Genetics

Modified no.

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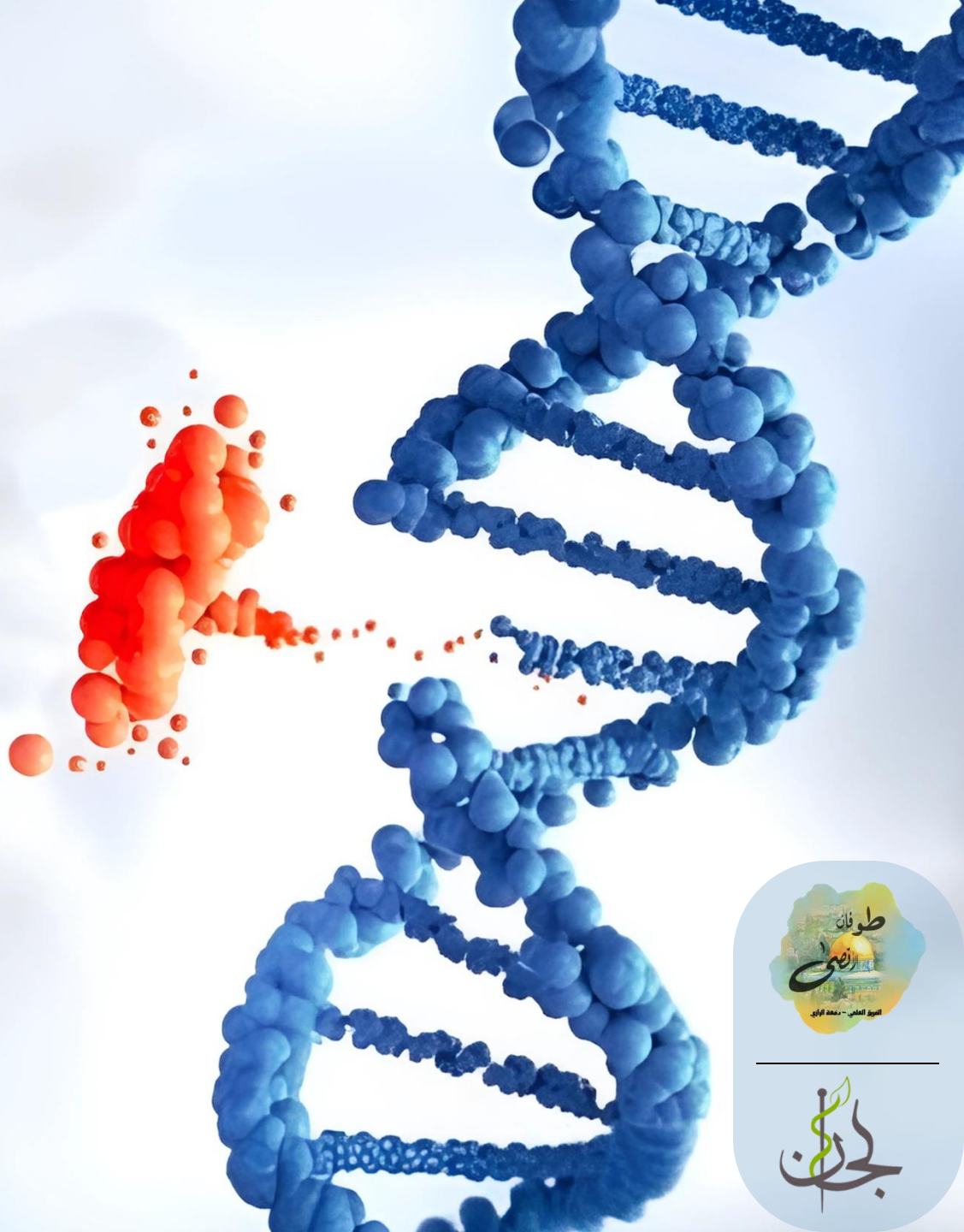


Immunogenetics

This lecture is full of repeated information that was already covered in immunology and other topics 😊

Topics covered include the types of immunity and the genetics related to the immune system

GOOD LUCK!!!

Color code

- Slides
- Doctor
- Additional info
- Important

THE IMMUNE RESPONSE: BASIC CONCEPTS

The Innate Immune System

Innate → Non-specific
Adaptive → specific → stronger

- When a pathogenic microorganism is **encountered**, the body's **first line** of defense includes **phagocytes** (like neutrophils and macrophages) (a type of cell that **engulfs** and destroys the microorganism) and the **complement system.**

B-cells can also engulf foreign materials

- The **complement proteins** can **(1)** destroy microbes directly by **perforating** their cell membranes, causing lysis and death, and they can also **(2)** **attract phagocytes** and other immune system agents to microbes by **coating the microbial surface** **(complement proteins bind to the surface of a pathogen)** (it is because of this assisting role that the term *complement* originated) → **This helps phagocytes recognize and target the foreign material more effectively, as the presence of bound complement proteins marks it for destruction.**

- **Natural killer cells,** a specific type of **lymphocyte**, can respond to **certain viral infections and some tumor cells.**
- Phagocytes, complement, and natural killer cells are all part of the **innate immune system,** which is capable of responding very rapidly to pathogens. **They provide a fast and non-specific defence against invading pathogens.**

- Phagocytes engulf foreign materials using special receptors called **Toll-like receptors (TLRs).** TLRs recognize specific patterns on pathogens (like lipopolysaccharides on Gram-negative bacteria or peptidoglycans on Gram-positive bacteria). Some phagocytes can also detect for example viral double-stranded RNA. Once recognized, **they engulf and destroy the invader.**

- Toll-like receptors were originally discovered in fruit flies and later on, homologous receptors were identified in humans on phagocytes like macrophages. TLRs bind to these foreign structures, triggering phagocytosis

- **All multicellular organisms possess an innate immune system**

The Adaptive Immune System

- The second type of immune system is the **adaptive immune system**. While the innate immune system provides a fast, general response, it may not fully eliminate some infections. In such cases, the adaptive immune system takes over, offering a **highly specific and amplified response**.

- Key components of the adaptive immune response (Fig. 9-1) include **T lymphocytes** (or **T cells**) and **B lymphocytes** (or **B cells**). These cells develop in the body's **primary lymphoid organs** (**bone marrow for B cells and the thymus for T cells**).

- **In the thymus (where T-cells learn to recognize self-peptides and tolerate them)**, developing T cells are exposed to a wide variety of the body's peptides. Those that can recognize and tolerate the body's own peptides are selected, and those that would attack the body's peptides are eliminated.

- The B and T cells progress to **secondary lymphoid tissues**, such as the lymph nodes, spleen, and tonsils, where they encounter disease-causing microorganisms. **They remain ready to respond when an infectious agent is detected.**

- **Mature B lymphocytes** secrete circulating **antibodies,** which combat infections. The B lymphocyte component of the immune system is sometimes called the **humoral immune system** because it produces antibodies that circulate in the blood stream.

