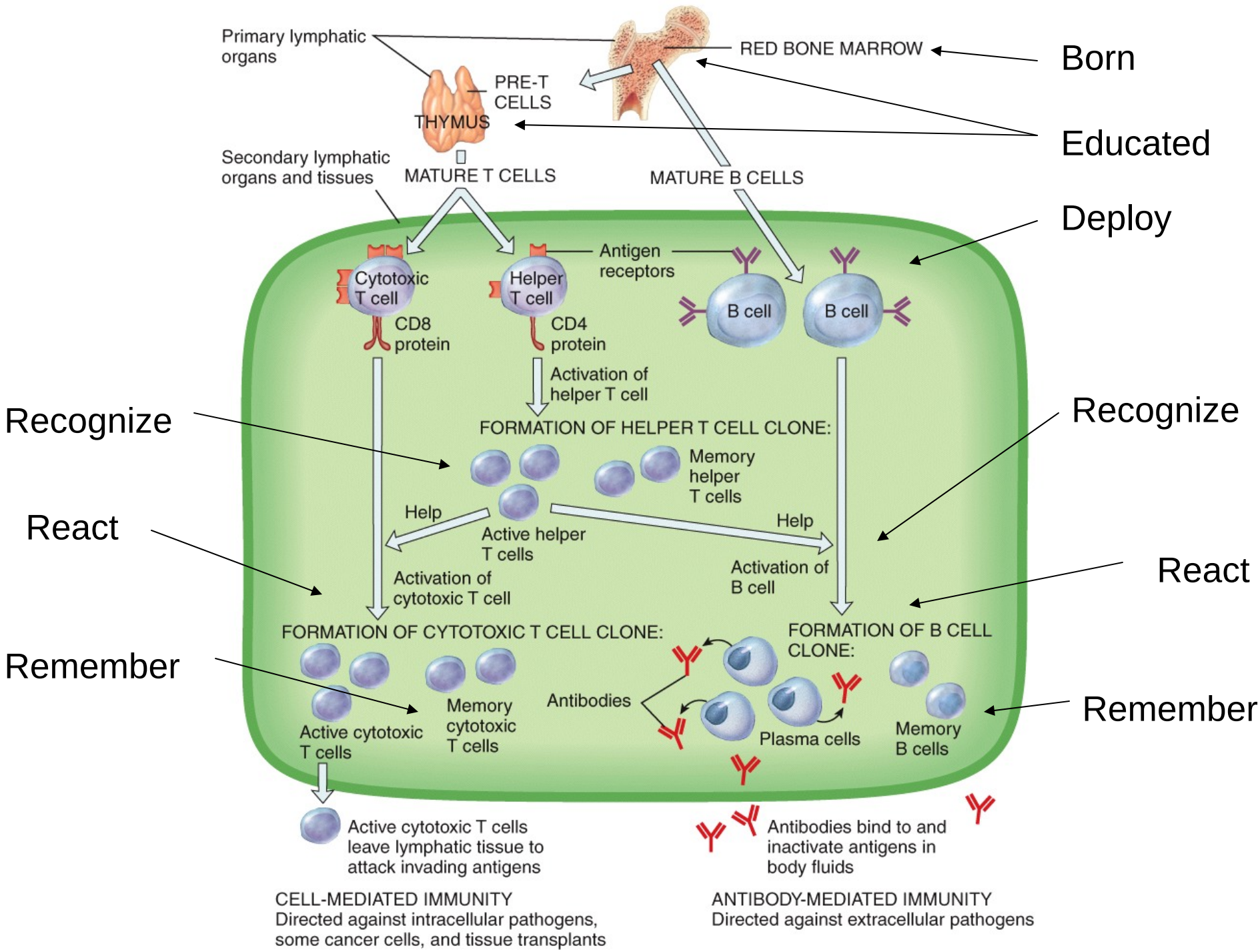
2 µm

After Naïve Immunocompatent Tc (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


Primary lymphatic organs
RED BONE MARROW
Born
PRE-T CELLS
THYMUS
Educated
Secondary lymphatic organs and tissues
MATURE T CELLS
MATURE B CELLS
Deploy
Antigen receptors
Cytotoxic T cell
Helper T cell
B cell
B cell
CD8 protein
CD4 protein
Activation of helper T cell
Recognize
FORMATION OF HELPER T CELL CLONE:
Recognize
Memory helper T cells
Help
Help
React
Active helper T cells
Activation of cytotoxic T cell
Activation of B cell
React
FORMATION OF CYTOTOXIC T CELL CLONE:
FORMATION OF B CELL CLONE:
Remember
Antibodies
Memory cytotoxic T cells
Active cytotoxic T cells
Plasma cells
Memory B cells
Remember
Active cytotoxic T cells leave lymphatic tissue to attack invading antigens
Antibodies bind to and inactivate antigens in body fluids
CELL-MEDIATED IMMUNITY
Directed against intracellular pathogens, some cancer cells, and tissue transplants
ANTIBODY-MEDIATED IMMUNITY
Directed against extracellular pathogens

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).

2. 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.

3. 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).

4. 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

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

8. 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

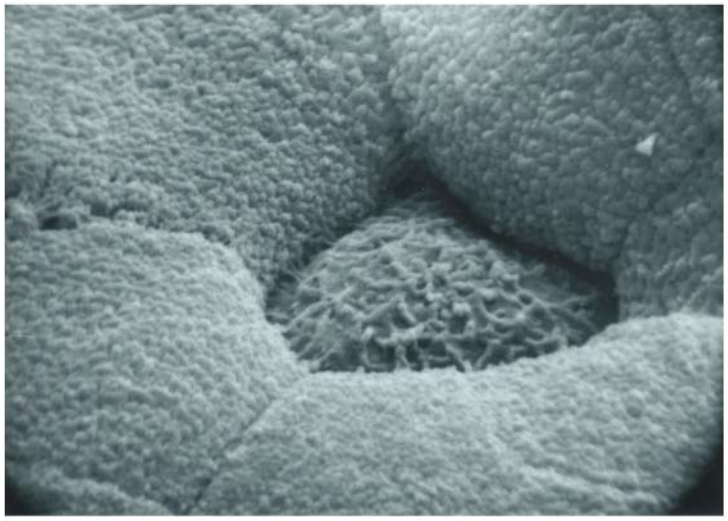
- Note: the “recognition step” relies on interaction between the MHCP and matched receptors on T cell and B cell
- receptors on both T cells and B cells are matched to the same antigen
- Therefore --- we activate both T and B cells at the same time against the same pathogen
- Why?

M Cells

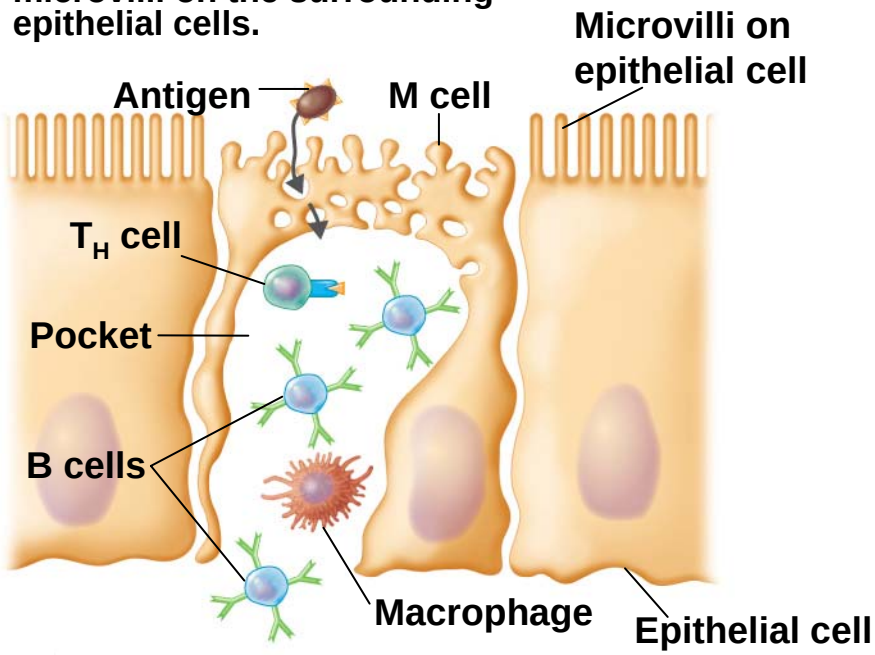
This is how immune cells try to find out (i.e. recognize) what type of pathogens may "break into" the sterile compartments of your body.

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 = <u>MHCP-I and MHCP-II</u>

- 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?

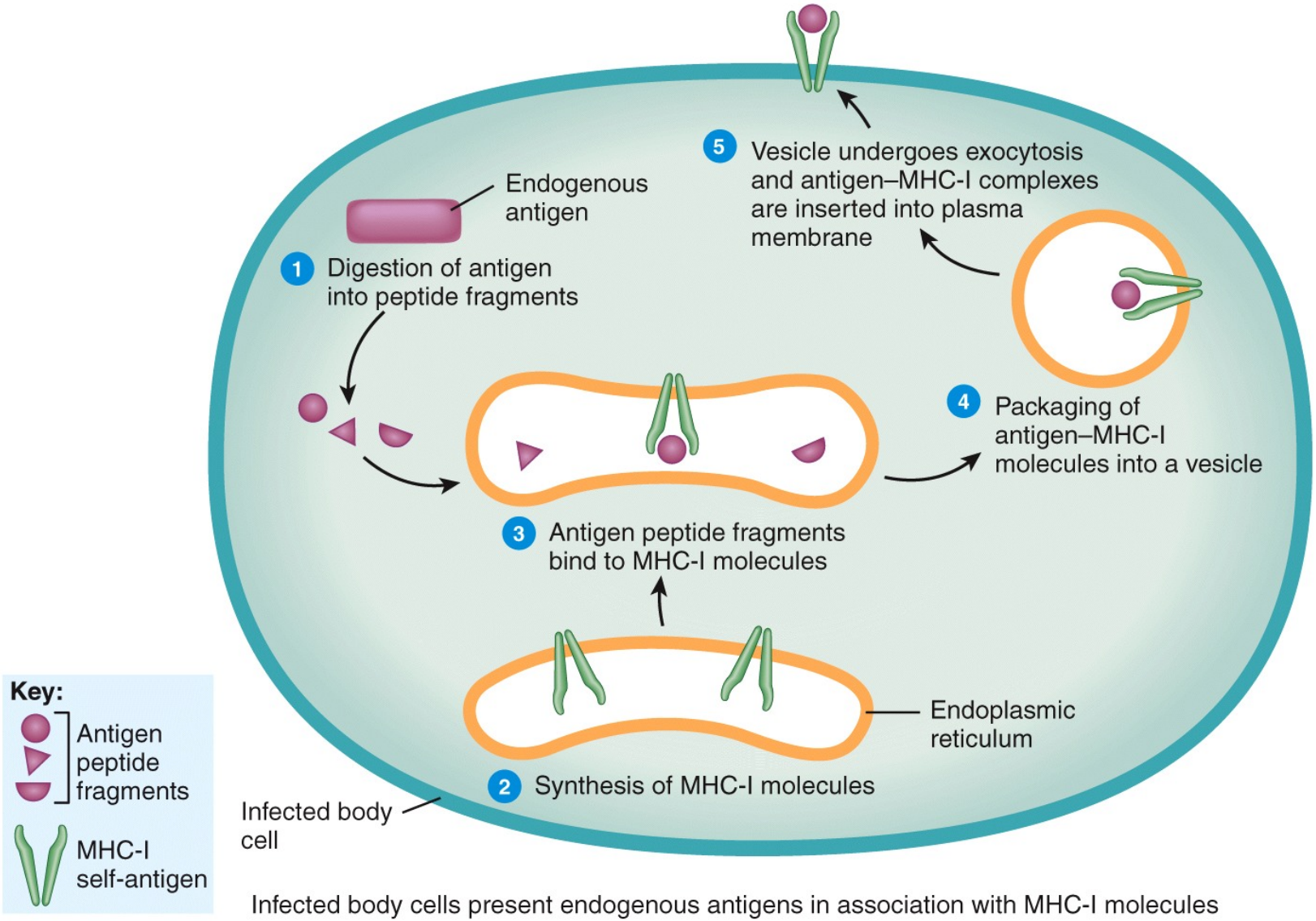
- Inside MHCP-I cells “non normal proteins” (i.e. cancerous) or foreign antigen, (e.g. virus and bacterial antigens) are partially digested
- Their “epitopes” are placed inside a MHC “place holder”
- The MHC-epitope is then inserted into the plasma membrane
- Active cytotoxic Tc can identify the MHC-epitope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

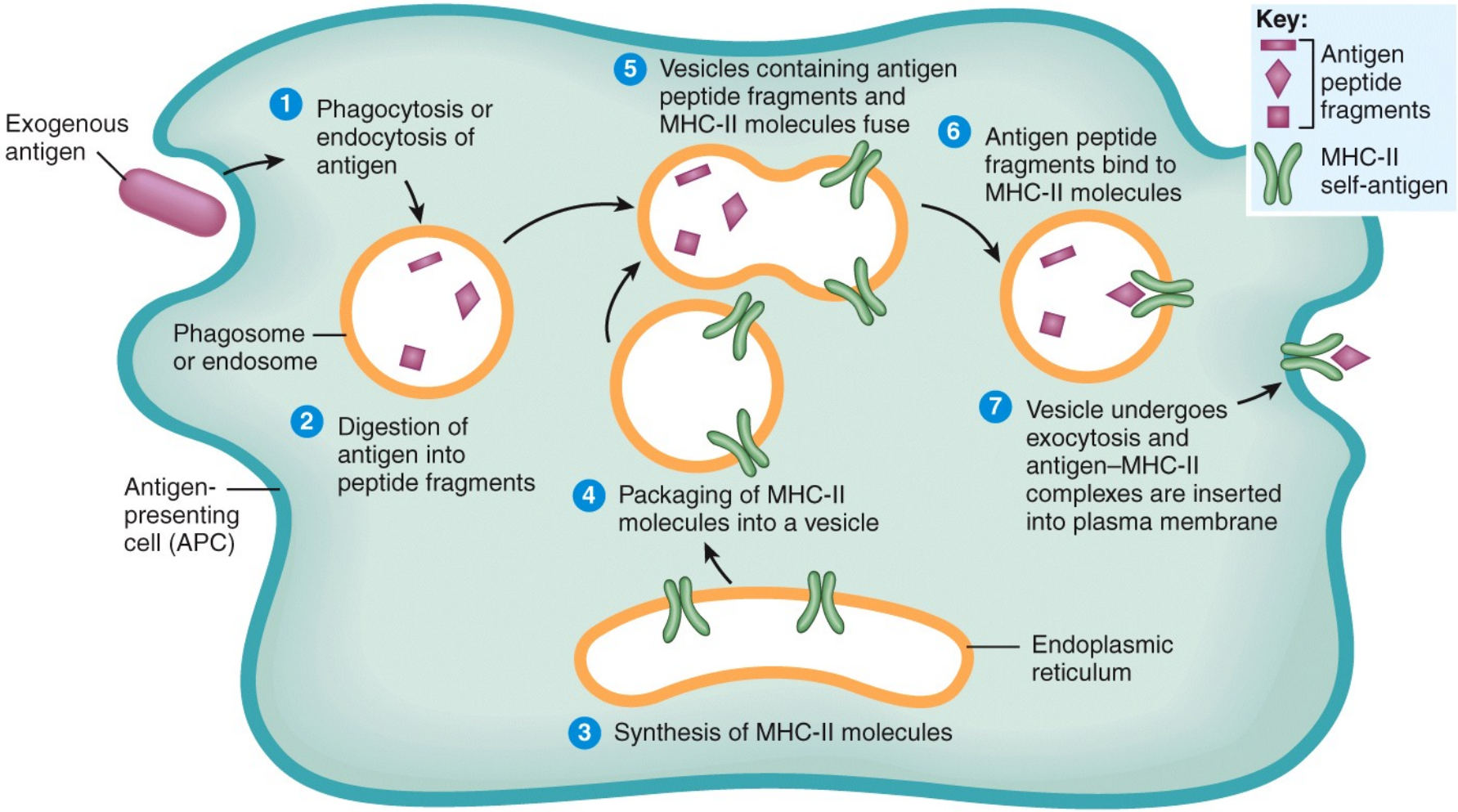
Endogenous Antigens Processed by Host Cells Using MHC-I

Recognized by Cytotoxic T cells (Tc)



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

Exogenous Antigens Processed by APCs Using MHC-II Recognized by Helper T Cells (T_H)

