

immunology

Immunity

Immunology has its origins in the study of how the body protects itself against infectious diseases caused by microorganisms, such as bacteria, viruses, protozoa, and fungi, and also parasitic organisms, such as helminth worms.

innate immune system that utilises certain 'hard-wired' strategies to provide a rapid, general, response when alerted by certain typical signals of infection (essentially forming a first-line of defence);

adaptive immune system that is able to develop highly specific responses (and a persistent 'immune memory') to target infection with extraordinary accuracy. Both systems work in close cooperation and, to an important extent, the adaptive immune system relies upon the innate immune system to alert it to potential targets, and shape its response to them.

Immune tissues

All immune cells originate in the bone marrow, deriving from haematopoietic stem cells, but an important set of immune cells (T lymphocytes) undergo maturation in an organ known as the thymus.

1-primary lymphoid tissues.(The thymus and bone marrow are known as)

2-Secondary lymphoid tissues, namely the lymph nodes, spleen and mucosa-associated lymphoid tissues (MALT) are important sites for generating adaptive immune responses and contain the lymphocytes

Anything that causes an immune response is called an ***antigen***. An antigen may be harmless, such as grass pollen, or harmful, such as the flu virus. Disease-causing antigens are called ***pathogens***.

In humans, **the immune system** begins to develop in the embryo. The immune system starts with **hematopoietic** (from Greek, "blood-making") stem cells.

These stem cells differentiate into the **major players** in the immune system (**granulocytes, monocytes, and lymphocytes**).

. Stem cells continue to be produced and differentiate throughout your lifetime.

Antimicrobial Compounds

Several antimicrobial compounds mediate the innate response.

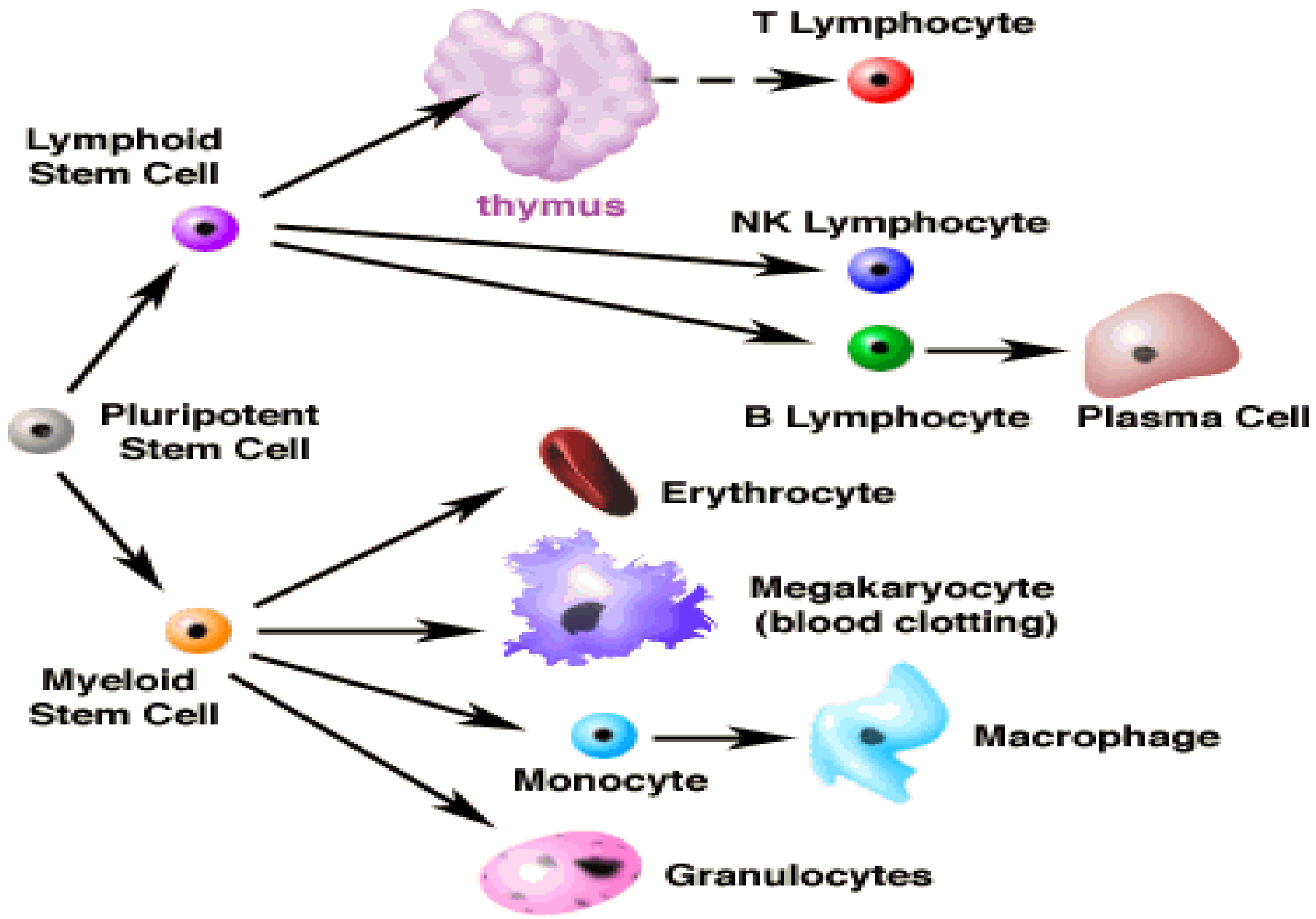
- **Lysozyme**--hydrolytic enzyme in tears and mucous; cleaves peptidoglycan in bacterial cell walls
- **Interferon**--produced by virus-infected cells; binds to nearby cells (it is a paracrine factor), inducing a generalized antiviral state
- **Complement**--inactive circulating serum proteins that act on pathogen cell membranes
- **Collectins**--surfactant materials; kills bacteria by disrupting their lipid membranes or agglutinating them
- **Toll-Like Receptors**---(TLRs) membrane-bound receptors that react via pattern recognition to certain classes of molecules; TLR4, for example, recognizes lipopolysaccharide (LPS) on gram-negative bacteria