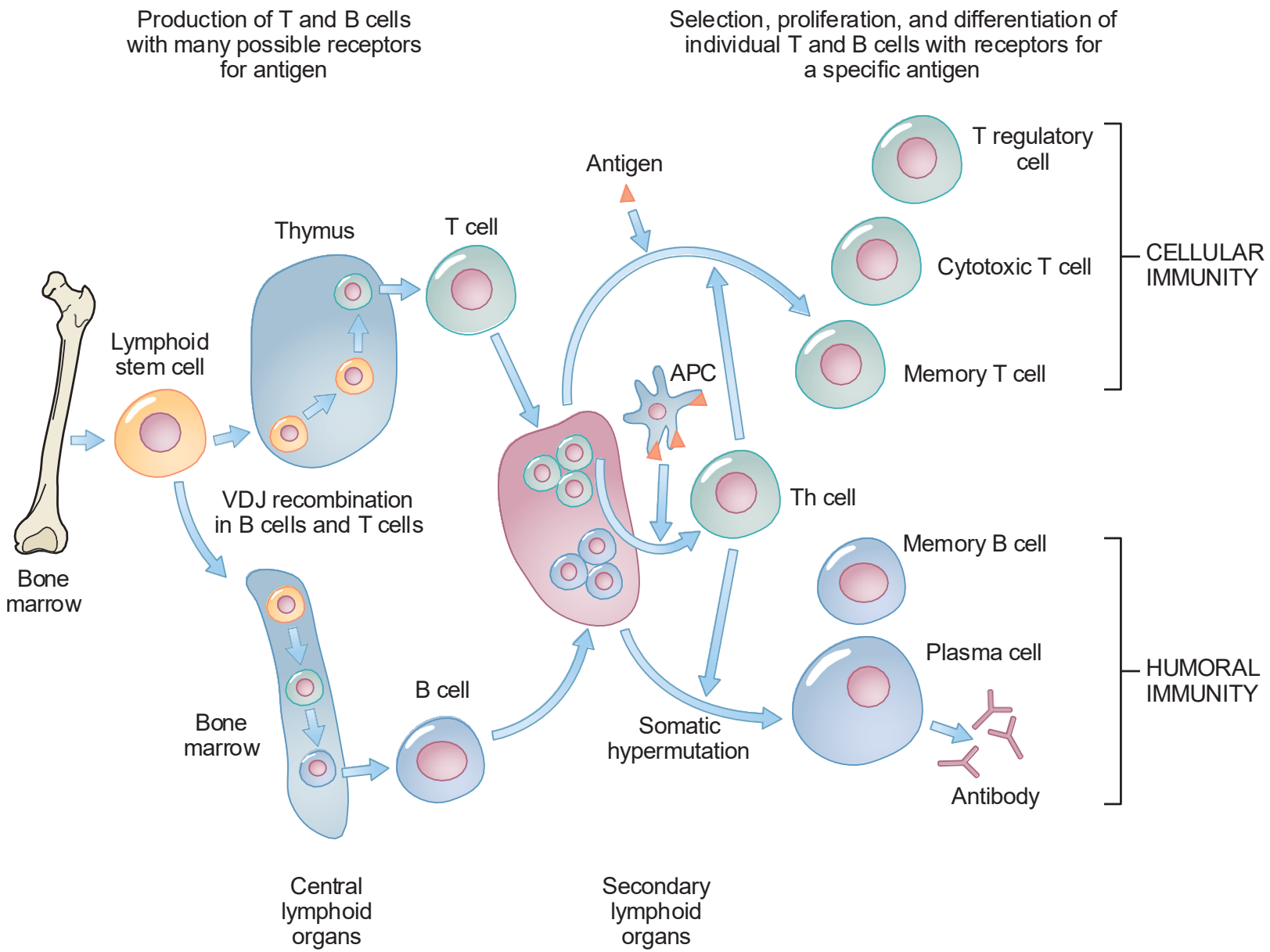
•Types of T-cells:

- **Helper T lymphocytes** stimulate B lymphocytes and other types of T lymphocytes to respond to infections more effectively, and **cytotoxic T lymphocytes** can directly kill infected cells.
- **Regulatory T cells: Help control and balance the immune response to prevent overactivation.**

- These antibodies specifically bind to foreign materials , forming complexes that help **phagocytes** recognize and eliminate the pathogens. This antibody-mediated defence is known as the **humoral immune response,** which is a part of **adaptive immune system**. It is called **(humoral)** because the antibodies function in the body's fluids , especially in the blood.

- Because of this **direct interaction** with infected cells, the T-cell component of the immune system is sometimes called the **cellular immune system.** It is estimated that the body contains several trillion B and T cells.

- **B cells → antibodies → humoral immunity**
- **T cells → direct killing/helping → cellular immunity**


Production of T and B cells with many possible receptors for antigen
Selection, proliferation, and differentiation of individual T and B cells with receptors for a specific antigen
Bone marrow
Lymphoid stem cell
Thymus
T cell
VDJ recombination in B cells and T cells
Bone marrow
B cell
Central lymphoid organs
Antigen
APC
Th cell
Somatic hypermutation
Secondary lymphoid organs
T regulatory cell
Cytotoxic T cell
Memory T cell
CELLULAR IMMUNITY
Memory B cell
Plasma cell
Antibody
HUMORAL IMMUNITY

EXPLANTION FOR THE PREVIOUS SLIDE

- In the **bone marrow, progenitor cells** either continue developing into **B lymphocytes** or migrate to the **thymus** to develop **into T lymphocytes,** these (bone marrow and thymus) are known as *the* **primary /central lymphoid organs**.
- **After maturation**, B and T cells travel to the **secondary lymphoid organs**, such as the lymph nodes, spleen, and tonsils. These are the sites where immune cells encounter foreign materials, typically presented by **antigen-presenting cells** like macrophages and dendritic cells.
- **APCs** engulf and degrade the foreign material, then present fragments of it on their surface. This antigen presentation activates both T cells and B cells:
- B cells, upon activation, undergo changes such as **somatic hypermutation** and differentiate into **plasma cells**, which secrete antibodies specific to the antigen. Some plasma cells **become memory B cells**, which enable a faster and stronger response upon re-exposure to the same antigen in the future. This process defines **humoral immunity**.

- T cells recognize antigens presented by APCs and differentiate into various types:
  - **Helper T cells (CD4+):** Assist in activating B cells and other immune cells.
  - **Cytotoxic T cells (CD8+)**
  - **Regulatory T cells**
  - **Memory T cells**.
- This T-cell-mediated response is referred to as **cellular immunity**.