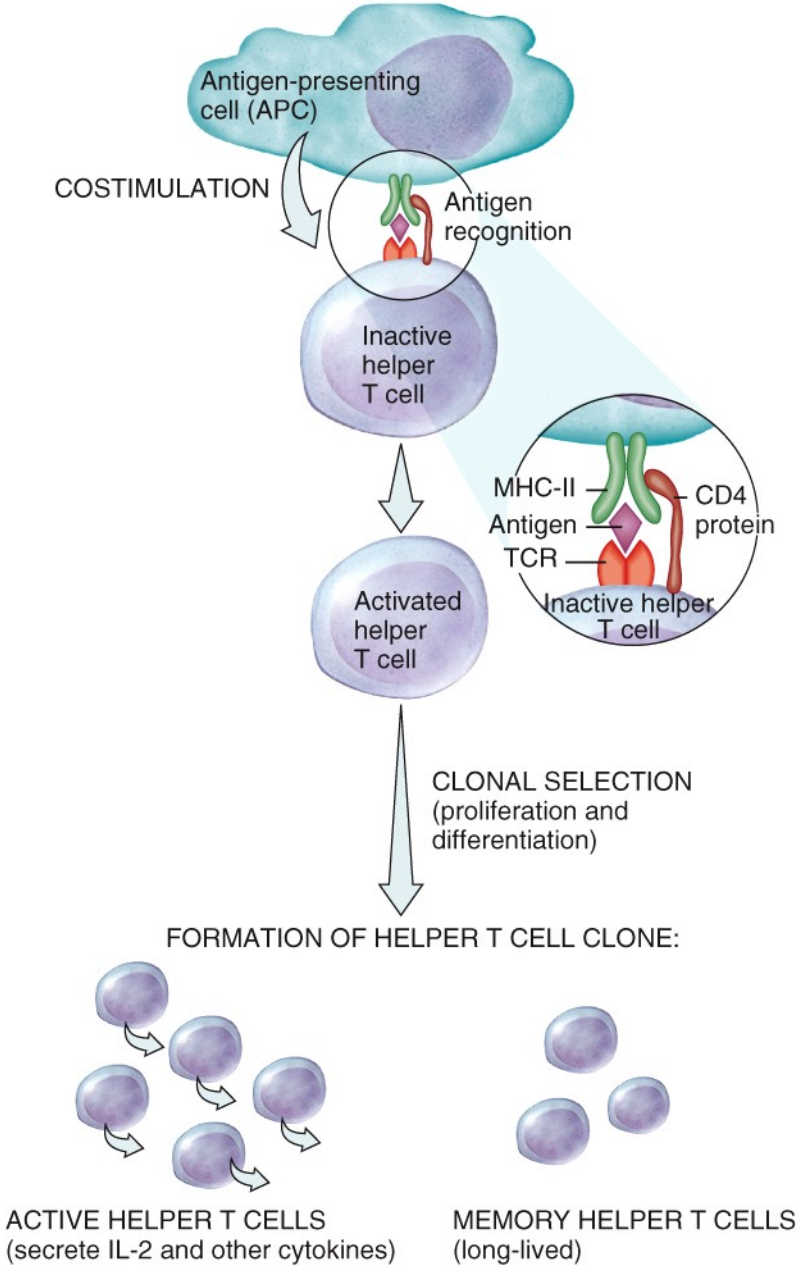


APCs present exogenous antigens in association with MHC-II molecules

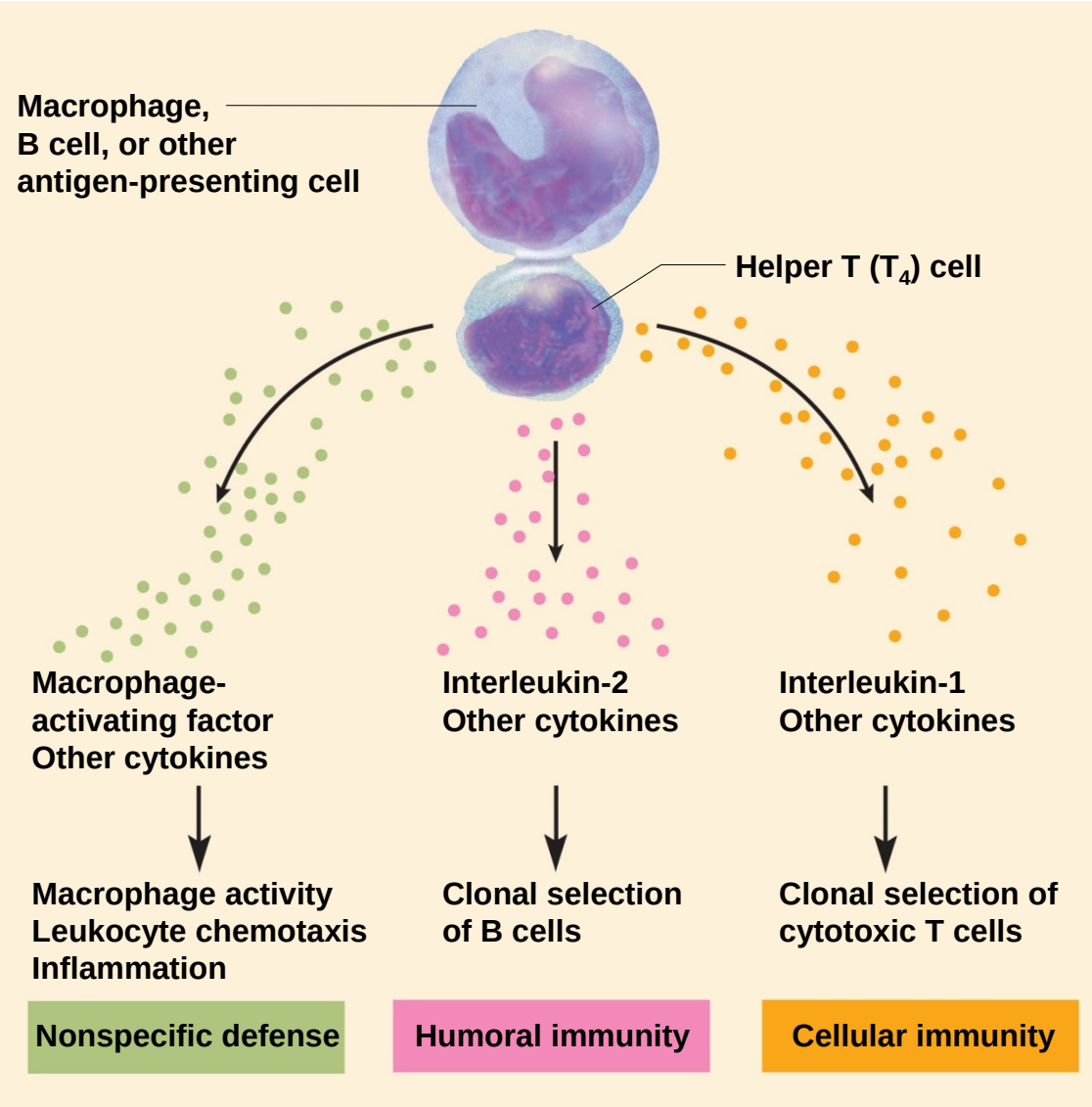
Activation of Helper T Cells

This is the recognition phase.

Immune system first needs to activate helper T cells then able to activate cytotoxic T cells, B cells, and enhance macrophage and inflammation



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!

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

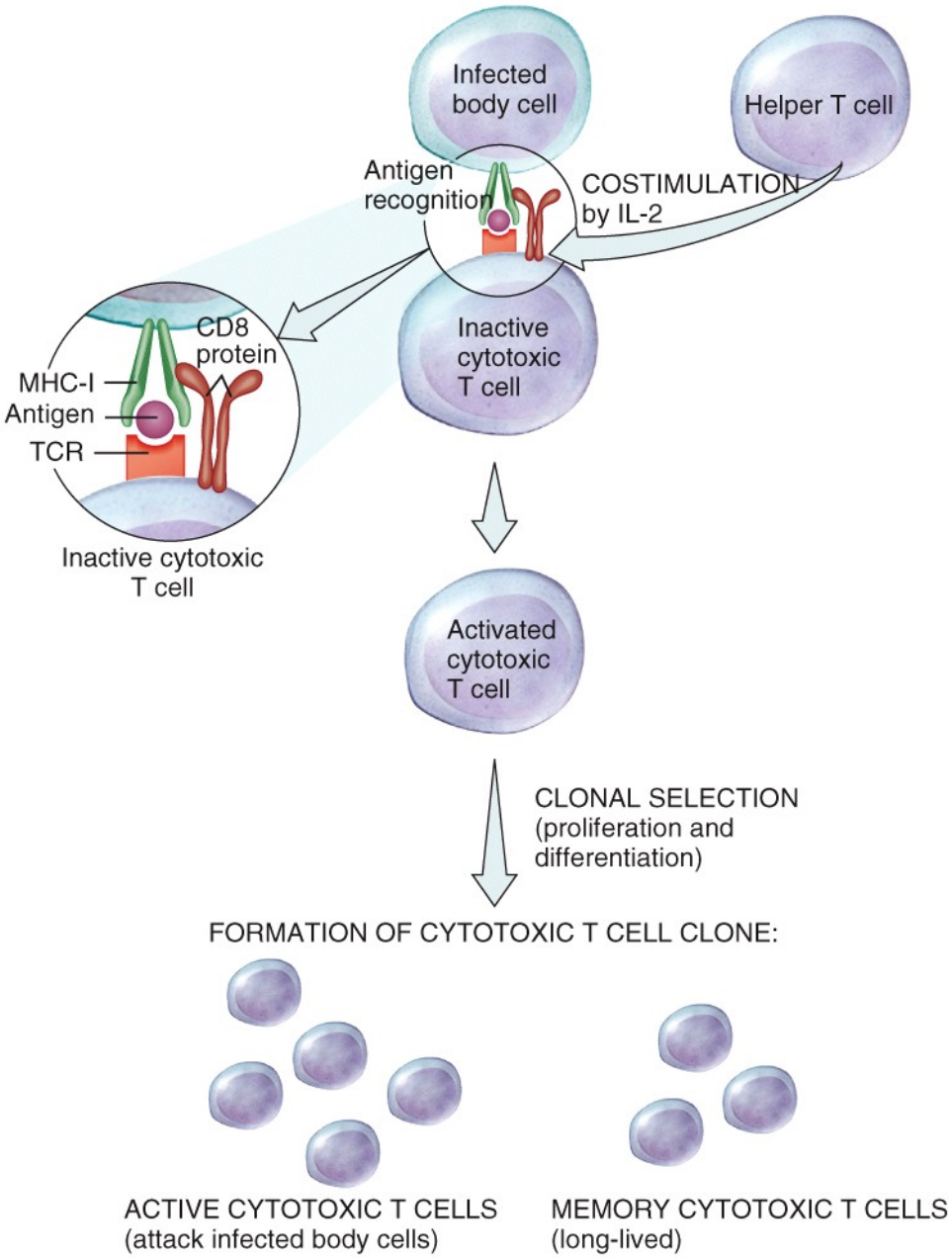
- Helper T cell are necessary for an immune responses
- First Step /// helper T cell bind to APC (e.g. macrophage) forming the Ag-MHCP II complex
- Second Step /// Macrophage secretes interleuken I // this then stimulate helper T cells to secrete interleukin II
  - The interleukin II then exerts three 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

This is the react phase.

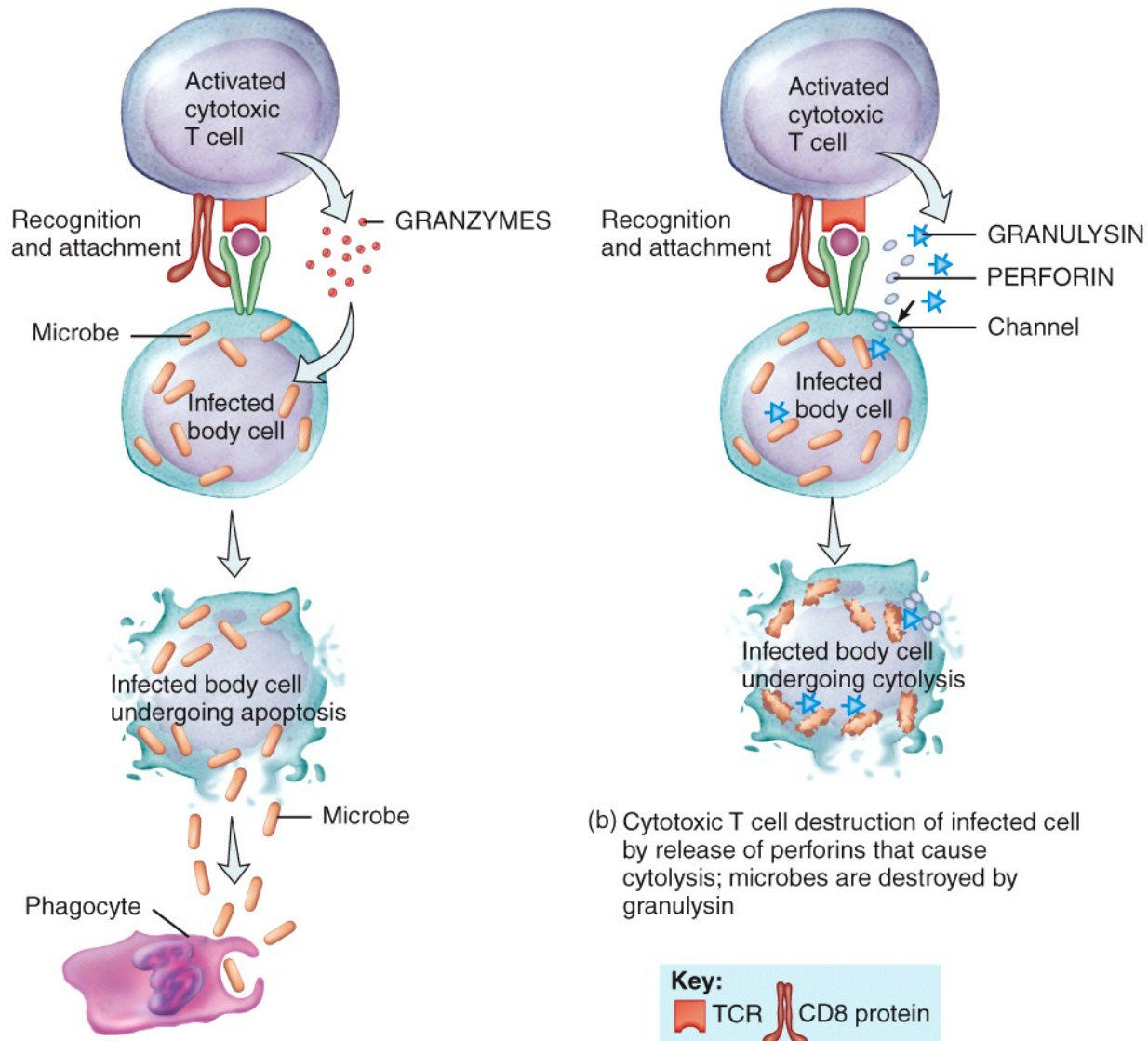
Recognition followed by Helper T Cell costimulation // Then Clonal Selection

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

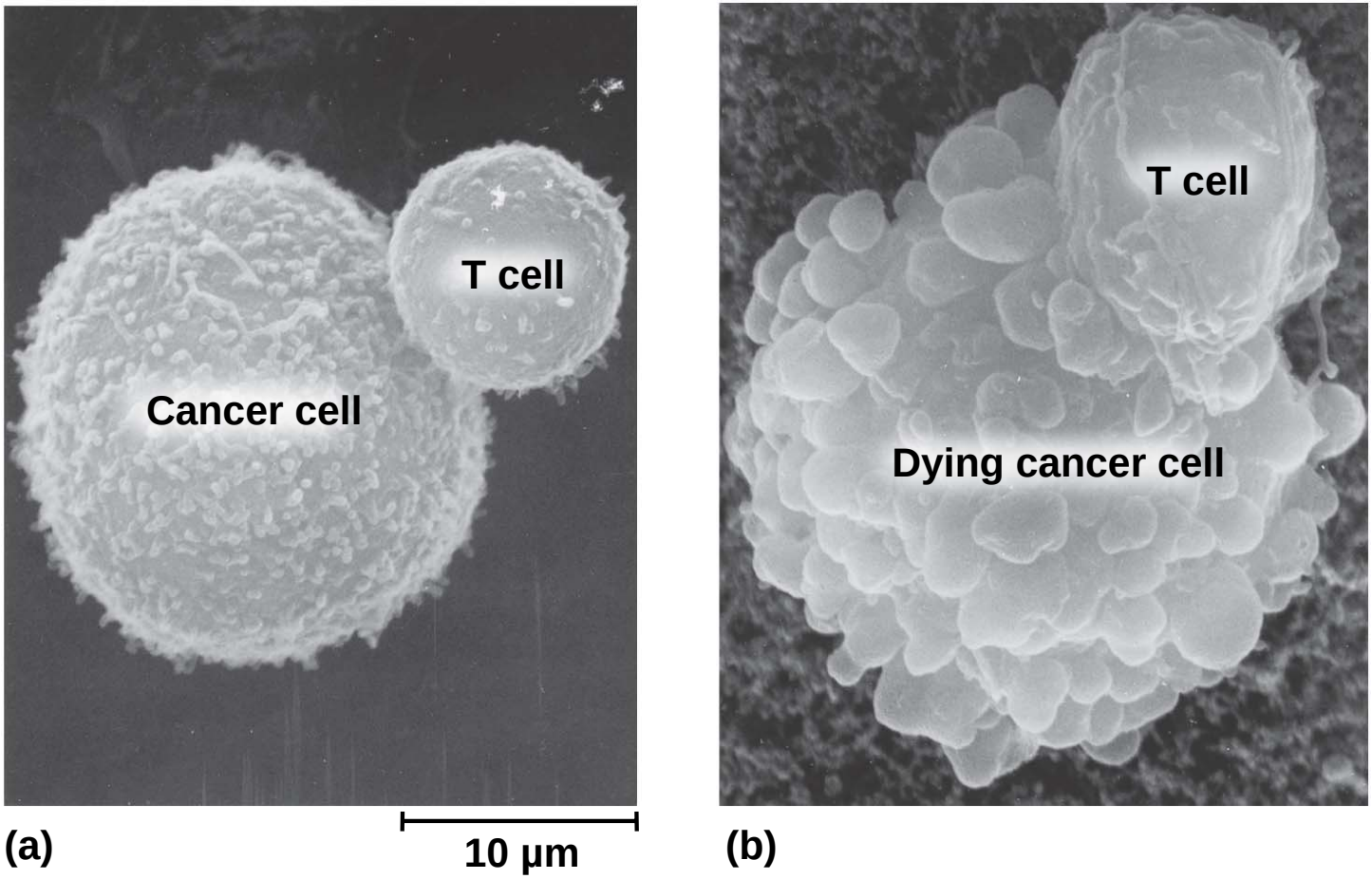
Note two different methods to destroy infected cells with exogenous antigen



(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 (first) exposure to foreign antigen