The blood system

Normal Adult Blood Cell Counts

Red Blood Cells	$5.0 \times 10^6/\text{mm}^3$	
Platelets	$2.5 \times 10^5/\text{mm}^3$	
Leukocytes	$7.3 \times 10^3/\text{mm}^3$	
	Neutrophil	50-70%
	Lymphocyte	20-40%
	Monocyte	1-6%
	Eosinophil	1-3%
	Basophil	<1%

Agranulocyte



1-Innate immunity

Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include:

- **Phagocytic cells (macrophages, neutrophils; more generally, -antigen-presenting cells (APCs))**
- **- Barriers (e.g. skin)**
- **Antimicrobial compounds**
- **Inflammation**

Inflammation is one of the first responses of the immune system to infection or irritation. Inflammation is stimulated by chemical factors released by injured cells and serves to establish a physical barrier against the spread of infection, and to promote healing of any damaged tissue following the clearance of pathogens.^[5]

The process of acute inflammation is initiated by cells already present in all tissues, mainly resident macrophages, dendritic cells, histiocytes, Kupffer cells, and mastocytes.). At the onset of an infection, burn, or other injuries, these cells undergo activation and release inflammatory mediators responsible for the clinical signs of inflammation.

Adaptive immunity refers to antigen-specific immune response. The adaptive- immune response is more complex than the innate. The antigen first must be processed and recognized