The B-Cell Response: Humoral Immune System

Antibody production

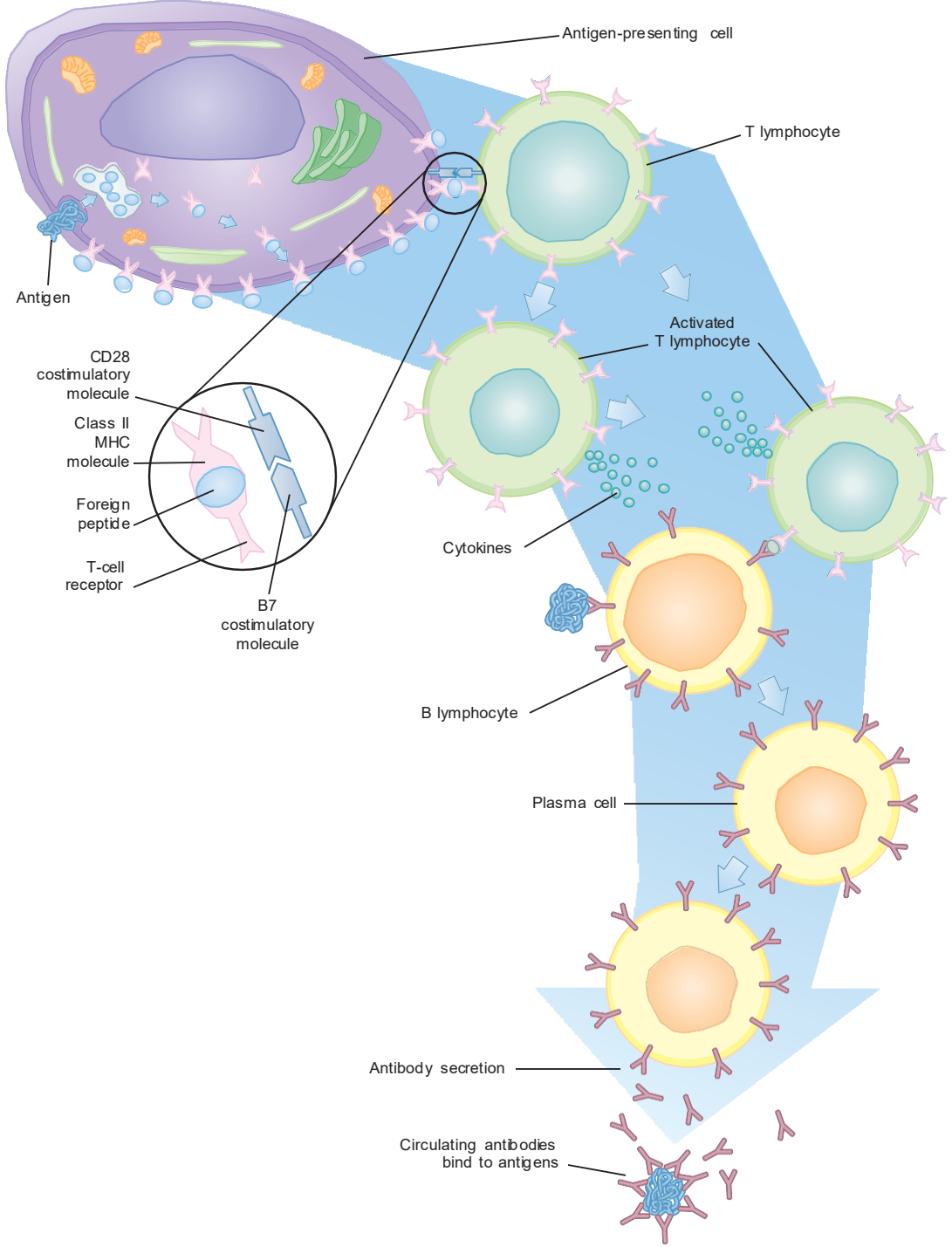
- A **major element of the adaptive immune response** begins when specialized types of **phagocytes**, which are part of the innate immune system, **engulf** invading microbes and **then present** peptides derived from these microbes on their cell surfaces.

Once these microbial peptides are displayed, other immune cells, such as **B** cells, can recognize them. These phagocytes, now acting as **APCs**, are essential for initiating the adaptive response. The most efficient APCs in the body are **macrophages** and **dendritic cells in (secondary lymphoid tissues)**. These cells are highly capable in engulfing, undergo phagocytosis, destruction and presenting parts of the foreign material.
B cells themselves, although part of the **humoral immune system**, also have the ability to engulf microbes and present antigens on their surface.

- These cells, which include **macrophages** and **dendritic cells**, are termed **antigen-presenting cells (APCs). B cells** are also **capable of engulfing microbes and presenting foreign peptides on their cell surfaces.**

- The **APCs** **alert the adaptive immune system** to the presence of pathogens in two ways. **First**, the foreign peptide is transported to the surface of the APC by a **class II major histocompatibility complex (MHC)** molecule, which carries the foreign peptide in a specialized groove (Fig. 9-2).

- **This complex, which projects into the extracellular environment, is recognized by T lymphocytes, which have receptors on their surfaces that are capable of binding to the MHC-peptide complex**.



We are looking at the **humoral immune system**.

1. **APCs** such as macrophages or dendritic cells engulf and destroy foreign material.
2. These APCs then **present fragments of the foreign material on their surface** using **class II MHC molecules**.
3. **T lymphocytes** recognize this **MHC–antigen complex**.

A co-stimulatory signal also occurs between the **B7 molecule** on the APC binds to **CD28** on the T lymphocyte, enhancing activation.

4. Once activated, **T lymphocytes identify the foreign material** and help **B lymphocytes** recognize it as well.
5. The **B lymphocytes** then undergo **genetic hyperstimulation/ hypermutation**, transforming into **plasma cells** that produce **specific antibodies** against the foreign material.
6. Some **T lymphocytes** differentiate into **helper T cells**, which interact with B cells to confirm the presence of foreign material.

Some T cells may become **cytotoxic T cells**, capable of directly destroying the infected or foreign material.

7. This entire immune response is triggered by the APCs' ability to **process, destroy, and present** the foreign antigen on their surface.
8. The **activated B cells** secrete antibodies that **specifically bind to and eliminate the foreign material** from the body.

- **In addition**, the APCs, upon encountering a pathogen, **display costimulatory molecules** on their cell surfaces as a signal that foreign pathogens have been encountered (Fig. 9-3).

- Binding to the MHC-peptide complex stimulates the **helper T lymphocyte to secrete cytokines,** which are signaling proteins that mediate communication between cells.

- In particular, these cytokines help to stimulate the subset of B lymphocytes whose cell surface receptors, termed **immunoglobulins,** can bind to the invading microorganism's peptides (see Fig. 9-3). **They recognize and bind to specific antigens. Once activated, B cells differentiate into plasma cells which secrete antibodies.**

- The immunoglobulin's capacity to bind a specific foreign peptide (i.e., its **affinity** for the peptide) is determined by its shape and other characteristics.

Immunoglobulins (antibodies) bind specifically and with high affinity to their target antigens. This high affinity is determined by the shape, structure, and chemical properties of the foreign material. The specific binding helps neutralize pathogens or mark them for destruction by other components of the immune system.