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

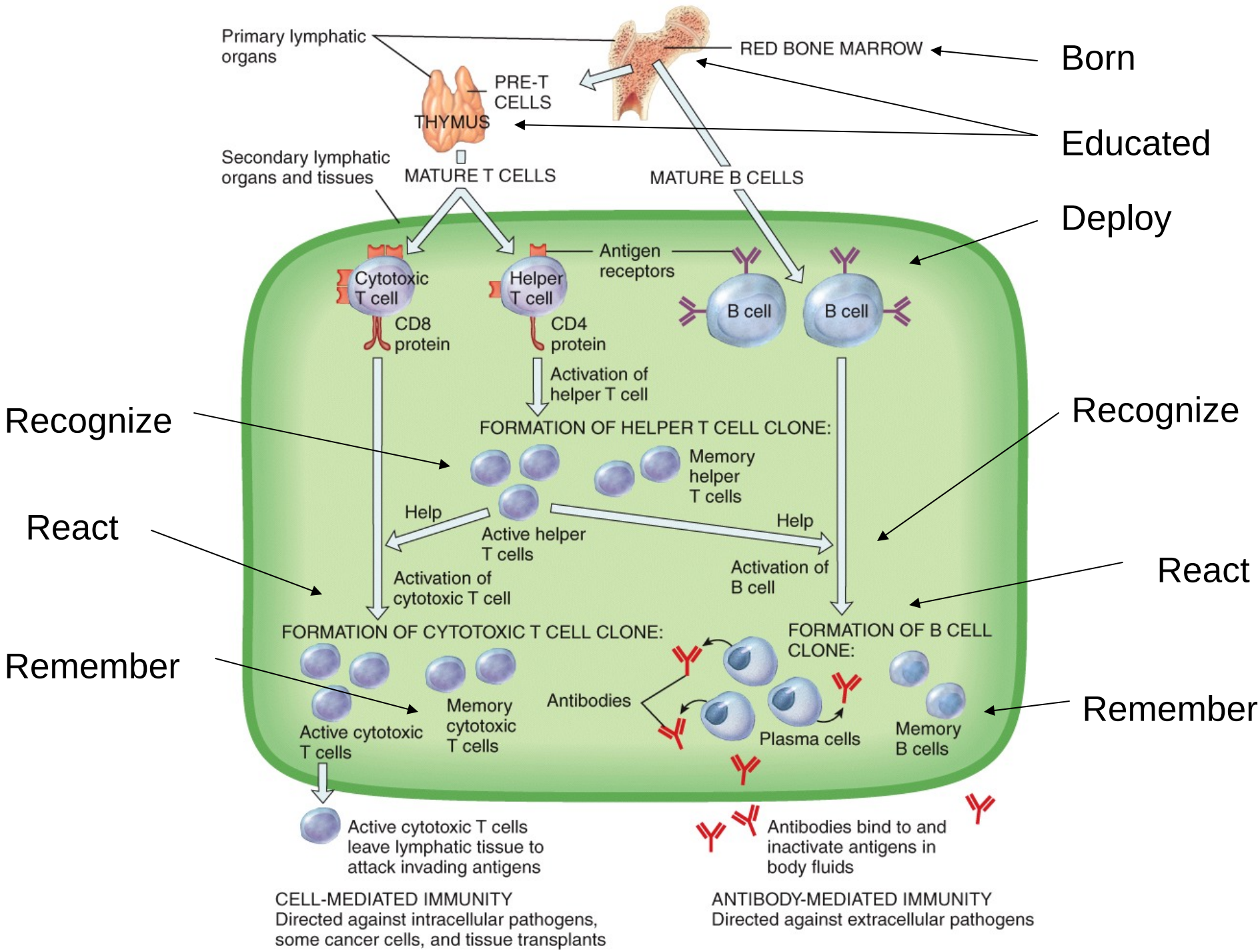
  – T_M are long-lived // more numerous than naïve T cells

  – T_M <u>require fewer steps to be re-activated, so they respond more rapidly</u>

Humoral Immunity (B Cells)

(Events Following Deployment)

The Three Rs


Primary lymphatic organs
RED BONE MARROW
Born
PRE-T CELLS
THYMUS
Educated
Secondary lymphatic organs and tissues
MATURE T CELLS
MATURE B CELLS
Deploy
Antigen receptors
Cytotoxic T cell
Helper T cell
B cell
B cell
CD8 protein
CD4 protein
Activation of helper T cell
Recognize
FORMATION OF HELPER T CELL CLONE:
Recognize
Memory helper T cells
Help
Help
React
Active helper T cells
Activation of cytotoxic T cell
Activation of B cell
React
FORMATION OF CYTOTOXIC T CELL CLONE:
FORMATION OF B CELL CLONE:
Remember
Antibodies
Memory cytotoxic T cells
Active cytotoxic T cells
Plasma cells
Memory B cells
Remember
Active cytotoxic T cells leave lymphatic tissue to attack invading antigens
Antibodies bind to and inactivate antigens in body fluids
CELL-MEDIATED IMMUNITY
Directed against intracellular pathogens, some cancer cells, and tissue transplants
ANTIBODY-MEDIATED IMMUNITY
Directed against extracellular pathogens

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

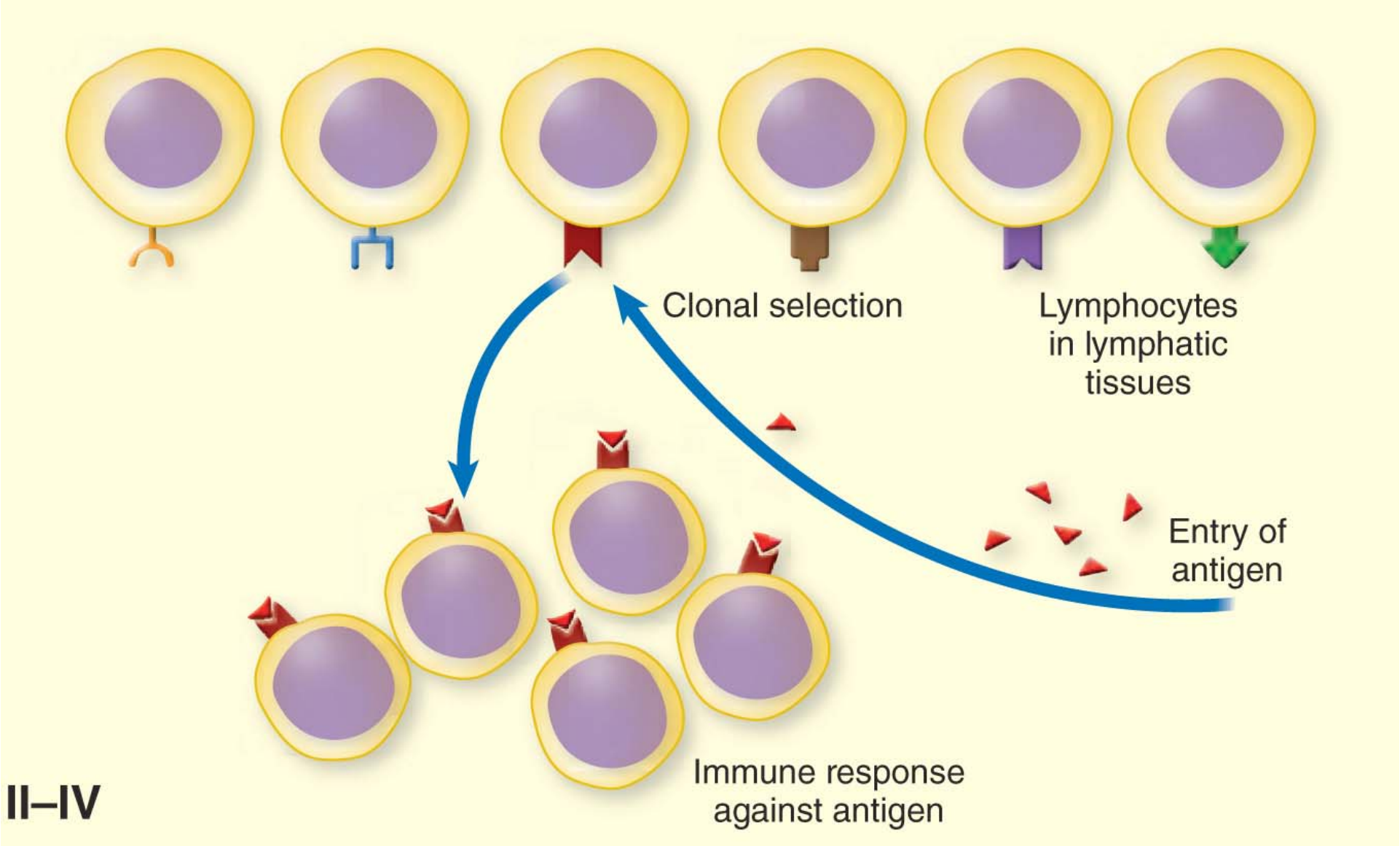
- Generally speaking - B cell response goes no further
- Requires a Helper T cell to bind to the B cell"s Antigen-MHCP complex
  - B-cell-T_H-Antigen-MHCP complex then secretes interleukins that activate B cell
  - Results in clonal selection
    - Some B cells become plasma cells / produce antibodies
    - 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



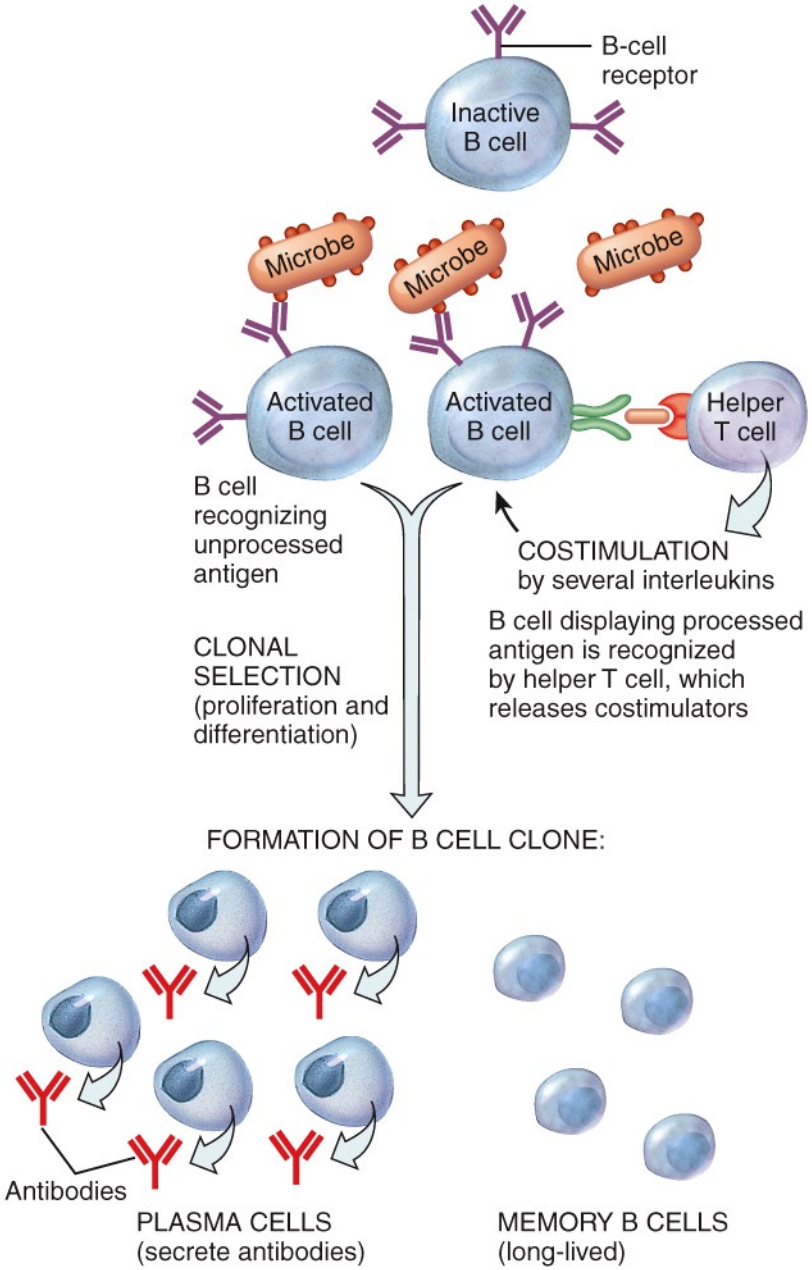
Activation of B Cells

This is the recognize phase

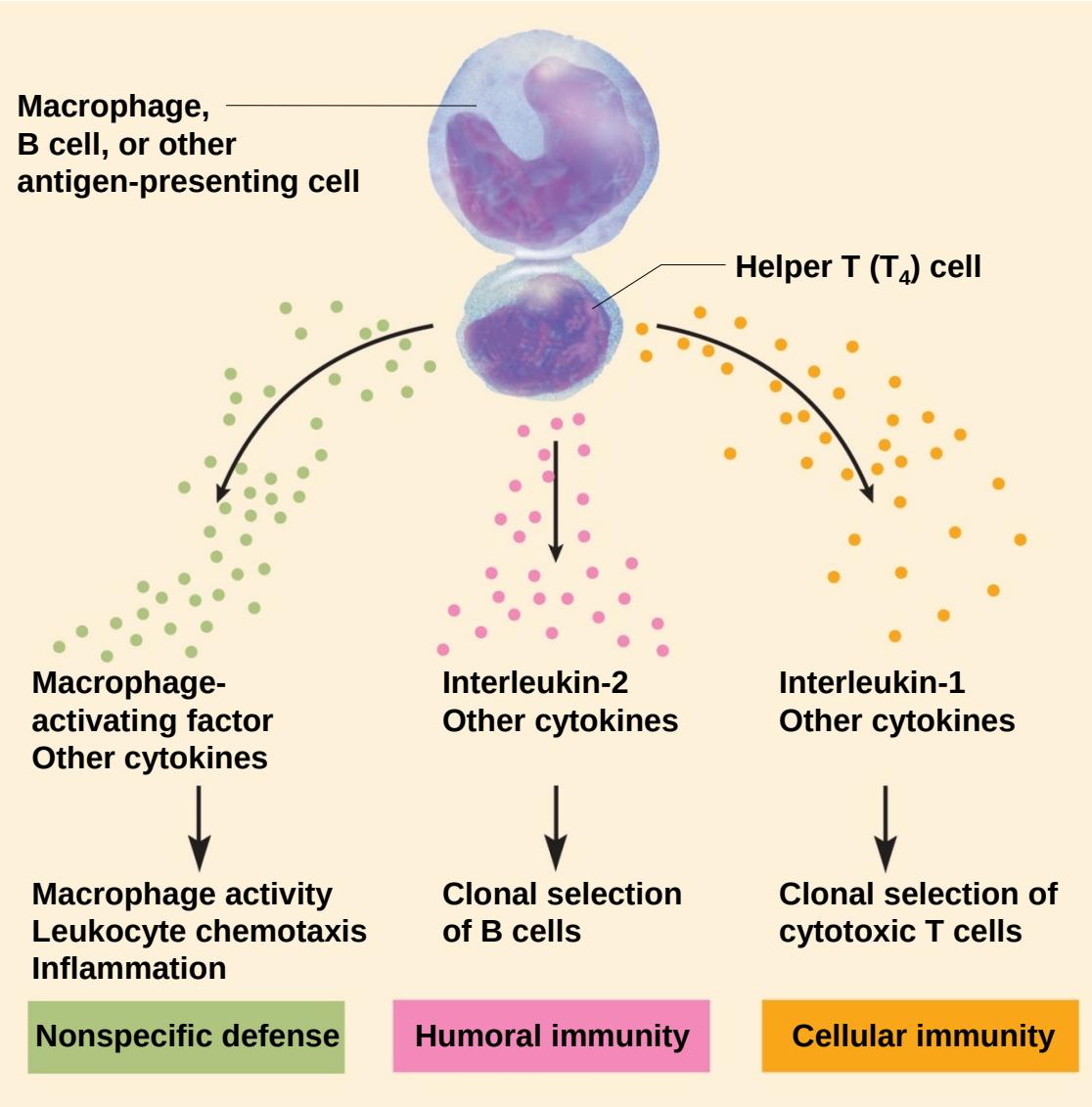
If B cells enter clonal selection without the Helper T cells (T cell independent) then…

The B cell activation is less robust without memory

T cell dependent uses Helper T cell costimulation // stronger response and memory.



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!

How Do We Classify Immunity?

1. Is the immunity acquired by either a natural or artificial process?

2. Is the immunity acquired by either an active or passive process?

(There are four possibilities)

What is the meaning of natural and artificial?

- Natural
  - Stimulus activates immune response in an individual
  - Acquired through normal human experience
  - Production of one's own antibodies or T cells
- Artificial

What is the meaning of active and passive?

- Active
  - Host will use their immune cells to make antibodies and/or Tc
- Passive
  - Host receives antibodies from another source
  - Antibodies received from donor across membrane // E.g. fetus acquires antibodies from mother through placenta or from mother's milk through breastfeeding
  - Antibodies received from injection of serum

What are the four types of acquired immunity?

- Natural active immunity
  - Pathogen enters host and stimulates B and T cells
  - production of one's own antibodies and/or T cells
  - booster shots – may need periodic immunizations to stimulate immune memory to maintain a high level of protection
- Natural passive immunity
  - Antibodies "naturally" produced by mother then "transferred" to newborn
  - Mother's IgG small enough to cross placenta and enter fetus
  - Mother's IgG and IgA cross tissue to enter breast milk

What are the four types of acquired immunity?

- Artificial active immunity
  - Vaccinations
  - Inject host with attenuated virus, toxin, or weakened bacteria
  - Stimulates host immune system to make memory T and memory B cells
- Artificial passive immunity
  - Harvest antibodies from another source
  - Inject antibodies into host to render pathogen harmless

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Table 13.10 The Four Types of Acquired Immunity

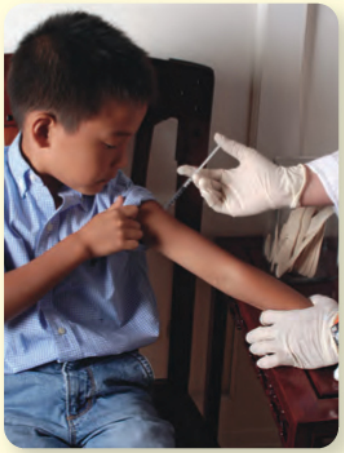
Natural Immunity is acquired through the normal life experiences of a human and is not induced through medical means.