Types of Acquired Immunity

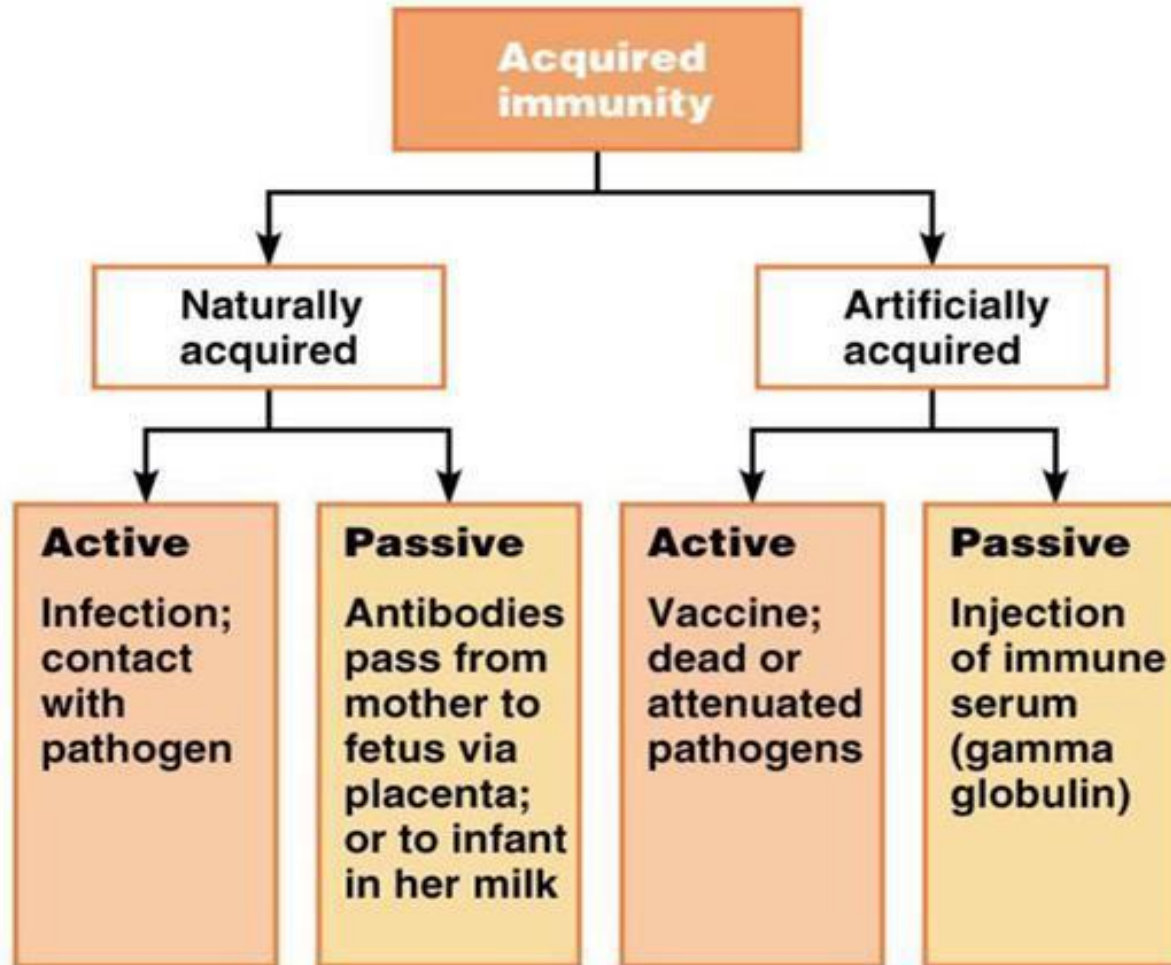


Figure 21.12

Table 1. Examples of Active and Passive Immunity

Type of Immunity	How Acquired by Host	Examples
Active Immunity	As a result of exposure to an infectious agent or one of its products (antigens)	Antibodies are produced by the host in response to the infectious agent itself (e.g. recovery from the disease), or in response to artificial immunization (vaccination) with some product derived from the infectious agent (e.g. toxoid, killed cells, structural components of cells, inactivated virus, etc.).
Passive Immunity	As a result of the acquisition of antibodies which have been produced in another animal (by active means) or derived from cells grown in tissue culture (monoclonal antibodies)	-Injection of immune serum from an individual previously immunized or recovered from disease, e.g. hepatitis; ----Injection of serum from an animal hyperimmunized with tetanus toxoid; --Placental transfer of antibodies from mother to fetus; Transfer of antibodies from mother to infant in milk by nursing.

Key to the adaptive immune response is the lymphocyte:

T lymphocytes and B lymphocytes (commonly known as T cells and B cells).

Although both originate in the bone marrow, T cells mature in the **thymus**, whilst B cells mature **in the bone marrow**.

During an organism's early development a large number of B- and T cells are produced, each of which has the ability to recognise a specific, molecular target

An additional aspect of the maturation process for T cells is that further distinct subsets

are produced – **helper T cells (also called CD4+ T cells)** and **cytotoxic T cells (also called CD8+ T cells)**.

Adaptive immunity utilises many kinds of receptor to coordinate its activities:.

T cells carry T-cell receptors (TCR),

whilst B cells carry B-cell receptors (BCR),

and variations in the fine structure of these receptors account for the individual specificity described above.