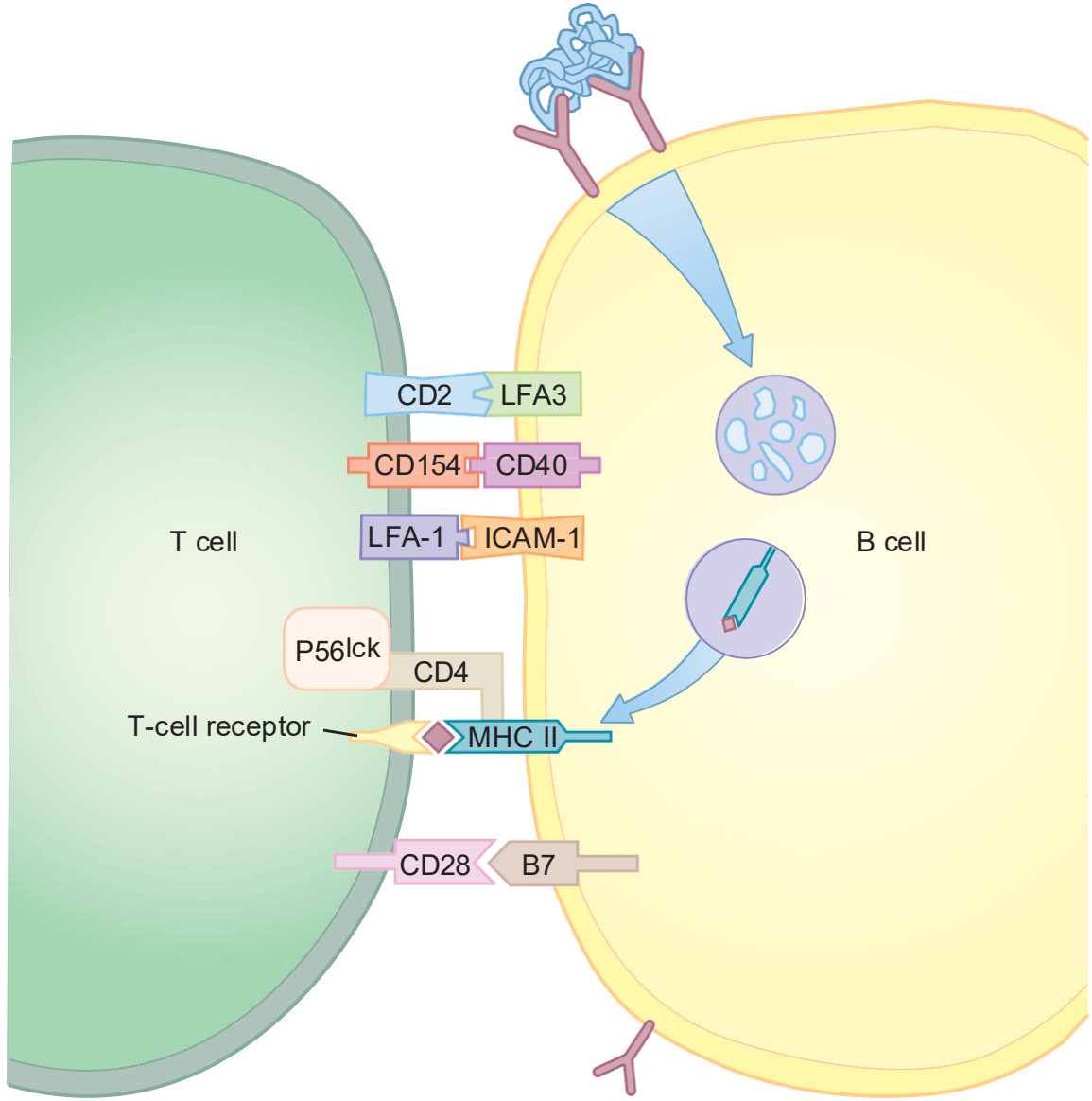


FIG 9-3 A detailed view of the binding between a helper T cell and a B cell. In addition to the binding of the T-cell receptor to the MHC-peptide complex, a number of other molecules interact with one another, such as the costimulatory B7-CD28 complex. MHC, major histocompatibility complex. (Modified from Roitt I, Brostoff J, Male D. *Immunology*. 6th ed. St. Louis: Mosby; 2001.)

Interaction between T cells and B cells.

- The **T-cell receptor** recognizes foreign material that was initially taken up and presented by **APCs**. Now, the T cell engages with the B cell that has encountered the same foreign material. At the same time, B cells are also capable of engulfing the pathogen and presenting its antigen to T cells using MHC class II molecules.
- So, this is a **mutual interaction** → the T cell helps activate the B cell, and the B cell presents antigens that keep the T cell engaged.
- In addition to the binding between the T-cell receptor and the MHC-peptide complex, other molecules contribute to and strengthen this interaction. These include **co-stimulatory molecules** such as **B7 on B cells** and **CD28 on T cells**, among others.
- All of these interactions help coordinate the immune response against the foreign material.

- **In the adaptive immune system**, It is estimated that upon initial exposure to a foreign microbe, as few as 1 in every 1 million B lymphocytes happens to produce cell-surface receptors capable of binding to the microbe. **This number is too small to fight an infection effectively and the receptor's binding affinity is likely to be relatively poor.**

•At first, this small subset of B cells isn't sufficient to fight off the infection on its own. But once they're stimulated by the antigen and receive help from activated T cells, the response is **AMPLIFIED**.

- Once this relatively small population of B lymphocytes is stimulated, they begin an adaptive process in which additional DNA sequence variation is generated via the process of **somatic hypermutation** **(process that introduces mutations in the genes encoding the variable region of the B-cell receptor (which becomes the antibody))**

- **These DNA mutations, which are confined to the genes that encode the cell- surface receptors, in turn produce alterations in the receptors' binding characteristics (e.g., the shape of the protein). Some of these variant receptors possess a higher level of binding affinity for the microorganism.**

- The B cells that produce these receptors are favorably **selected** because they bind the pathogen for a longer period of time. They thus **proliferate rapidly**.
- **The better a receptor binds to the antigen, the more likely that B cell is to be selected for survival and expansion. This is called affinity maturation. The immune system essentially selects the B cells with the highest-affinity receptors to proliferate rapidly, creating a specialized population of B cells.**

- These B cells then differentiate and become **plasma cells(antibody secreting cells),** which secrete their cell-surface receptors, or **immunoglobulins**, into the blood stream. The secreted molecules, which are structurally identical to the receptors on the B cell's surface, are **antibodies**.

These antibodies then circulate in the body, binding to the same foreign material that triggered the immune response in the first place, neutralizing it or marking it for destruction.

- After initial stimulation by the disease pathogen, the process of B-cell differentiation and maturation into antibody-producing plasma cells requires about **5 to 7 days for completion.**

- Each plasma cell is capable of secreting approximately 10 million antibody molecules per hour **(which is a huge number)**. Anti- bodies bind to the pathogen's surface **antigens** and may **neutralize** the microorganism directly. More often, the antibody tags the pathogen for destruction by other components of the immune system, such as complement proteins and phagocytes.