Active
After recovering from infectious disease, a person will generally be actively resistant to reinfection for a period that varies according to the disease. In the case of childhood viral infections such as measles, mumps, and rubella, this natural active stimulus provides nearly lifelong immunity. Other diseases result in a less extended immunity of a few months to years (such as pneumococcal pneumonia and shigellosis), and reinfection is possible. Even a subclinical infection can stimulate natural active immunity. This probably accounts for the fact that some people are immune to an infectious agent without ever having been noticeably infected with or vaccinated for it.

Passive
Natural, passively acquired immunity occurs only as a result of the prenatal and postnatal mother-child relationship. During fetal life, IgG antibodies circulating in the maternal bloodstream are small enough to pass or be actively transported across the placenta. This natural mechanism provides an infant with a mixture of many maternal antibodies that can protect it for the first few critical months outside the womb, while its own immune system is gradually developing active immunity. Depending on the microbe, passive protection lasts anywhere from a few months to a year.

Another source of natural passive immunity comes to the baby by way of the mother's milk. Although the human infant acquires 99% of natural passive immunity in utero and only about 1% through nursing, the milk-borne antibodies provide a special type of intestinal protection that is not available from transplacental antibodies.

Artificial Immunity is that produced purposefully through medical procedures.

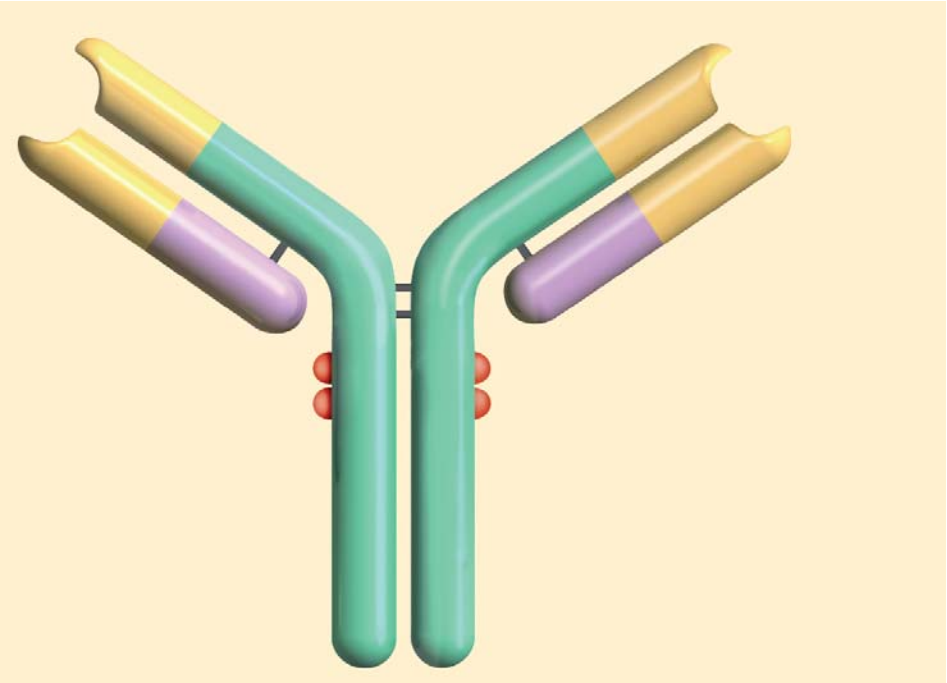


Active
Vaccination exposes a person to a specially prepared microbial (antigenic) stimulus, which then triggers the immune system to produce antibodies and lymphocytes to protect the person upon future exposure to that microbe. As with natural active immunity, the degree and length of protection vary.

Passive
Passive immunotherapy involves a preparation that contains specific antibodies against a particular infectious agent. Pooled human serum from donor blood (gamma globulin) and immune serum globulins containing high quantities of antibodies are frequently used.

(girl): © Florasco Productions/Corbis RF; (mother): © Ingram Publishing/Superstock (RF); (boy): © The McGraw-Hill Companies

Antibody
Structure & Function



immunoglobulin (Ig) – an antibody is a defensive gamma globulin (i.e. protein) found in the blood plasma, tissue fluids, body secretions, and some leukocyte membranes

(but not normally inside cells!)

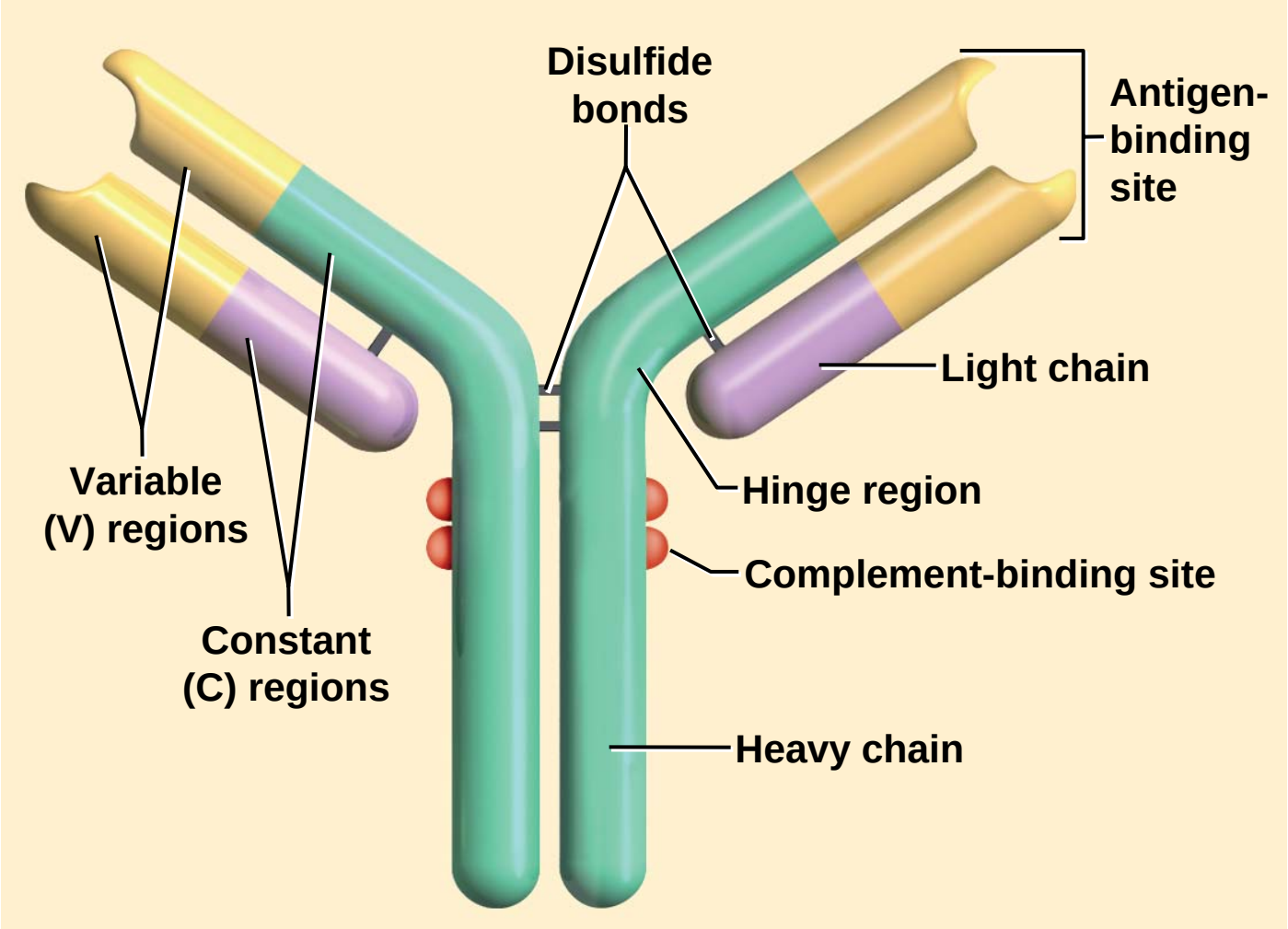
Antibodies (1 of 2)

- **antibody monomer** – the basic structural unit of an antibody
  - composed of four polypeptide chains linked by **disulfide (-S-S-) bonds**
  - two larger **heavy chains** about 400 amino acids long // heavy chains have a hinge region where antibody is bent
  - two **light chains** about half as long
  - **variable (V) region** in all four chains // gives the antibody its uniqueness

Antibodies (2 of 2)

- **antigen binding site** – formed from the V regions of the heavy and light chain on each arm // attaches to the epitope of an antigen molecule
  - Each monomer can bind to two epitopes
  - Epitopes can be on same cell or on two different cells (e.g. aglutination)
- **constant (C) region** has the same amino acid sequence within one person and determines mechanism of antibody action

Antibody Structure



Antibody Structure

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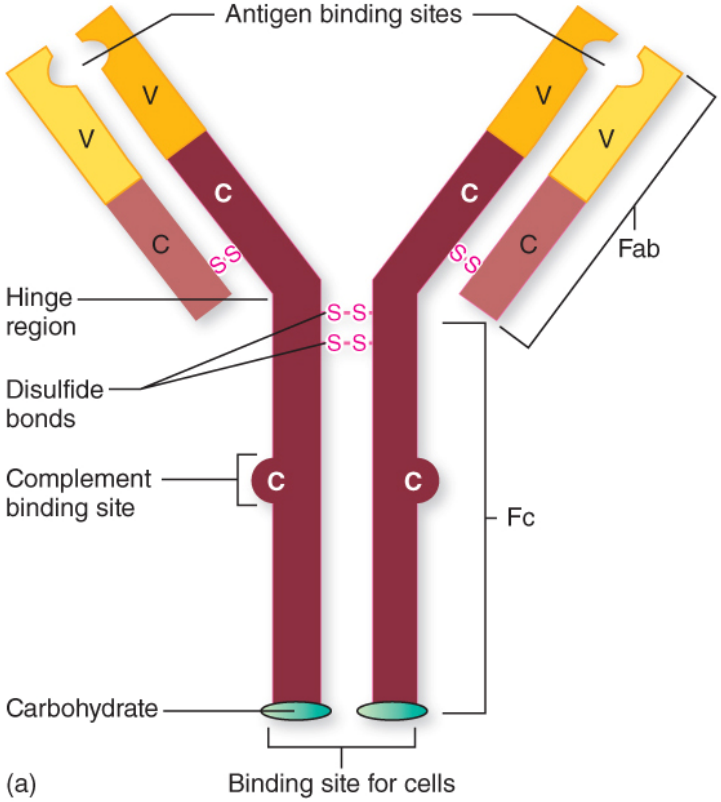
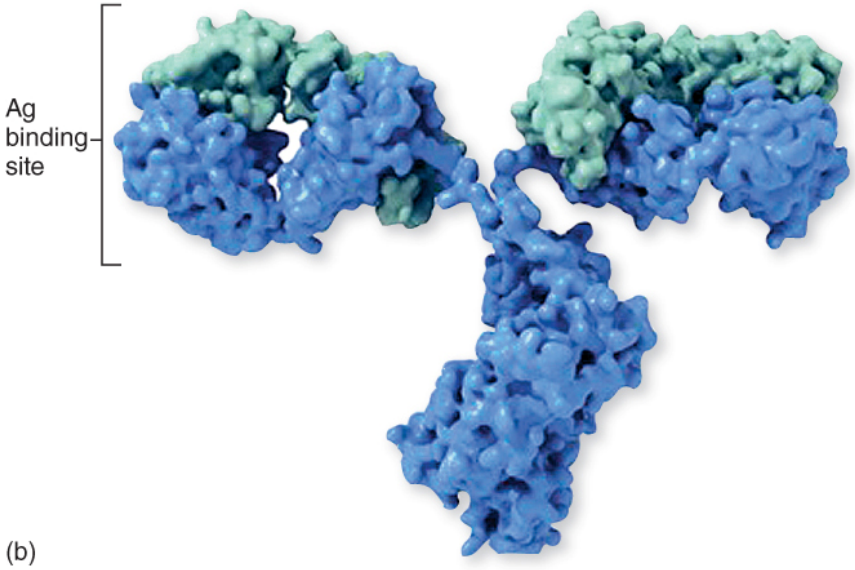


(a)



(b)

(b): U.S. National Library of Medicine

Five Classes of Antibodies

- Remember **"MADGE"** (IgM – IgA – IgD – IgG – IgE)
  - Note: a single plasma cell has the capacity to produce all the different classes of antibodies
  - Single plasma cells makes 2,000 antibodies per second for 7 days – clonal selection produces thousands of active plasma cells
  - A single plasma cells may start to produce IgM antibodies and then switch to produce IgG later in the infection

Five Classes of Antibodies

- Immunoglobulin M (IgM)

- pentamer in plasma and lymph
- secreted in primary immune response
- Agglutination of RBCs
- Able to activate complement ion

Five Classes of Antibodies

– **Immunoglobulin A (IgA)**

- Secretory dimer in mucus, saliva, tears, milk, and intestinal secretions
- prevents pathogen adherence to epithelia and penetrating underlying tissues
- provides passive immunity to newborns
- monomer in plasma

Five Classes of Antibodies

– **Immunoglobulin (IgD)**

- Monomer
- B cell membrane antigen receptor
- thought to function in B cell activation by antigens

Five Classes of Antibodies

– **Immunoglobulin (IgG)**

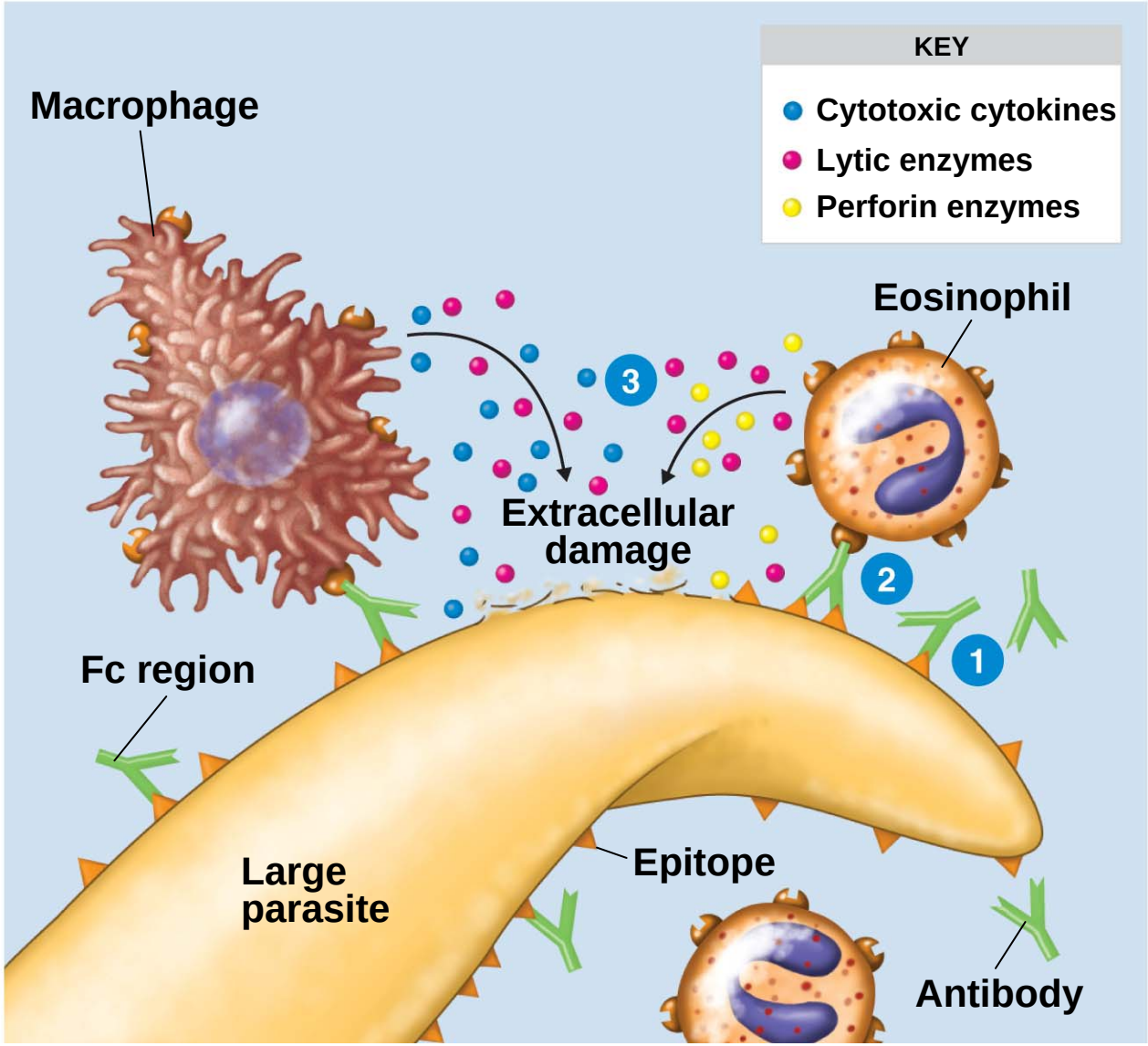
- Monomer
- constitutes 80% of circulating antibodies
- crosses placenta to fetus
- secreted in secondary immune response
- Able to activate complement

Five Classes of Antibodies

– **Immunoglobulin (IgE)**

- Monomer
- <u>transmembrane protein on basophils and mast cells</u>
- stimulates release of histamine and other chemical mediators of inflammation and allergy // produces immediate hypersensitivity reactions
- <u>binds to antigen on parasites</u> // attracts eosinophils to parasitic infections // result in respiratory burst to kill parasite

Antibody-dependent cell-mediated cytotoxicity (ADCC).