- **Another important activity** of the humoral immune response is the creation of **memory B cells,** a **subset of high-affinity-binding B cells that persist in the body after the infection has subsided.**

- These cells, which have already been highly selected for response to the pathogen, **provide a more rapid response** should the pathogen be encountered again later in the individual's life.

The word antigen is derived from: **antibody-generating molecules.**

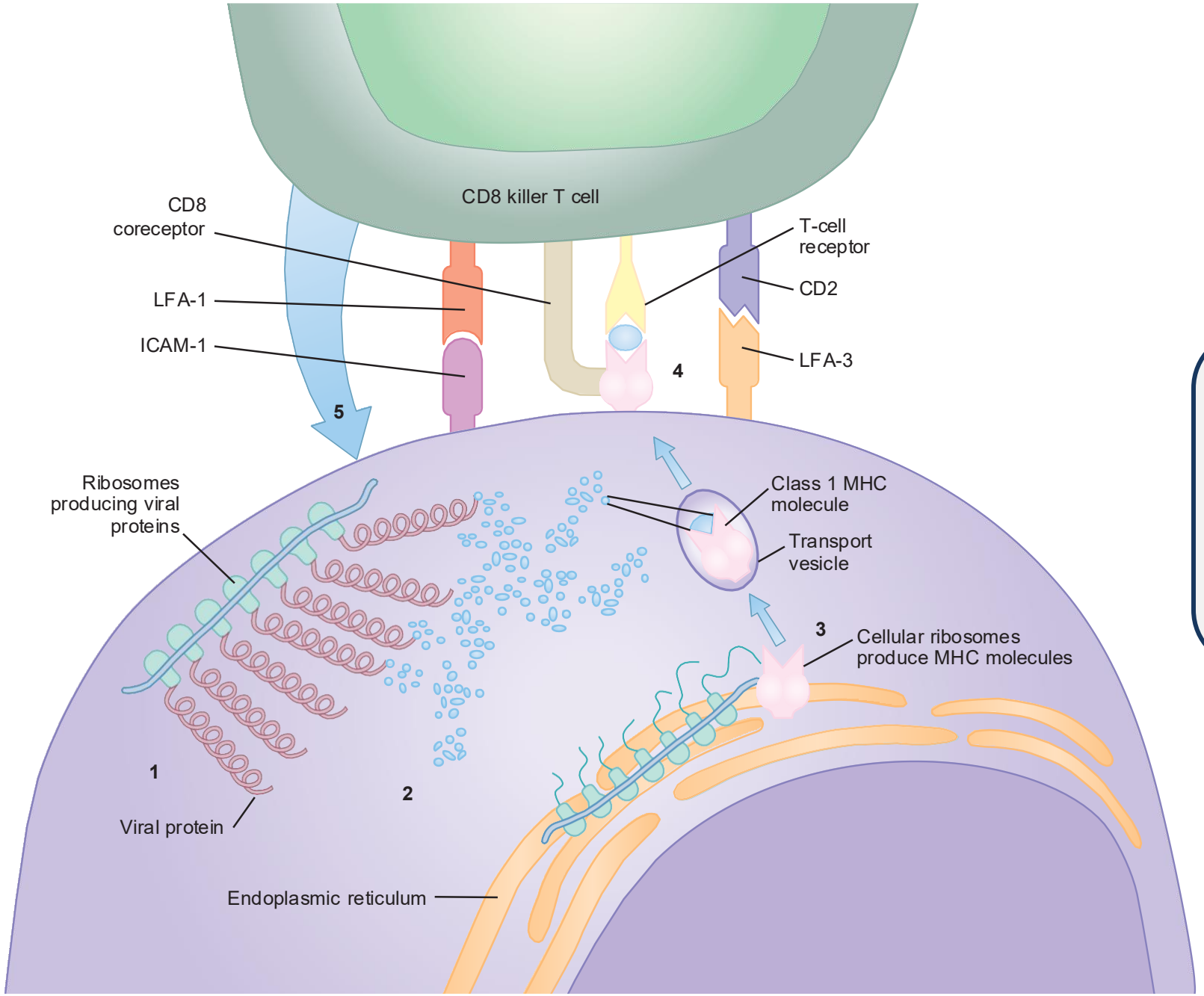
The Cellular Immune System

- A key member of the cellular immune response is the **class I MHC molecule,** which is found on the surfaces of **nearly all of the body's cells.**
- In a normal cell, the class I MHC molecule binds with small peptides **(8 to 10 amino acids long)** derived from the interior of the cell (proteins inside the cells). It migrates to the cell's surface, carrying the peptide with it and displaying it outside the cell. Because this is one of the body's own peptides, no immune response is elicited.

Since these peptides come from the cell's own proteins, the immune system recognizes them as normal, and **no immune response is triggered**. However, if the cell is infected (by a virus, for example), the peptides displayed by MHC class I may include **foreign or abnormal fragments**. These are recognized as **non-self** by **cytotoxic T cells** (CD8+), which have been trained during development in the **thymus** to distinguish between self and non-self antigens.

- In an infected cell, however, the class I MHC molecule can bind to **small peptides** that are derived from the infecting organism. Cell-surface presentation of foreign peptides by the class I MHC molecule alerts the immune system, T cells in particular.
- The MHC- peptide complex binds to receptors on the appropriate T cell's surface, which prompts the T cell to emit a chemical that destroys the infected cell (Fig. 9-4).

- Because of their ability to destroy cells in this way, these **T lymphocytes are termed cytotoxic T lymphocytes** or **killer T lymphocytes.*** Each cytotoxic T lymphocyte can destroy one infected cell every **1 to 5 minutes.**



This is a cytotoxic T lymphocyte interacting with a virus-infected cell. Viral proteins are degraded inside the cell and presented on its surface by MHC class I molecules. The T-cell receptor binds to this complex, triggering the release of molecules that kill the infected cell.

- In contrast to cytotoxic T cells, which destroy infected cells directly, helper T (TH) cells respond to the presence of pathogens by secreting **cytokines.**
- These molecules in turn stimulate the development of other components of the immune system, such as B cells and cytotoxic T cells.

- TH cells are classified into subsets, depending on which cytokines they secrete. For example**, TH1 cells, which are involved primarily in combatting intracellular pathogens**, **secrete interleukin-2 (IL-2), interferon-γ, and tumor necrosis factor β.**
- **TH2 cells**, which **secrete IL-4, IL-5, IL-6, and IL-13, help to fight multicellular parasites and are involved in allergic responses.**
- Other helper T-cell subsets include **TH17 cells**, which **secrete IL-17, and TH22 cells, which secrete IL-22.**

- As in the B-cell component of the adaptive immune system, a subset of long-lived T cells is retained **(memory T cells)** to **quickly respond** to a foreign pathogen should it be encountered again in the future. Yet another type of T cell, the **regulatory T cell,** helps **to regulate the immune system so that self peptides are not inadvertently attacked.**

The Innate, Humoral, and Cellular Immune Systems: A Comparison

- We have 2 types of immunity: innate & adaptive; adaptive is divided into : humoral & cellular

- The innate system, because it recognizes general features of pathogens, can react very quickly to foreign elements. While doing so, it signals the adaptive immune system to initiate a fine-tuned response to the pathogen.