(a) **Organisms, such as many parasites, that are too large for ingestion by phagocytic cells must be attacked externally.**

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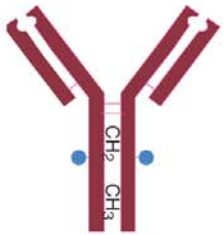
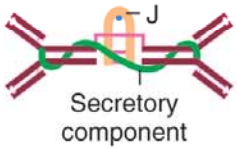
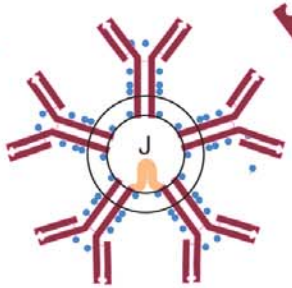
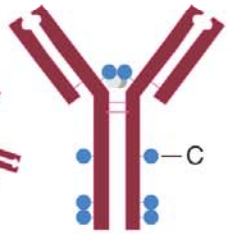
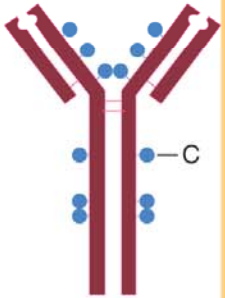
Table 13.8 Characteristics of the Immunoglobulin (Ig) Classes

	Monomer	Dimer, Monomer	Pentamer	Monomer	Monomer
	IgG	IgA	IgM	IgD	IgE
					
Number of Antigen Binding Sites	2	4, 2	10	2	2
Molecular Weight	150,000	170,000–385,000	900,000	180,000	200,000
Percentage of Total Antibody in Serum	80%	13%	6%	1%	0.002%
Average Half-Life in Serum (Days)	23	6	5	3	2.5
Crosses Placenta?	Yes	No	No	No	No
Fixes Complement?	Yes	No	Yes	No	No
Fc Binds to	Phagocytes				Mast cells and basophils
Biological Function	Monomer produced by plasma cells in a primary response and by memory cells responding the second time to a given antigenic stimulus; most prevalent antibody circulating throughout the tissue fluids and blood; neutralizes toxins, opsonizes, fixes complement	Dimer is secretory antibody on mucous membranes; monomer in small quantities in blood	Produced at first response to antigen; can serve as B-cell receptor	Receptor on B cells; triggering molecule for B-cell activation	Antibody of allergy; worm infections; mediates anaphylaxis, asthma, etc.

What four actions are used by antibodies to defeat pathogens?

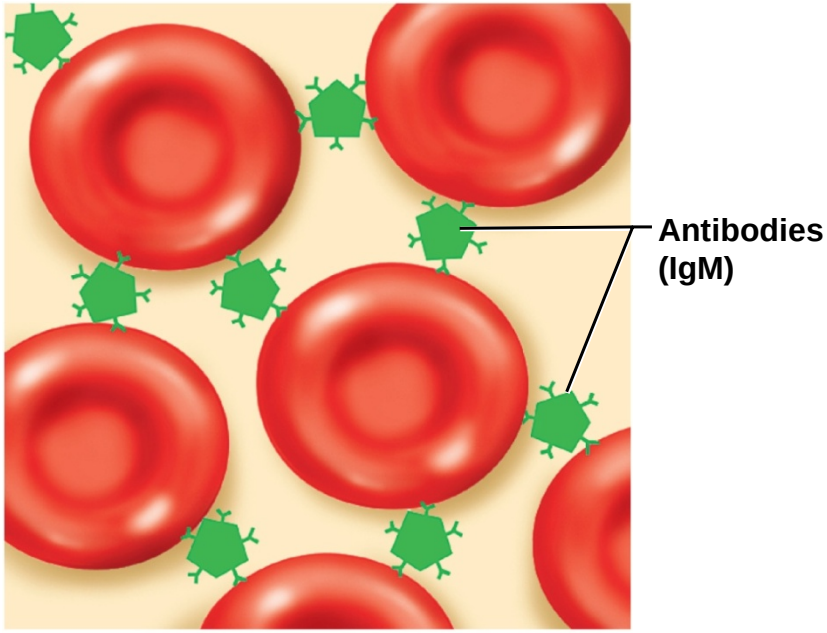
- #1) Neutralization = antibodies mask pathogenic region of antigen
- #2) Complement fixation
  - antigen binds to IgM or IgG, antibody changes shape, initiates complement binding which leads to inflammation, phagocytosis, immune clearance, or cytolysis
  - primary defense against foreign cells, bacteria, and mismatched RBCs

What are the four actions used by antibodies to defeat pathogens?

- #3) Agglutination // antibody has 2-10 binding sites
  - binds to multiple enemy cells immobilizing them from spreading

- #4) Precipitation // antibody binds antigen molecules (not cells)
  - creates antigen-antibody complex that precipitates // potentially dangerous because falls in between epithelial cells //
  - IgG and IgM able to initiate complement within membranes which may destroy surrounding tissue
  - Ag-Ab complex normally phagocytized by eosinophils or immune clearance mediated by C3b-RBC-Ag-Ab complex carried to spleen's macrophage

Agglutination



(a)

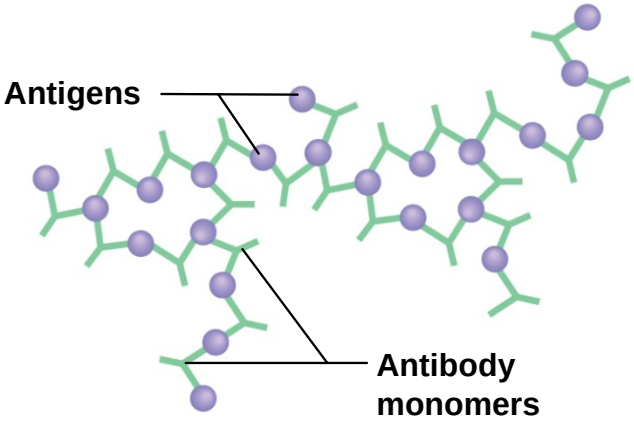


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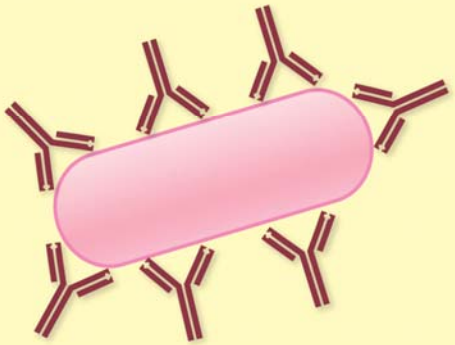
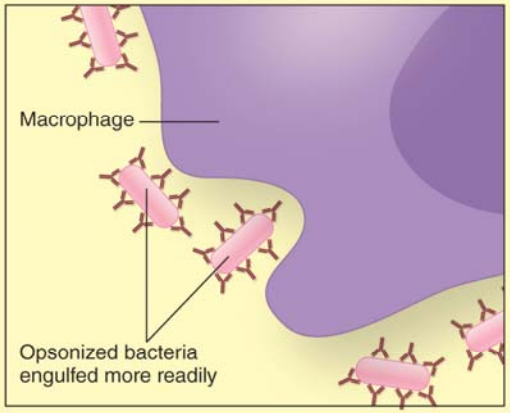
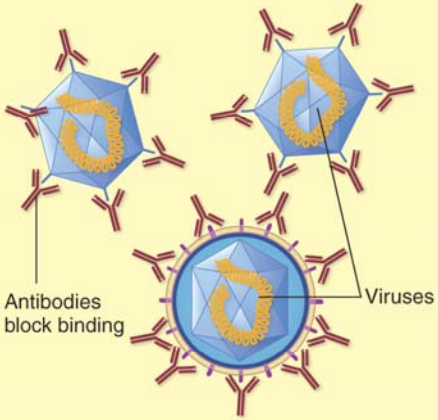
Table 13.7 Summary of Antibody Functions



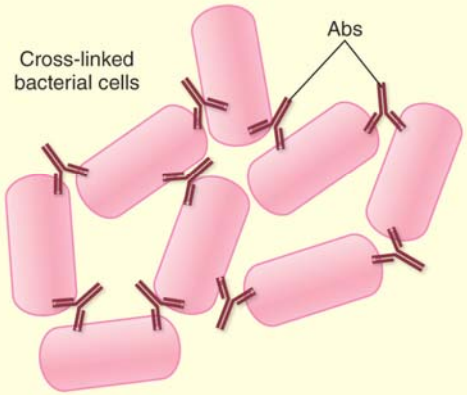
Antibodies coat the surface of a bacterium, preventing its normal function and reproduction in various ways.



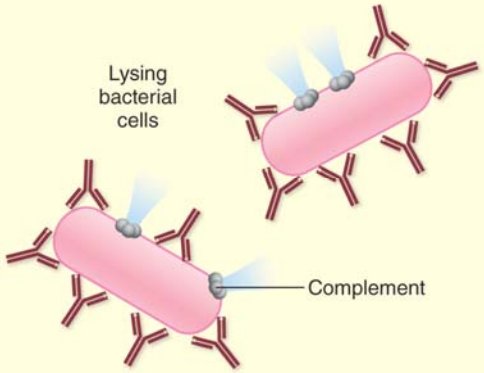
Antibodies called opsonins stimulate **opsonization** (ahp″-son-uh-zaz′-shun), a process that makes microbes more readily recognized by phagocytes, which dispose of them. Opsonization has been likened to putting handles on a slippery object to provide phagocytes a better grip.



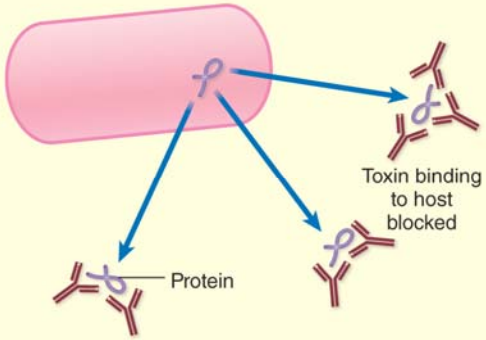
In **neutralization** reactions, antibodies fill the surface receptors on a virus or the active site on a microbial enzyme to prevent it from attaching normally.



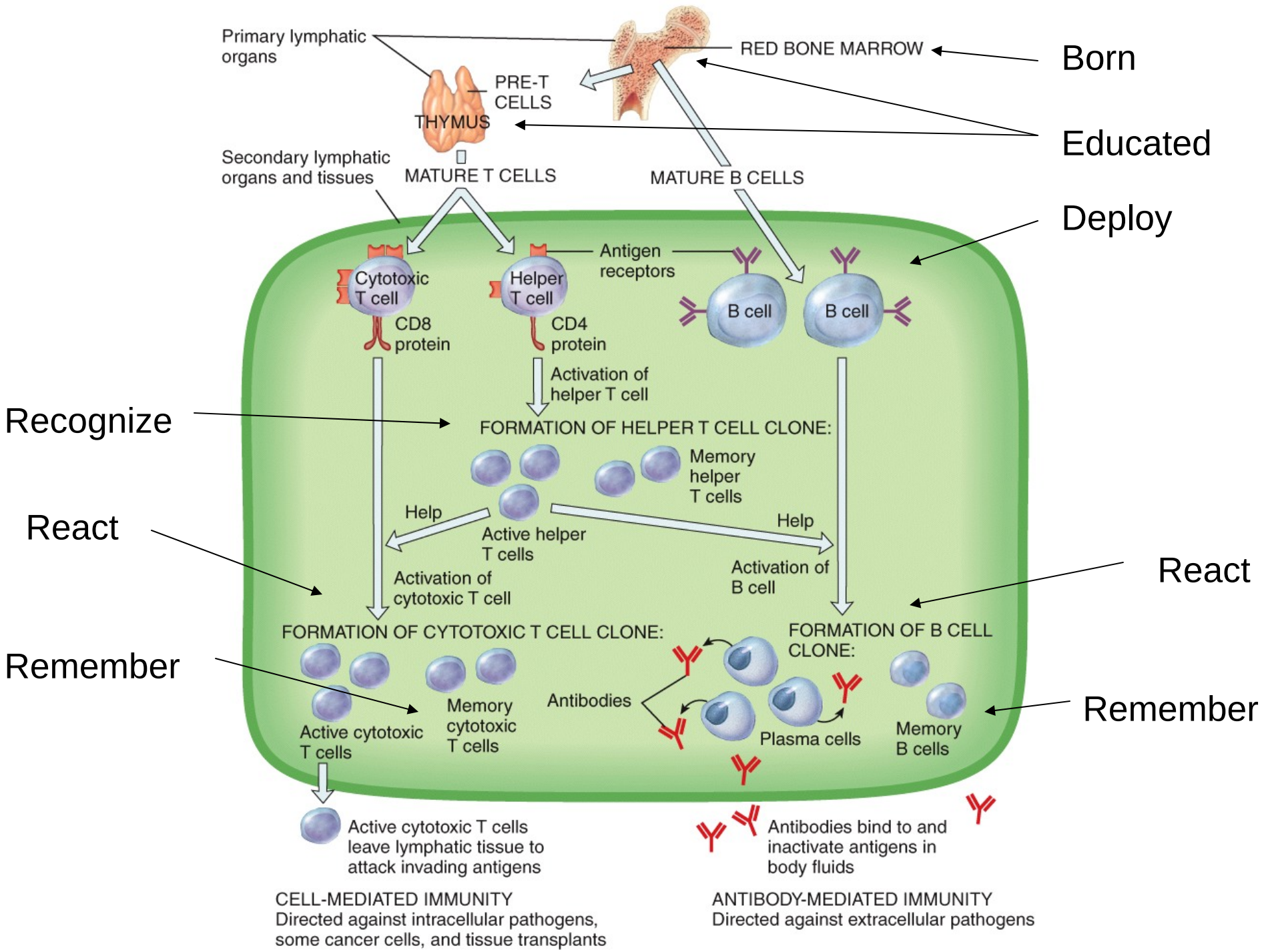
The capacity for antibodies to aggregate, or **agglutinate,** antigens is the consequence of their cross-linking cells or particles into large clumps. Agglutination renders microbes immobile and enhances their phagocytosis. This is a principle behind certain immune tests discussed in chapter 15.



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



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


Primary lymphatic organs
RED BONE MARROW
Born
PRE-T CELLS
THYMUS
Educated
Secondary lymphatic organs and tissues
MATURE T CELLS
MATURE B CELLS
Deploy
Antigen receptors
Cytotoxic T cell
Helper T cell
B cell
B cell
CD8 protein
CD4 protein
Activation of helper T cell
Recognize
FORMATION OF HELPER T CELL CLONE:
Memory helper T cells
Help
Active helper T cells
Help
React
Activation of cytotoxic T cell
Activation of B cell
React
FORMATION OF CYTOTOXIC T CELL CLONE:
FORMATION OF B CELL CLONE:
Remember
Antibodies
Active cytotoxic T cells
Memory cytotoxic T cells
Plasma cells
Memory B cells
Remember
Active cytotoxic T cells leave lymphatic tissue to attack invading antigens
Antibodies bind to and inactivate antigens in body fluids
CELL-MEDIATED IMMUNITY
Directed against intracellular pathogens, some cancer cells, and tissue transplants
ANTIBODY-MEDIATED IMMUNITY
Directed against extracellular pathogens

What is the difference between a primary & secondary humoral response?

- Primary immune response – immune reaction brought about by the first exposure to an antigen
  - appearance of protective antibodies delayed for 3 to 6 days while naïve B cells multiply and differentiate into plasma cells
  - as plasma cells produce antibodies, the **antibody titer** (level in the blood plasma) rises
    - IgM appears first, peaks in about 10 days, soon declines
    - IgG levels rise as IgM declines, but IgG titer drops to a low level within a month

What is the difference between a primary & secondary humoral response?

- primary response leaves one with an immune memory of the antigen
  - during clonal selection, some of the clonal becomes memory B cells
  - found mainly in germinal centers of the lymph nodes
  - memory cells able to mount a very quick secondary response // matter of hours not days!

What is secondary humoral immunity?