- Without this signal, the adaptive immune system is incapable of responding to an infection. After several days during which the adaptive system "learns" the characteristics of the pathogen, it can launch a massive, specialized response.

- Through the creation of memory B and T cells, the adaptive immune system allows the organism to respond quickly and effectively to a pathogen should it be encountered again. No such memory cells exist for the innate immune system.

- The humoral immune system is specialized to combat extracellular infections, such as circulating bacteria and viruses. The cellular immune system combats intracellular infections, such as parasites and viruses within cells. However, this division of labor is not strict, and there is again a great deal of interaction between the humoral and cellular components of the immune system.

now let's dive deep into the role of genes in the production of antibodies & T-cell receptor recognition

IMMUNE RESPONSE PROTEINS: GENETIC BASIS OF STRUCTURE AND DIVERSITY

Immunoglobulin Molecules and Genes

- As illustrated in Figure 9-5, each **antibody** (or immunoglobulin) molecule is composed of four chains: an identical pair of longer **heavy chains** and an identical pair of shorter **light chains,** which are linked together by disulfide bonds.

- There are five different types of heavy chains (termed γ, μ, α, δ, and ε) and two types of light chains (κ and λ). The five types of heavy chains determine the major **class** (or **isotype**) to which an immunoglobulin (Ig) molecule belongs: γ, μ, α, δ, and ε correspond to the immunoglobulin isotypes IgG, IgM, IgA, IgD, and IgE, respectively.

- Immature B lymphocytes produce only IgM, but as they mature, a rearrangement of heavy chain genes called **class switching** occurs. This produces the other four major classes of immunoglobulins, each of which differs in amino acid composition, charge, size, and carbohydrate content.

It is composed of two heavy chains, two light chains and disulfide bonds that are formed between them

As you can see, the 2 long chains are the heavy chains & they are identical. The 2 short ones are light chains & they are identical

The antibody is composed of :
antigen binding site (it is a highly variable; our body produces plenty of variable antibodies)

constant region (when Ab-Ag is formed, this region is the one responsible for the activation of complement system & phagocytes)

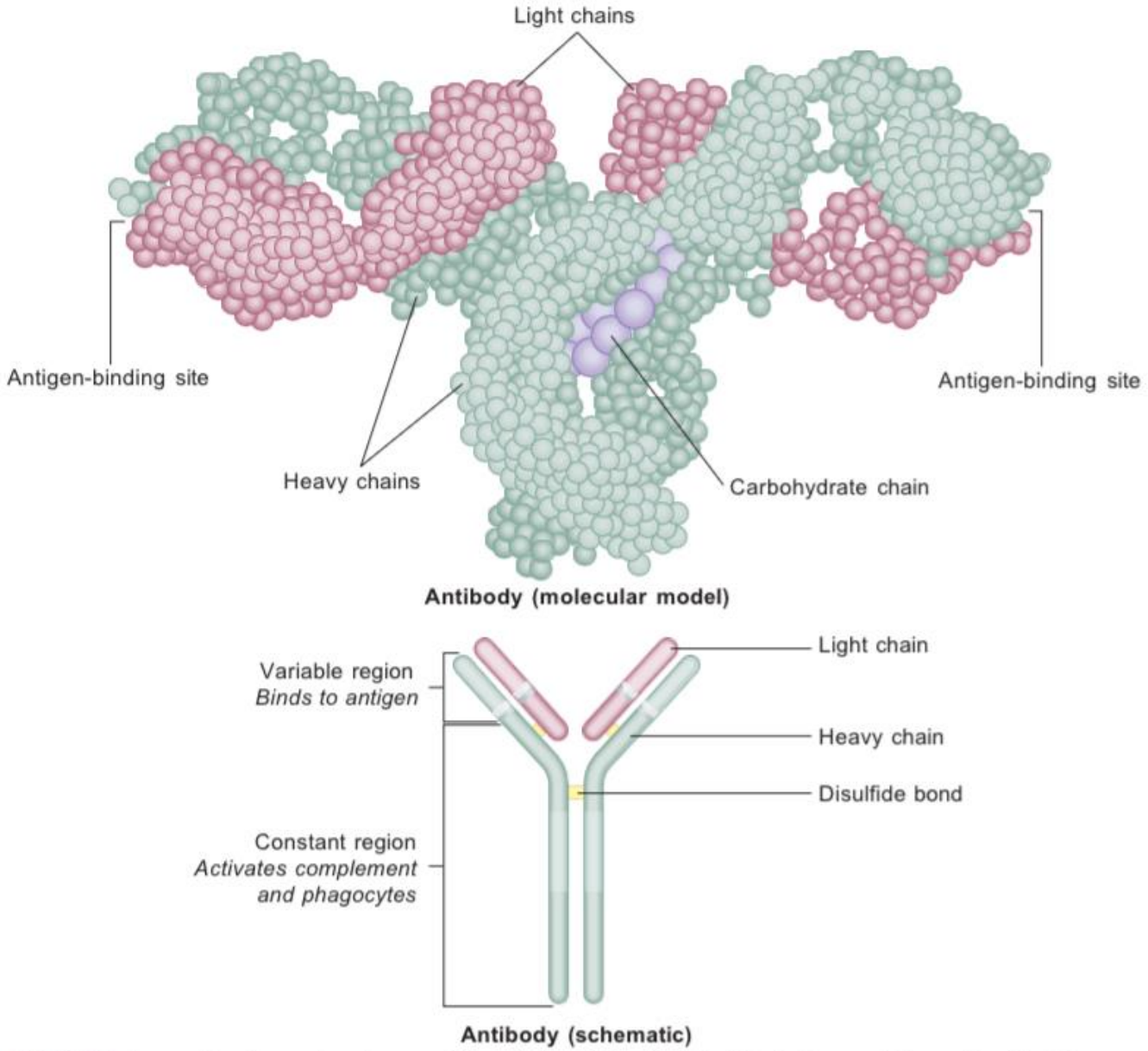


FIG 9-5 An antibody molecule consists of two identical light chains and two identical heavy chains. The light chain includes variable, joining, and constant regions; the heavy chain includes these regions as well as a diversity region located between its variable and joining regions. The *upper portion* of the figure depicts a molecular model of antibody structure.

- The heavy and light chains both contain a **constant** and a **variable** region, which are located at the carboxyl (C)-terminal and amino (N)-terminal ends of the chains, respectively.