- Occurs when re-exposed to the same antigen
- plasma cells form within hours
- IgG titer rises sharply and peaks in a few days
- response is so rapid that the antigen has little chance to exert a noticeable effect on the body
- no illness results
- low levels of IgM also secreted and quickly declines
- IgG remain elevated for weeks to years // conferring long lasting protection
- The “memory function” does not last as long in humoral immunity as it does in cellular immunity

Humoral Immunity Responses

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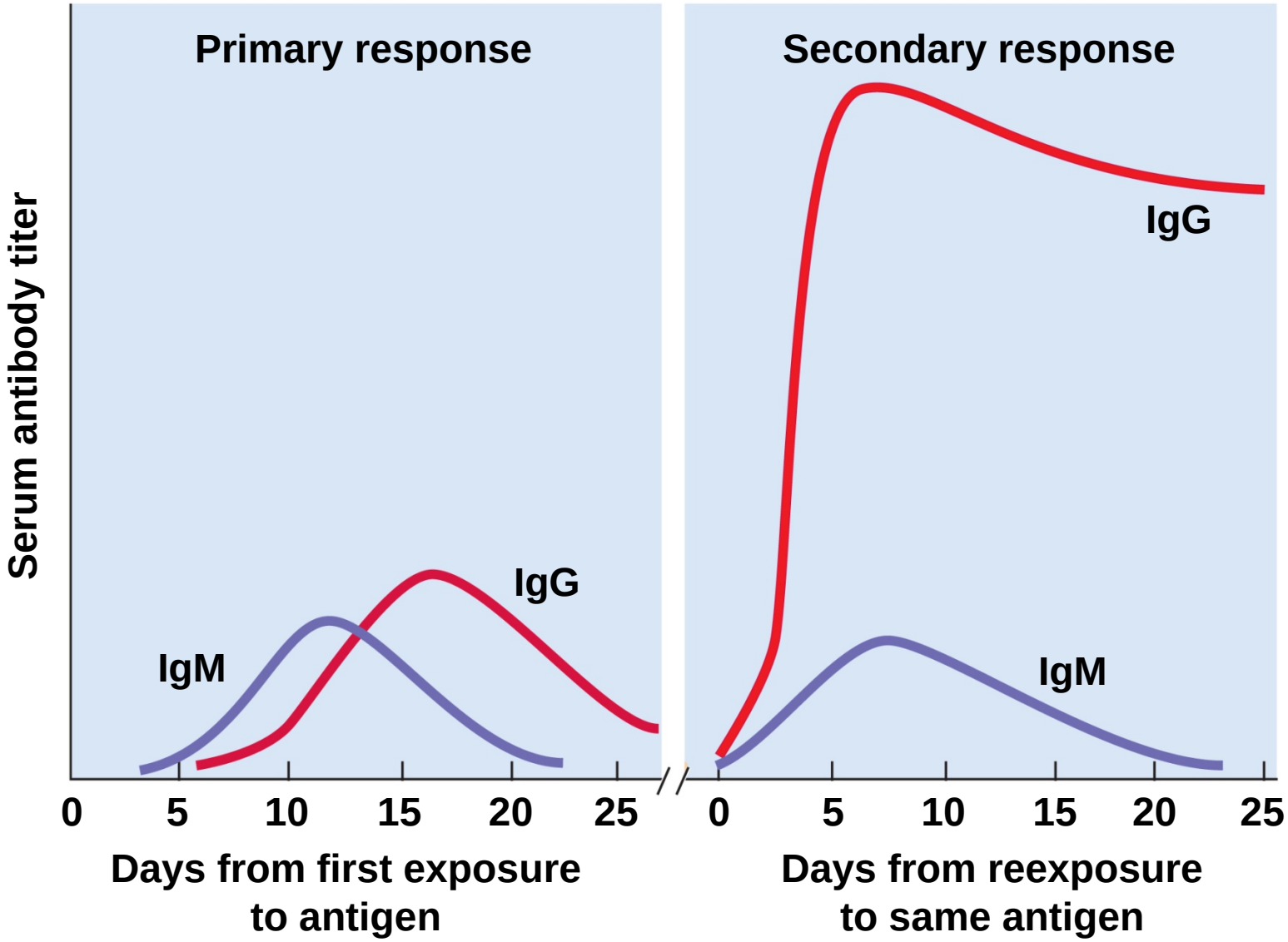

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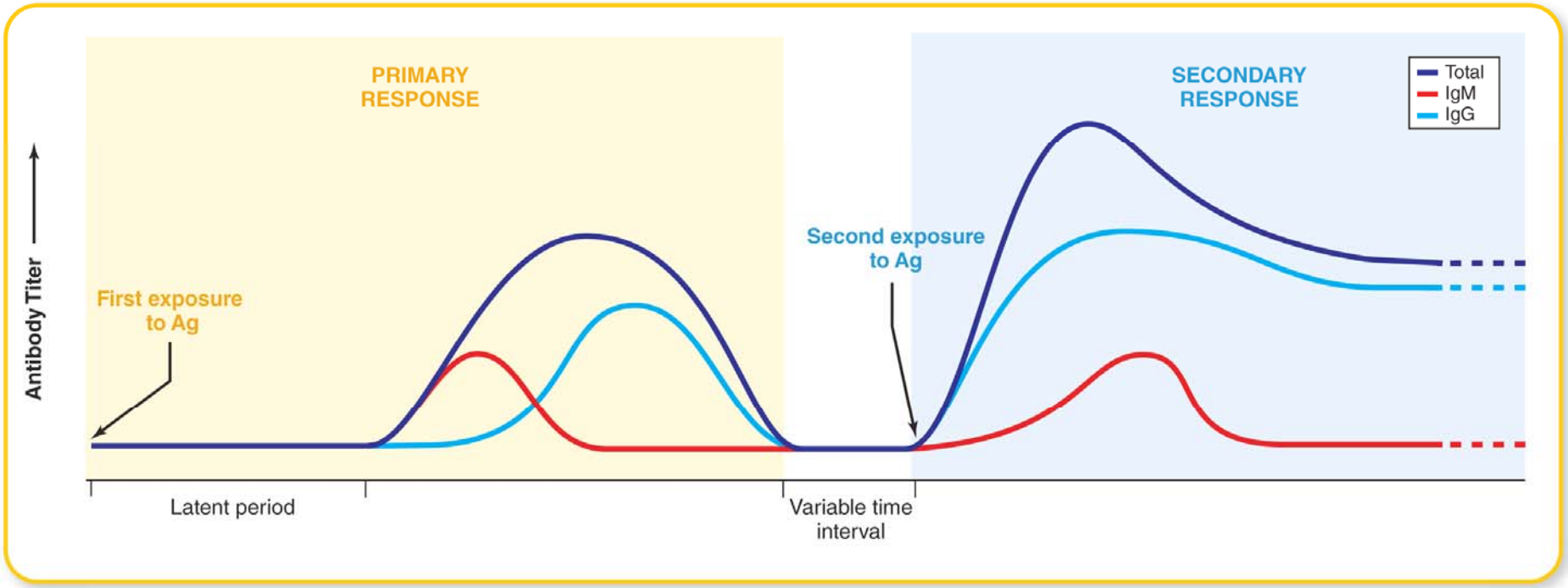
Table 13.9 Primary and Secondary Response to Antigens



Upon the first exposure to an antigen, the system undergoes a **primary response**. The earliest part of this response, the *latent period*, is marked by a lack of antibodies for that antigen, but much activity is occurring. During this time, the antigen is being concentrated in lymphoid tissue and is being processed by the correct clones of B lymphocytes. As plasma cells synthesize antibodies, the serum titer increases to a certain plateau and then tapers off to a low level over a few weeks or months. Early in the primary response, most of the antibodies are the IgM type, which is the first class to be secreted by plasma cells. Later, the class of the antibodies (but not their specificity) is switched to IgG or some other class (IgA or IgE). After the initial response, there is no activity, but memory cells of the same specificity are seeded throughout the lymphatic system.

When the immune system is exposed again to the same immunogen within weeks, months, or even years, a **secondary response** occurs. The rate of antibody synthesis, the peak titer, and the length of antibody persistence are greatly increased over the primary response. The speed and intensity seen in this response are attributable to the memory B cells that were formed during the primary response. The secondary response is also called the **anamnestic response.** The advantage of this response is evident: It provides a quick and potent strike against subsequent exposures to infectious agents.

How may the adaptive immunity response vary between different people?

- Immune responses may be:
  - Just right / maintains healthy state
  - Too vigorous = hypersensitivity (e.g. Anaphylactic shock)
  - Too weak = immunodeficiency disease (e.g. AIDS)
  - Misdirected against wrong target cells = autoimmune diseases (i.e. Type 1 diabetes)

What is hypersensitivity?

- **Hypersensitivity** – an excessive immune reaction against antigens that most people tolerate

- Hypersensitivity includes:
  - **alloimmunity -** reaction to transplanted tissue from another person
  - **autoimmunity -** abnormal reactions to one's own tissues
  - **allergies** – reactions to environmental antigens (**allergens**)
    - dust, mold, pollen, vaccines, bee and wasp venom, poison ivy and other plants, foods such as nuts, milk, eggs, and shellfish, drugs such as penicillin, tetracycline, and insulin

Four Different Types of Hypersensitivity

- Four kinds of hypersensitivity based on the type of immune agents involved (antibodies or T cells) and response to antigen
  - Type I acute (immediate) hypersensitivity /// very rapid response
  - Type II - sub-acute /// slower onset (1 – 3 hours after exposure /// last longer – 10 to 15 hrs)
  - Type III - sub-acute /// slower onset (1 – 3 hours after exposure /// last longer – 10 to 15 hrs)
  - Type IV - delayed /// Cell mediated response
  - Note: Types I, II, and III are antibody mediated responses

Type I (acute) Hypersensitivity

- characterized by hypotension // vasodilatation
- includes most common allergies
- IgE-mediated reaction that begins within seconds of exposure
- usually subsides within 30 minutes, although it can be severe to fatal
- allergens bind to IgE on the membranes of mast cells
  - stimulate them to secrete histamine and other inflammatory and vasoactive chemicals
  - chemicals trigger glandular secretion, vasodilation, increased capillary permeability, smooth muscle spasms, and other effects

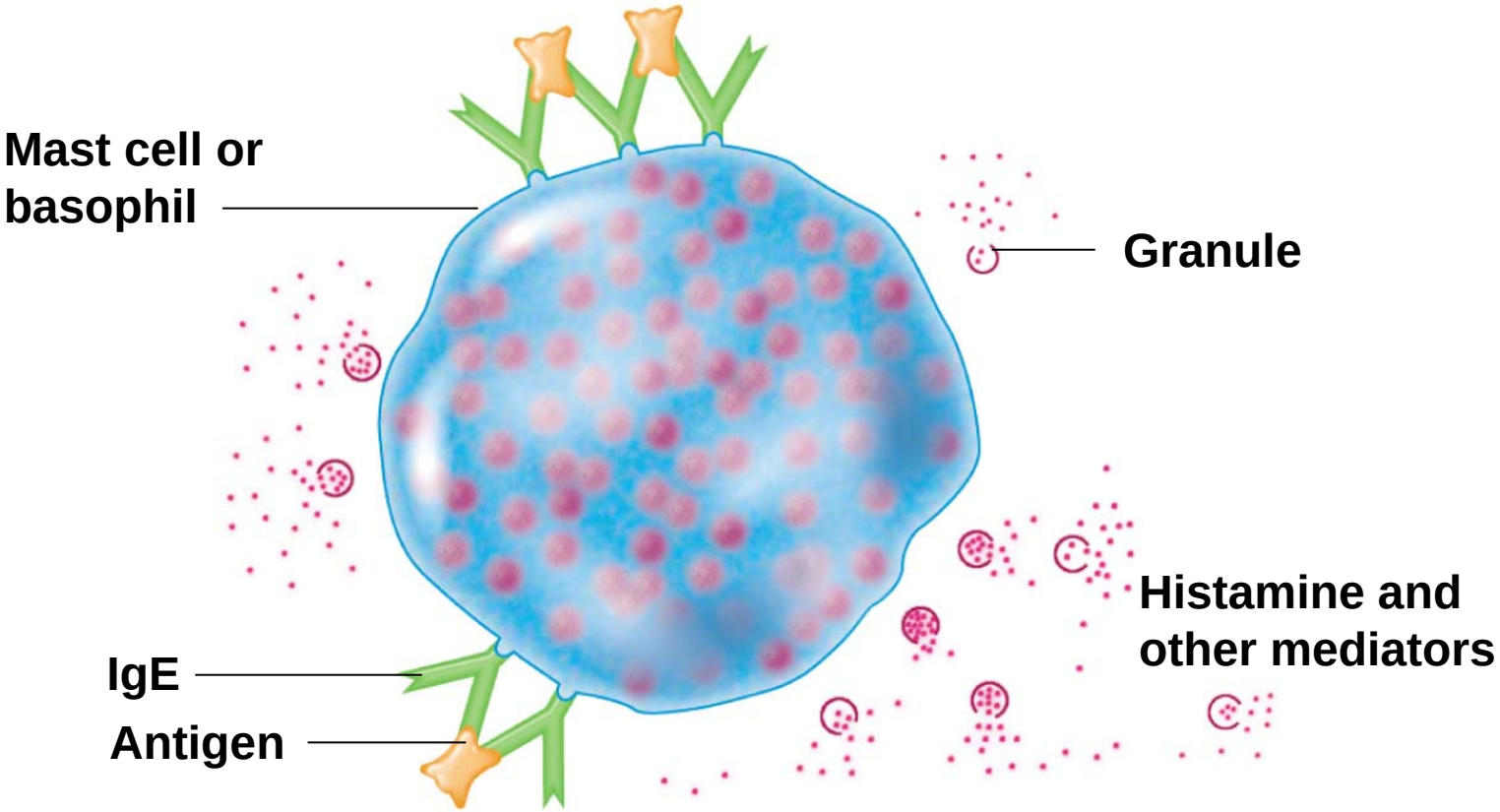
Type I (acute) Hypersensitivity

- clinical signs include:
  - local edema, mucus hypersecretion and congestion, watery eyes, runny nose, hives, and sometimes cramps, diarrhea and vomiting
- examples: food allergies and asthma – local inflammatory reaction to inhaled allergens

Type I (acute) Hypersensitivity

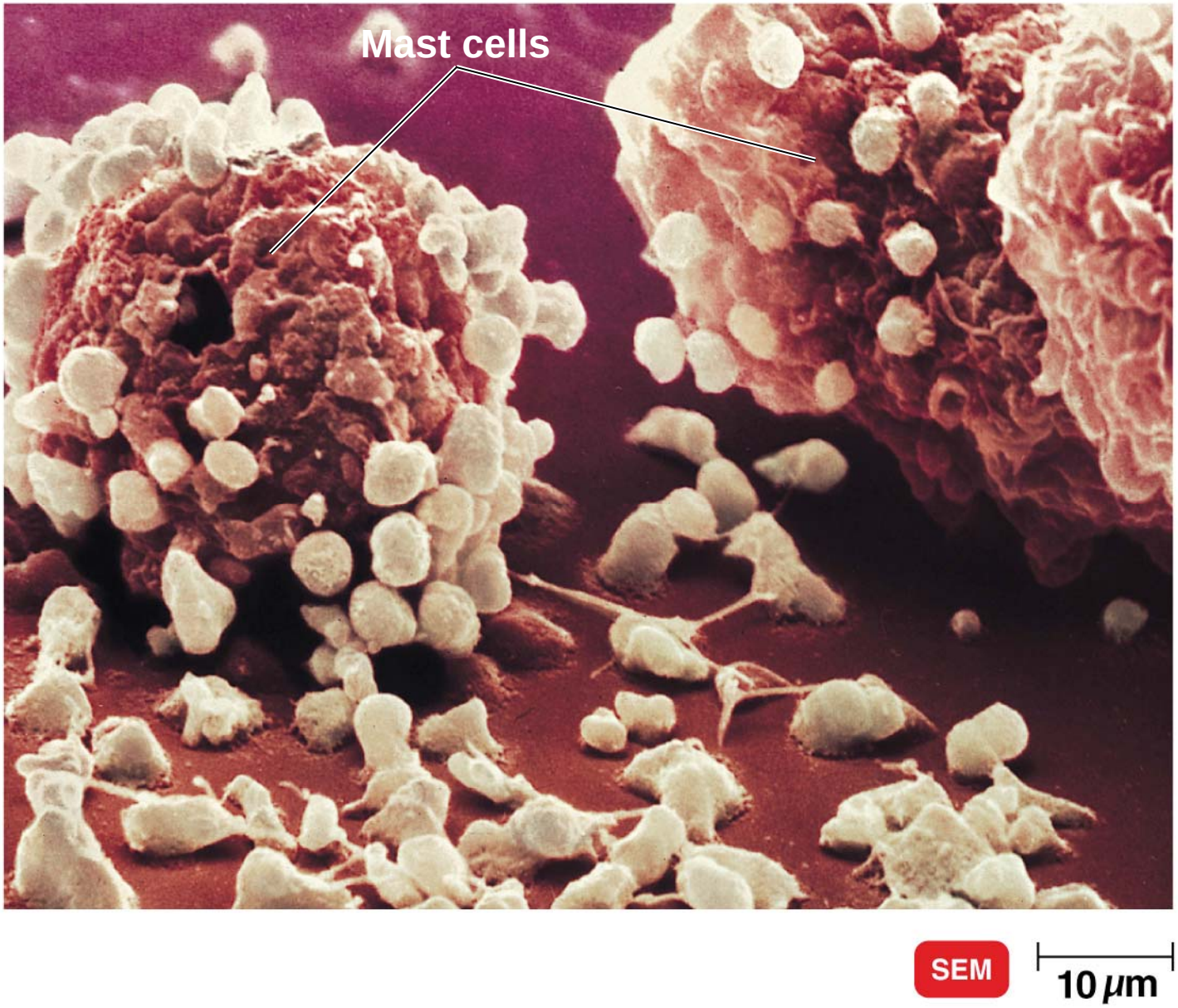
- Anaphylaxis
  - immediate, severe reaction Type I reaction
  - local anaphylaxis can be relieved with antihistamines
- Anaphylactic shock (e.g. in response to a bee sting)
  - severe, widespread acute hypersensitivity that occurs when an allergen is introduced to the bloodstream of an allergic individual
  - characterized by bronchoconstriction, dyspnea (labored breathing), widespread vasodilation, circulatory shock, and sometimes death
  - antihistamines are inadequate by themselves
  - epinephrine relieves the symptoms by dilating bronchioles, increasing cardiac output, and restoring blood pressure
  - fluid therapy and respiratory support are sometimes required

The mechanism of anaphylaxis.



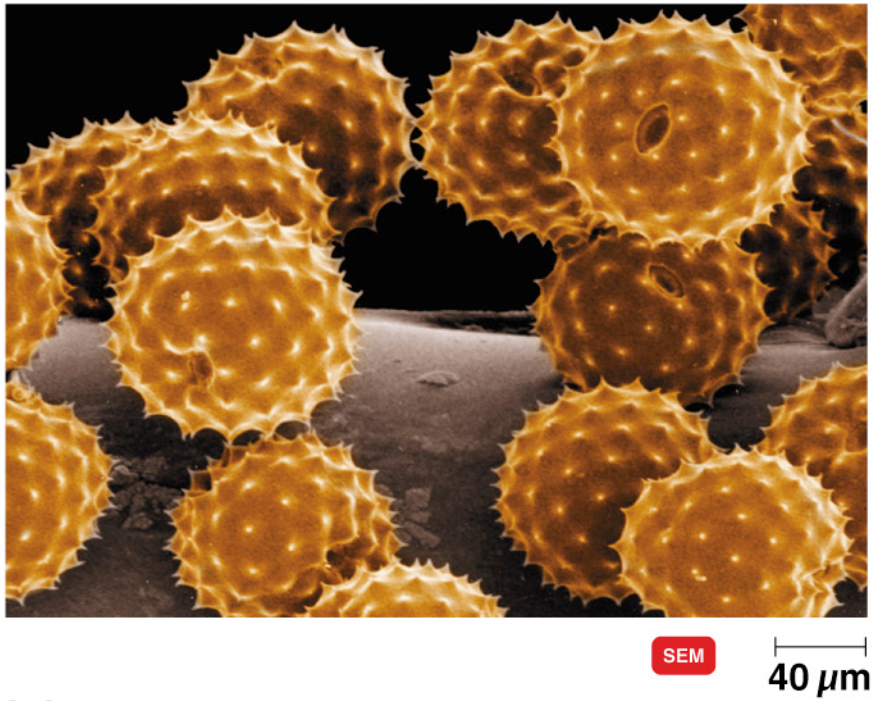
(a) IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.

The mechanism of anaphylaxis.



A degranulated mast cell that has reacted with an antigen and released granules of histamine and other reactive mediators

Localized anaphylaxis.



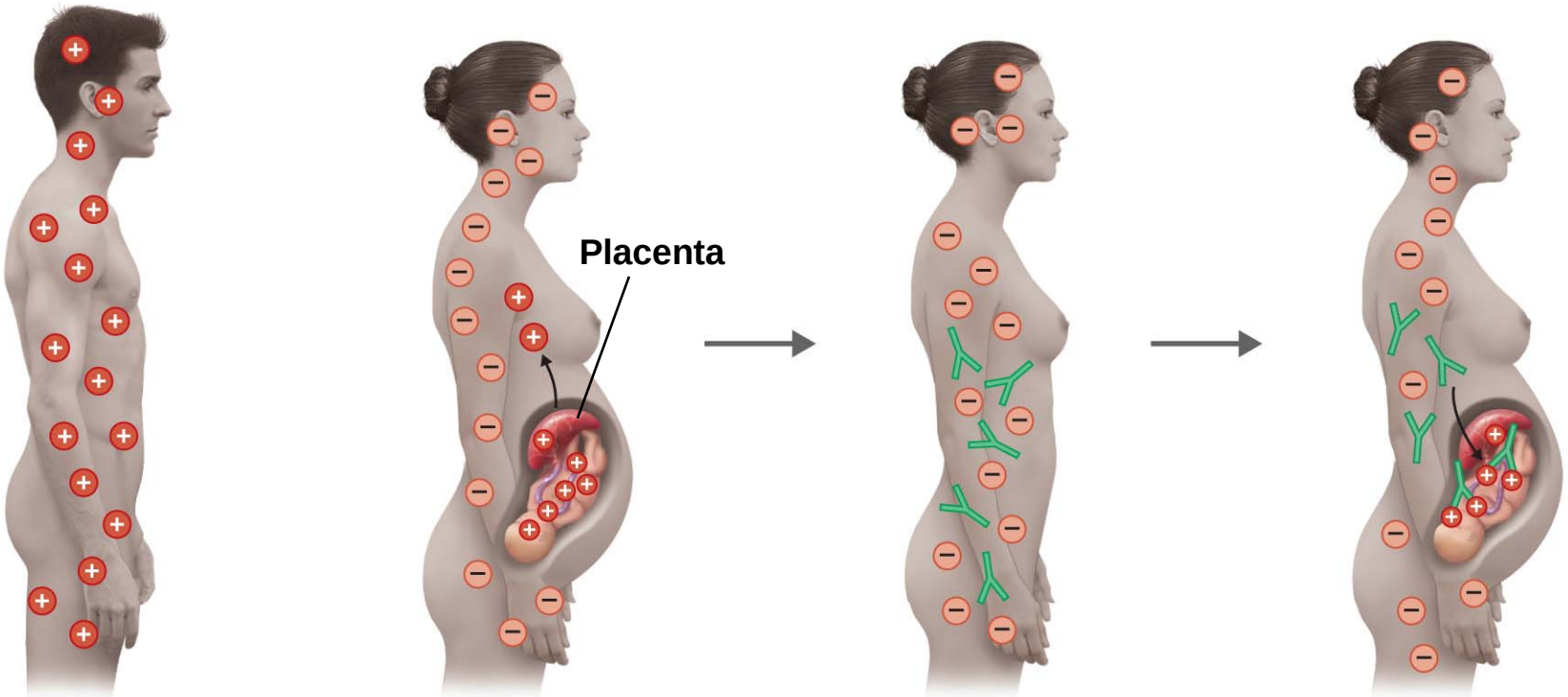
(a) A micrograph of pollen grains

(b) A micrograph of a house mite on fabric

Type II Hypersensitivity (Antibody-Dependent Cytotoxic)

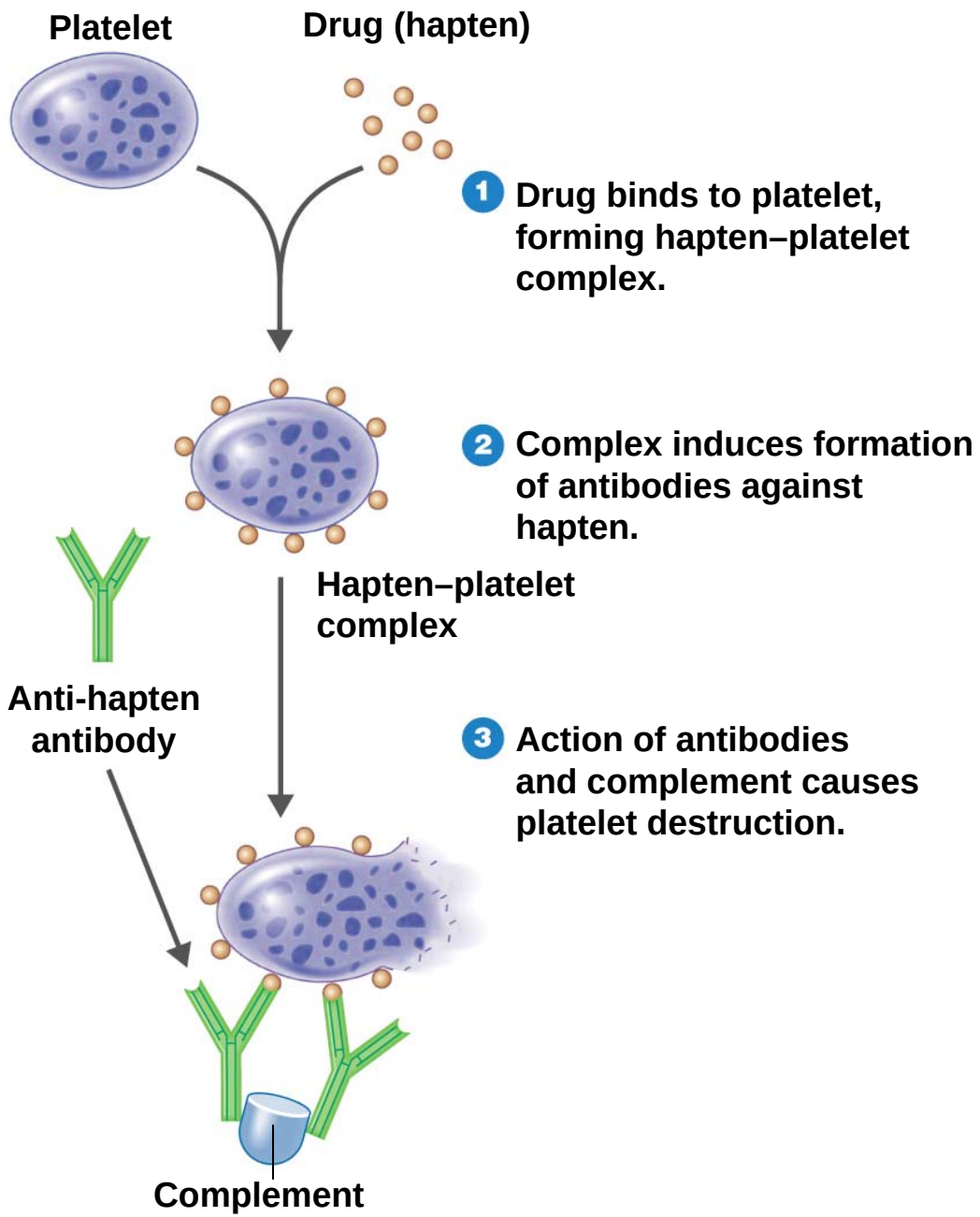
- occurs when IgG or IgM attacks antigens bound to cell surfaces
  - reaction leads to complement activation
  - and lysis or opsonization of the target cell
  - macrophages phagocytize and destroy opsonized platelets, erythrocytes, or other cells
- examples: blood transfusion reaction, pemphigus vulgaris, and some drug reactions

Hemolytic disease of the newborn.



1. Rh^+ father.
2. Rh^- mother carrying her first Rh^+ fetus. Rh antigens from the developing fetus can enter the mother's blood during delivery.
3. In response to the fetal Rh antigens, the mother will produce anti-Rh antibodies.
4. If the woman becomes pregnant with another Rh^+ fetus, her anti-Rh antibodies will cross the placenta and damage fetal red blood cells.

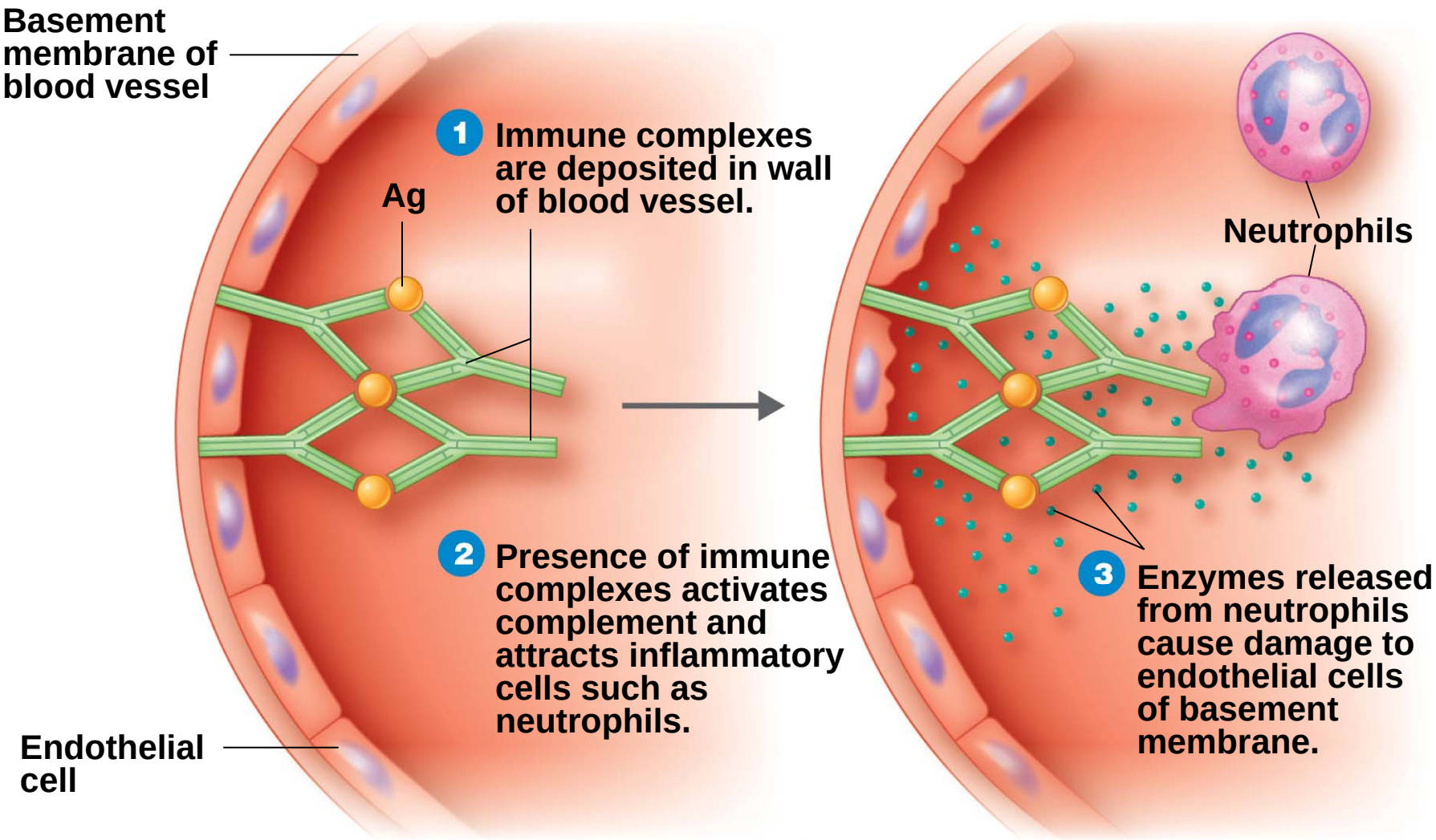
Drug-induced thrombocytopenic purpura.



Type III Hypersensitivity (Immune Complex)

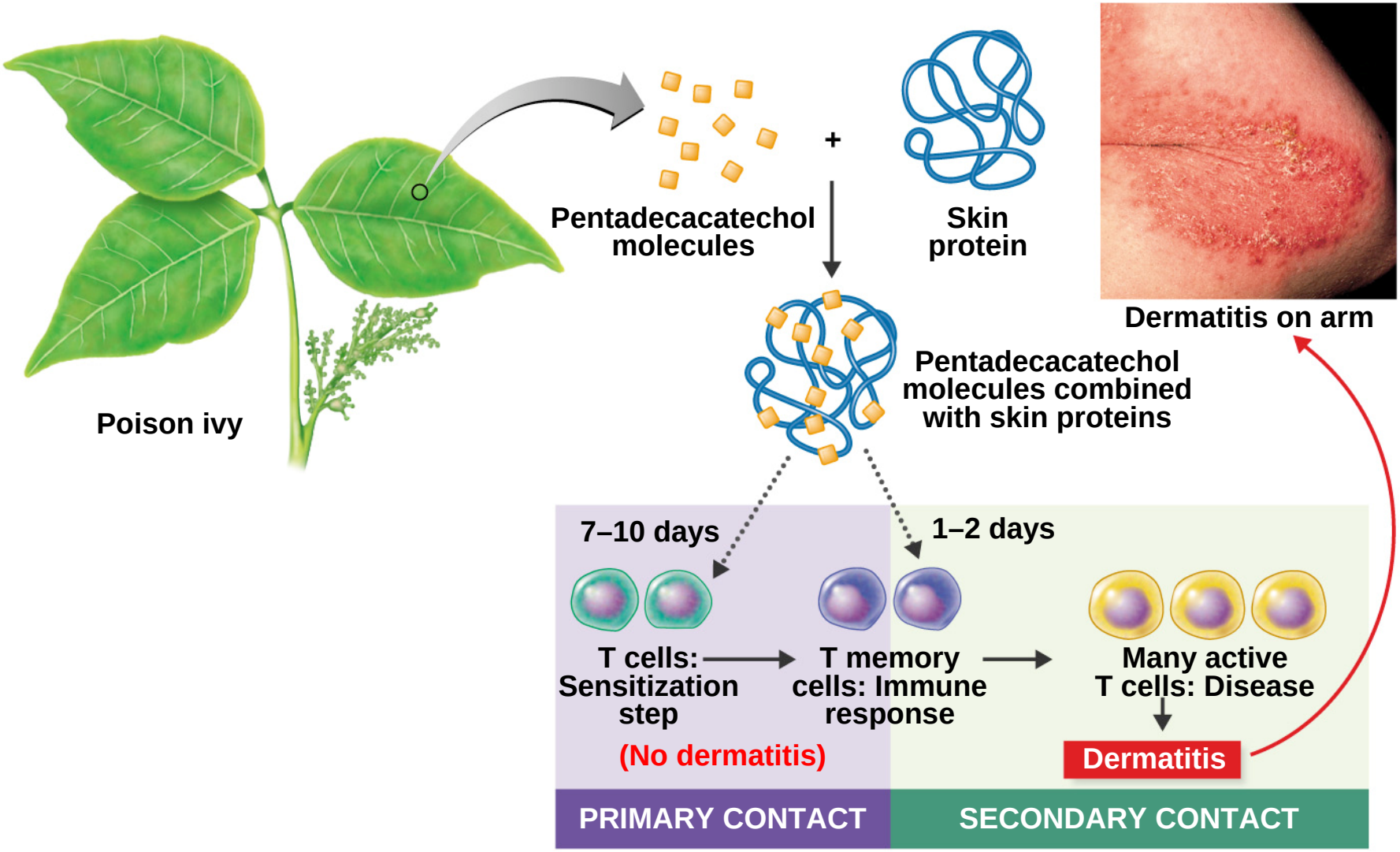
- occurs when IgG or IgM form antigen-antibody complexes with soluble antigen (toxins)
- antibodies and antigens form immune complexes that lodge in basement membranes
  - precipitate beneath endothelium of blood vessels and other tissues
  - at site, activate complement and trigger intense inflammation
  - examples: autoimmune diseases
    - acute glomerulonephritis
    - systemic lupus erythematosus // widespread inflammation of the connective tissues

Immune complex–mediated hypersensitivity.