- The arrangement of genes encoding the constant region determines the major class of the Ig molecule (e.g., IgA, IgE).

- The variable region is responsible for antigen recognition and binding and thus varies within immunoglobulin classes.

- Three distinct gene segments encode the light chains: C for the constant region, V for the variable region, and J for the region that joins the constant and variable regions. Four gene segments encode the heavy chains, with C, V, and J coding again for the constant, variable, and joining regions, respectively, and a "diversity" (D) region located between the joining and variable regions.

The Genetic Basis of Antibody Diversity

- Because the immune system cannot "know" in advance which types of microbes it will encounter, the system must contain a huge reservoir of structurally diverse immune cells so that at least a few cells can respond (i.e., bind) to any invading microbe. So the body is not able to recognize antigens before interacting with them بالعامية الجسم ما بيقدر يحزر انه حيتعرض لجسم غريب قبل ما يتفاعل معه جهاز المناعة

- Indeed, the humoral immune system is capable of generating approximately 100 billion structurally distinct antibodies.

  At one time, it was thought that because each antibody has a unique amino acid sequence, each must be encoded by a different gene. However, this one gene–one antibody hypothesis could not possibly be correct, because the human genome has only 20,000 to 25,000 protein-coding genes.

- Further study has shown that several mechanisms are responsible for generating antibody diversity in somatic cells:

1. Multiple Germline Immunoglobulin Genes (since birth)

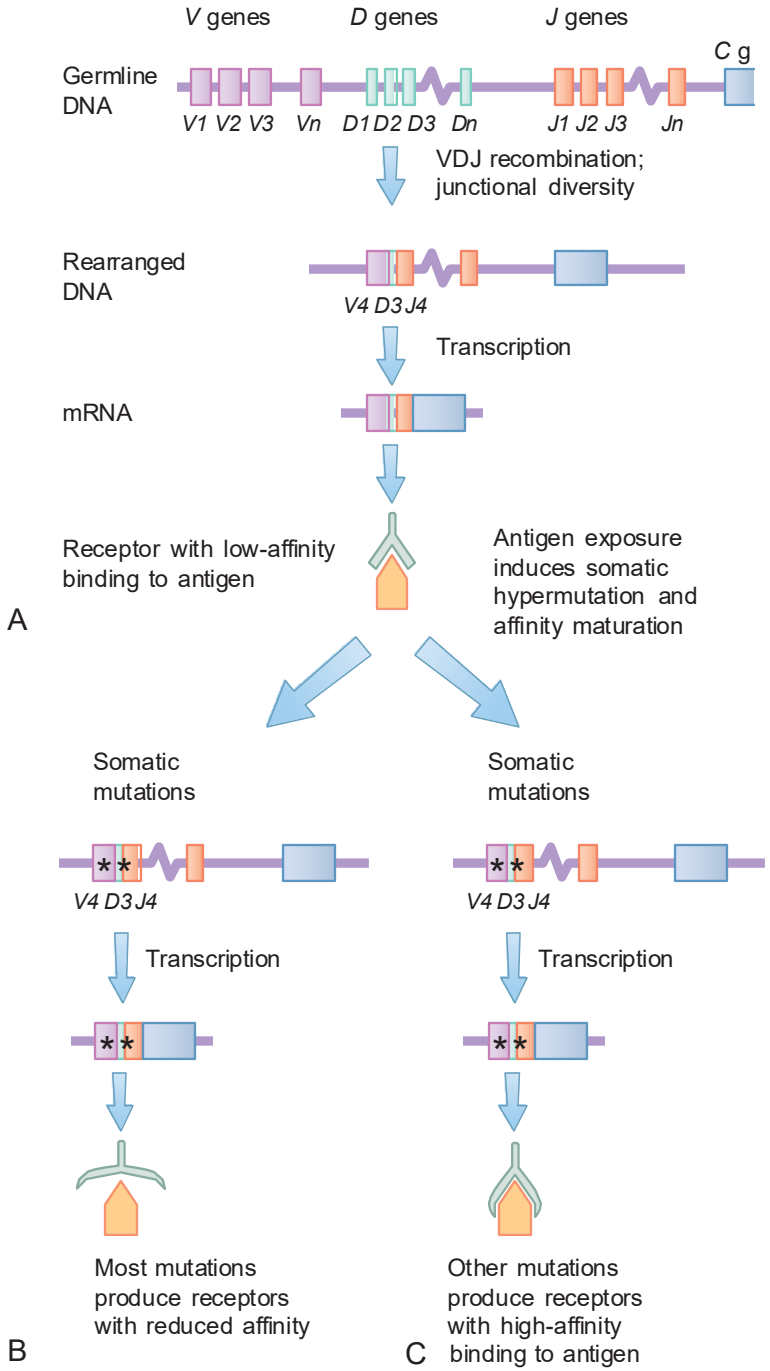
- Molecular genetic studies (cloning and DNA sequencing) have shown that for each heavy and light chain, an individual has more than 80 different V segments located contiguously in his or her germline and six different J segments. There are at least 30 D segments in the heavy chain region.

2. Somatic Recombination (VDJ Recombination)

- As immunoglobulin molecules are formed during B lymphocyte maturation, a specific combination of single V and J segments is selected for the light chain, and another combination of V, D, and J segments is selected for the heavy chain.
- This is accomplished by deleting the DNA sequences separating the single V, J, and D segments before they are transcribed into mRNA (Fig. 9-6). The deletion process is carried out in part by **recombinases** (encoded by the *RAG1* and *RAG2* genes), which initiate double-strand DNA breaks at specific DNA sequences that flank the V and D gene segments.
- After the deletion of all but one V, D, and J segment, the nondeleted segments are joined by ligases. This cutting-and-pasting process is known as **somatic recombination** (in contrast to the germline recombination that takes place during meiosis), somatic recombination occurs during response to foreign antigens

- Somatic recombination produces a distinctive result: unlike most other cells of the body, whose DNA sequences are identical to one another, mature B lymphocytes *vary* in terms of their rearranged immunoglobulin DNA sequences.

FIG 9-6 **A,** Somatic VDJ recombination in the formation of a heavy chain of an antibody molecule. The functional heavy chain is encoded by only one segment each from the multiple V, D, and J segments. This produces a subset of B cells whose receptors have low-affinity binding for a foreign antigen. Once the antigen is encountered in the secondary lymphoid tissue, somatic hypermutation **(B** and **C)** is initiated. Most of the mutated receptors have little binding affinity **(B),** but eventually somatic hypermutation produces a subset of receptors with high-affinity binding **(C).** The cells that contain these receptors become antibody-secreting plasma cells.



You can see the germline DNA containing many variable regions, many diversity regions, many joining regions but only 1 constant region

After deletion, joining will take place then transcription occurs producing an antibody (its amount will be small at the beginning)

When binding to the target antigen occurs= induction of somatic hypermutation & affinity maturation= somatic mutations in V & J regions leading to production of a **highly specific Ab to the Ag in large amounts**

Many mutations end up with high affinity receptors to the Ag while most mutations produce receptors without lower affinity (reduced affinity)

As previously mentioned, genetic recombination and rearrangement can generate between 100,000 to 1,000,000 antibody (Ab) combinations. From this pool, a subset will be specific to the particular targeted antigen (Ag) and will undergo amplification. During this process, somatic mutations occur, followed by transcription, leading to two possible outcomes:

1. Some antibodies will develop a high affinity for the antigen, these will be selectively stimulated to proliferate further.
2. Others will have reduced affinity and will not be favored for expansion.

3. Junctional Diversity

- As the V, D, and J regions are assembled, slight variations occur in the position at which they are joined, and small numbers of nucleotides may be deleted or inserted at the junctions joining the regions. This creates even more variation in antibody amino acid sequence.

4. Somatic Hypermutation

- Typically, only a small subset of B cells has cell-surface receptors (immunoglobulins) that can bind to a specific foreign antigen, and their binding affinity is usually low.
- Once this subset of B cells is stimulated by a foreign antigen, they undergo an **affinity maturation** process characterized by somatic hypermutation of the V segments of immunoglobulin genes, as mentioned previously.

- An enzyme termed *activation-induced deaminase* causes cytosine bases to be replaced by uracil. Error-prone DNA polymerases are recruited, and DNA repair processes are modified so that mutations can persist in the DNA sequence.
- Induction of mutations in B-cell (that are needed to create Ab specific to Ag), mutation rate is 1/1000 (which is greater than our normal DNA mutation rate (= 1/100,000,000 – 1/1,000,000,000), in which we try to reduce errors as much as possible)

5. Multiple Combinations of Heavy and Light Chains

- Further diversity is created by the random combination of different heavy and light chains in assembling the immunoglobulin molecule.
- Each of these mechanisms contributes to antibody diversity. Considering all of them together, it has been estimated that as many as 10^{11} distinct antibodies can potentially be produced by our B-cells.

T-Cell Receptors

- Like the immunoglobulins, T-cell receptors must be able to bind to a large variety of peptides derived from invading organisms.

- Unlike immunoglobulins, however, T-cell receptors are never secreted from the cell, and T-cell activation requires the presentation of foreign peptide along with an MHC molecule. يعني المستقبل بيكون على سطحهم و ما بيحتاج انتاج

- Approximately 90% of T-cell receptors are heterodimers composed of an α and a β chain, and approximately 10% are heterodimers composed of a γ and a δ chain(Fig.9-7).

- A given T cell has a population of either α-β receptors or γ-δ receptors.

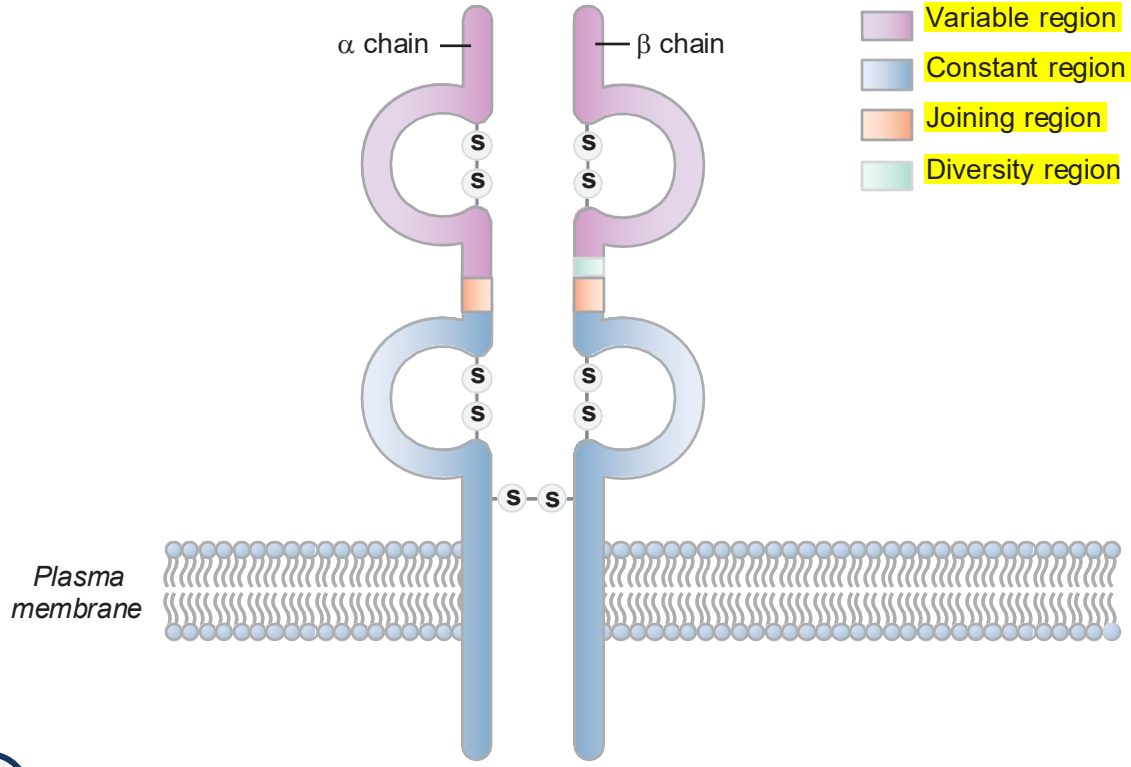


FIG 9-7 The T-cell receptor is a heterodimer that consists of either an α and a β chain or a γ and a δ chain. The complex of MHC molecule and antigen molecule is bound by the variable regions of the α and β chains. (Modified from Raven PH, Johnson GB. *Biology*. 3rd ed. St. Louis: Mosby; 1992.)

Diversity of T lymphocytes (as in B-cells)

We will also have memory T-cells (as in B-cells)

- Most of the mechanisms involved in generating immunoglobulin diversity—multiple germline gene segments, VDJ somatic recombination, and junctional diversity—are also important in generating T-cell receptor diversity.

- Somatic hypermutation does not occur in the genes that encode the T-cell receptors. This is thought to help avoid the generation of T cells that would react against the body's own cells (since T-cells main function is to kill cells directly rather than circulating antigens)

فوات الصّلاة من أعظم مصائب العبد

قال رسول الله صلّى الله عليه وسلّم: "**الذي تَفُوتُهُ صَلَاةُ العَصْرِ، كَأَنَّما وُتِرَ أَهْلَهُ ومَالَهُ**".

والموتور هو من أُخِذَ منه أهله وماله وهو ينظر إليهم، ومن فاتته الصّلاة أشبه بهذا الرّجل؛ لأنه اجتمعت عليه ألوان الهموم، فاجتمع عليه همّ إثم تضييع الصلاة، وهمّ فقد الثّواب الذي كان سيناله لو صلّى، كما اجتمع على الموتور همّ السّلب والفقد.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!