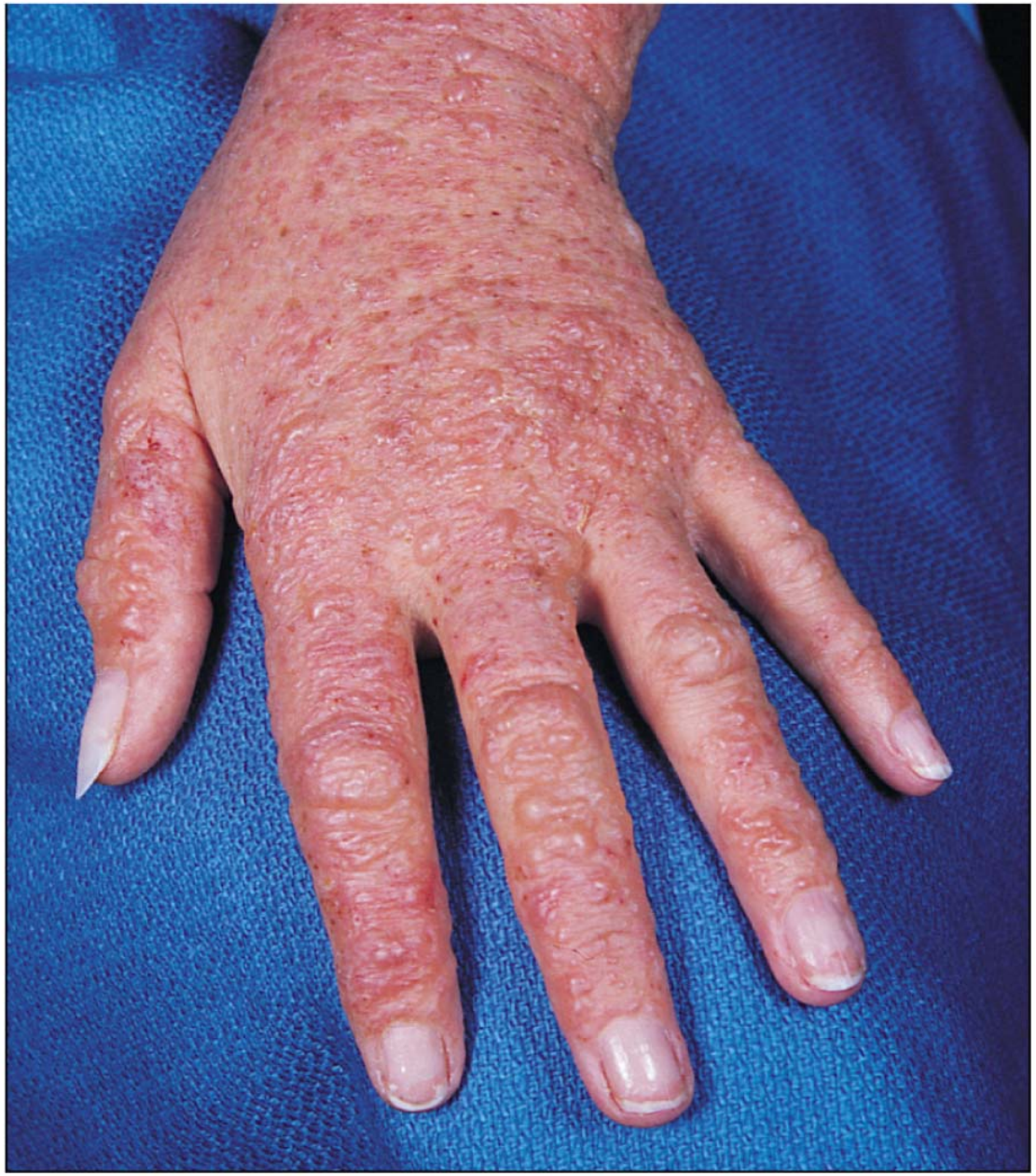
Type IV Hypersensitivity (Delayed)

- Delayed-type hypersensitivities due to T cells
- Cytokines attract macrophages and T_C cells // Initiate tissue damage
- Cell-mediated reaction in which the signs appear 12 to 72 hour after exposure // following 2nd exposure! – see next slide
  - begins with APCs in lymph nodes display antigens to helper T cells
  - TH cells secrete interferon and cytokines that activate cytotoxic T cells and macrophages
  - result is a mixture of nonspecific and Tc immune responses
- examples: haptens in cosmetics, poison ivy, graft rejection, TB skin test, beta cell destruction that causes type I diabetes mellitus

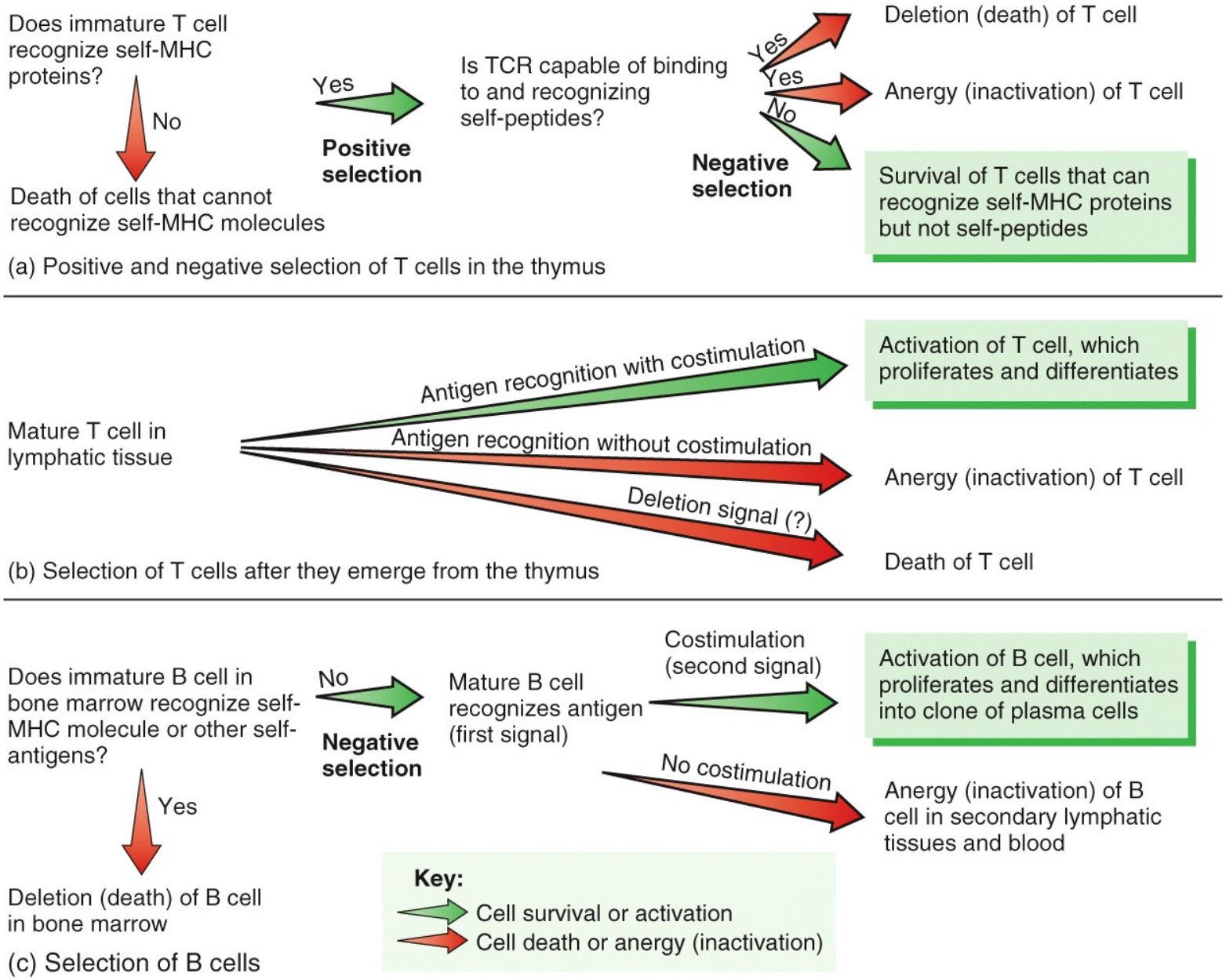


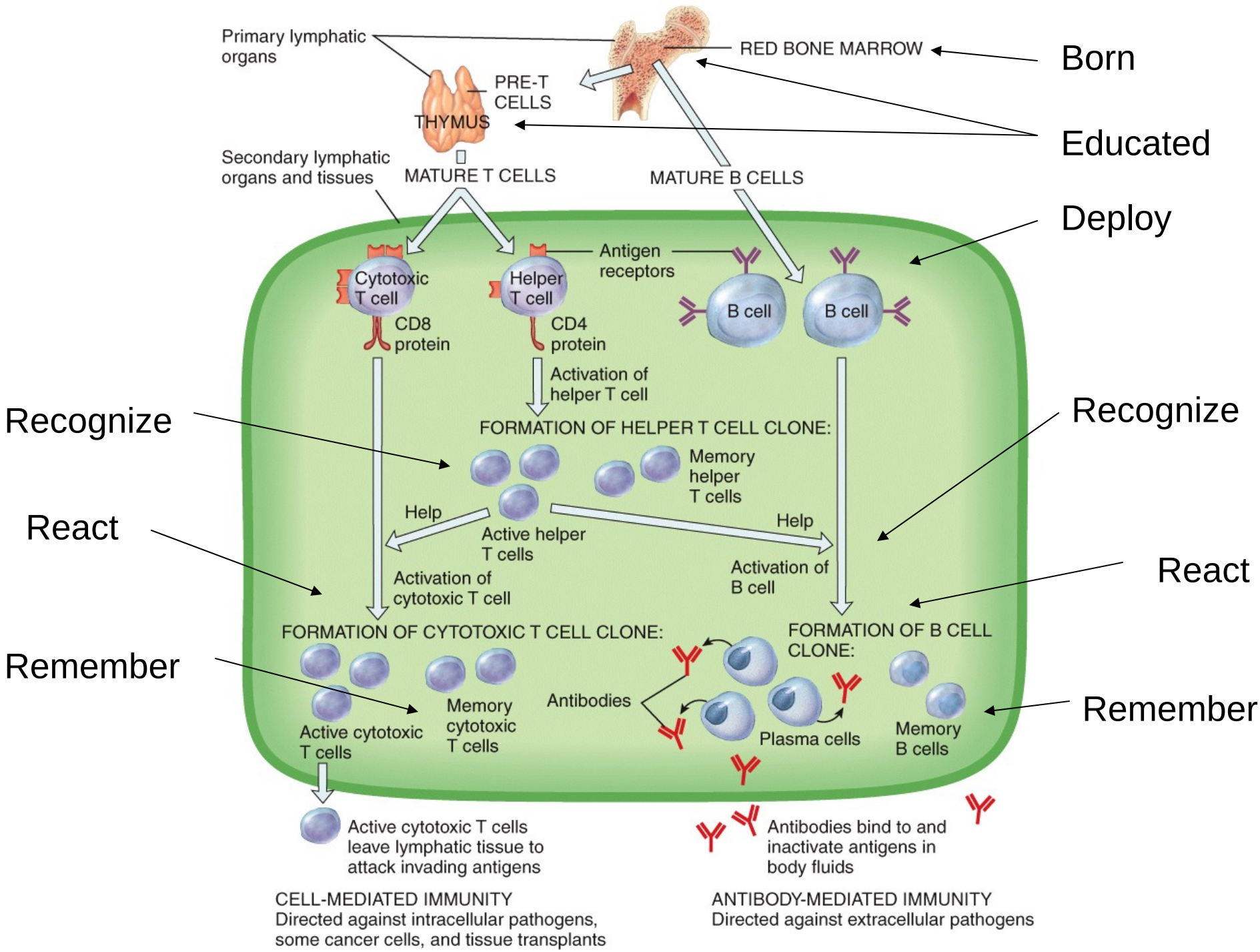
The development of an allergy (allergic contact dermatitis) to catechols from the poison ivy plant.

Allergic contact dermatitis.



Summary of Immunity




Primary lymphatic organs
RED BONE MARROW
Born
PRE-T CELLS
THYMUS
Educated
Secondary lymphatic organs and tissues
MATURE T CELLS
MATURE B CELLS
Deploy
Antigen receptors
Cytotoxic T cell
Helper T cell
B cell
B cell
CD8 protein
CD4 protein
Activation of helper T cell
Recognize
FORMATION OF HELPER T CELL CLONE:
Recognize
Memory helper T cells
Help
Help
React
Active helper T cells
Activation of cytotoxic T cell
Activation of B cell
React
FORMATION OF CYTOTOXIC T CELL CLONE:
FORMATION OF B CELL CLONE:
Remember
Antibodies
Memory cytotoxic T cells
Active cytotoxic T cells
Plasma cells
Memory B cells
Remember
Active cytotoxic T cells leave lymphatic tissue to attack invading antigens
Antibodies bind to and inactivate antigens in body fluids
CELL-MEDIATED IMMUNITY
Directed against intracellular pathogens, some cancer cells, and tissue transplants
ANTIBODY-MEDIATED IMMUNITY
Directed against extracellular pathogens

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

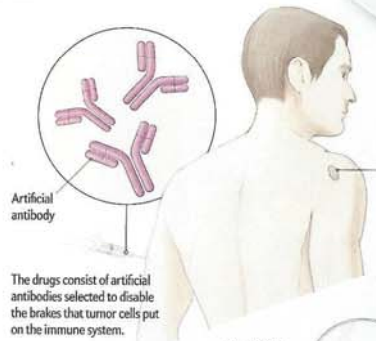
Dendritic cells normally patrol the body looking for bits of proteins called antigens that look unfamiliar. They present the offending antigens to other immune defenders, known as CD4+ and CD8+ T cells. The T cells then attack any other cells that bear the targeted antigen. By choosing antigens found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

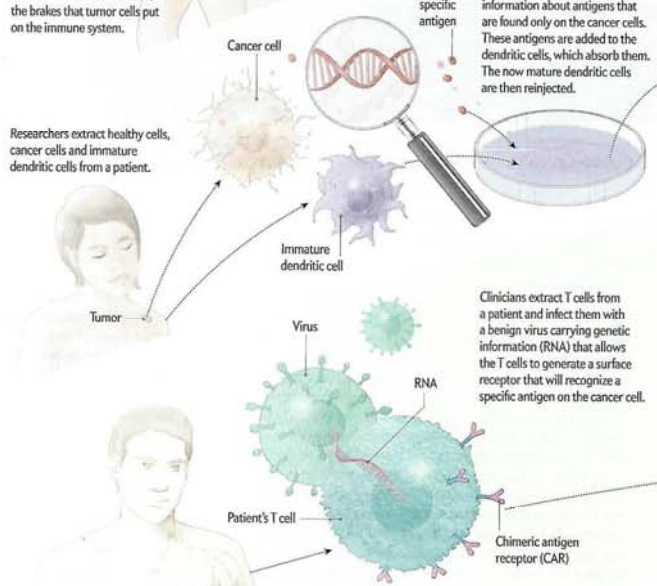
Chimeric antigen receptor (CAR) T cells combine attributes of two types of immune defenders: T cells and B cells. Molecules called receptors found on a CAR-T cell look like a hybrid of receptors on B cells and T cells. The CAR protein allows this unusual cell to both latch onto select antigens and destroy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



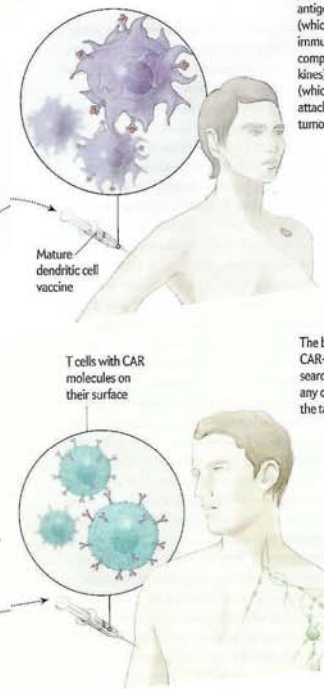
The drugs consist of artificial antibodies selected to disable the brakes that tumor cells put on the immune system.

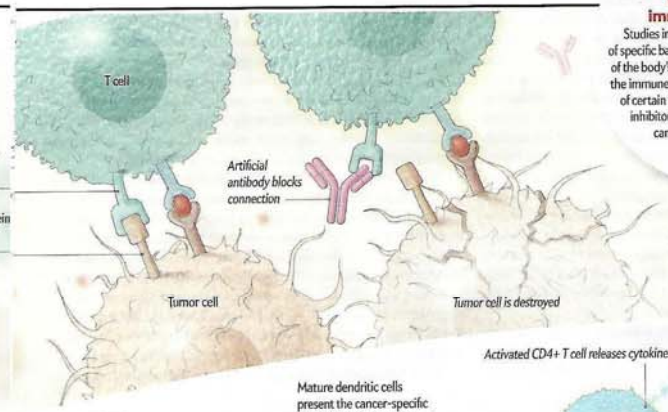


Many cancer cells hide from the immune system by displaying specific proteins that tell nearby T cells not to advance to the next stage of activation and, essentially, to leave the tumor alone.

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.



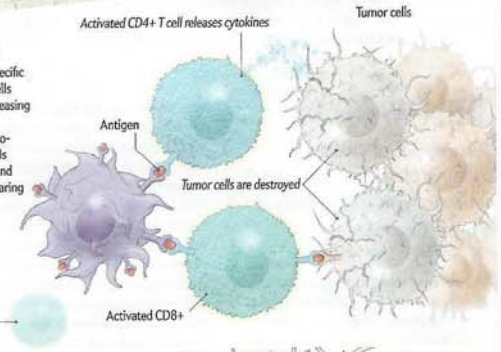


Could intestinal bacteria boost the effectiveness of immune treatments?

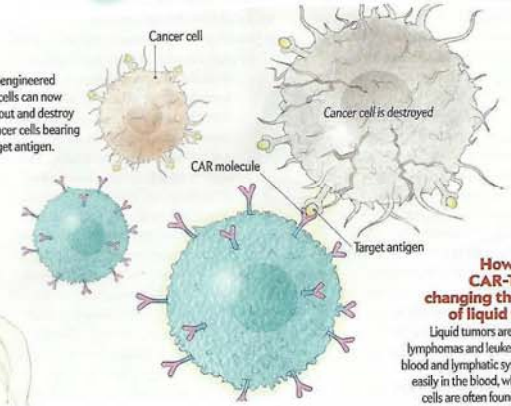
Studies in mice suggest that the presence of specific bacterial species in the intestine (part of the body's so-called microbiome) may boost the immune system's ability to slow the growth of certain types of tumors. Also, checkpoint inhibitors do a better job of eliminating cancer in rodents that harbor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

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.



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.

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Illustration by Shizuka N. Aoki

See Slide Presentation // Three Immune Strategies in Unit 3 Online Lecture Material