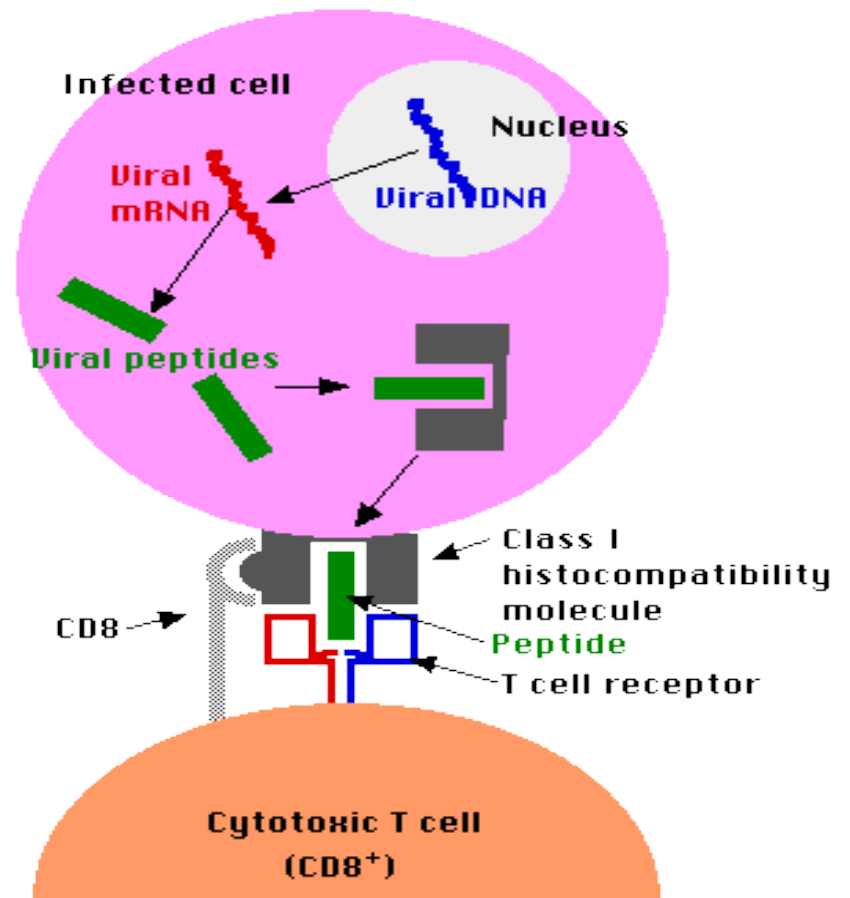
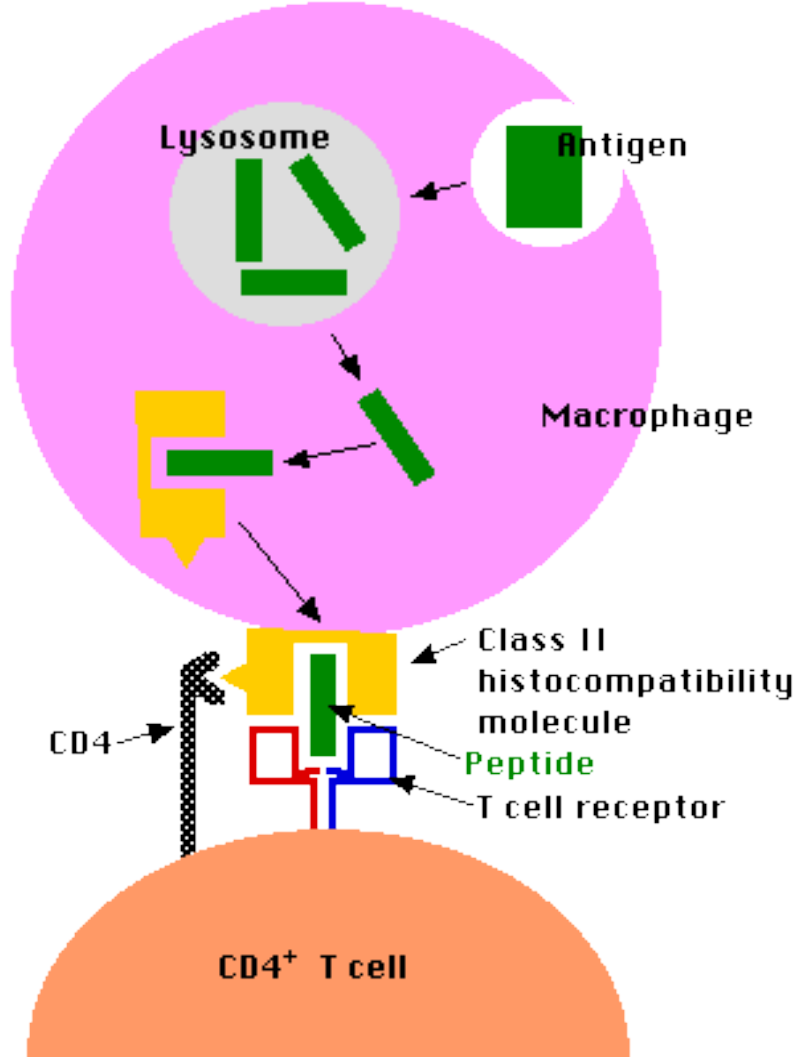
In addition, another set of receptors, encoded by the major histocompatibility complex (MHC), play an important role in adaptive immunity.

MHC class I receptors are displayed on a majority of body cells,

whilst **MHC class II**

Receptors are restricted to antigen-presenting cells (APCs)

Both of these receptor types interact with **TCRs**



The adaptive immune response consists of two branches,

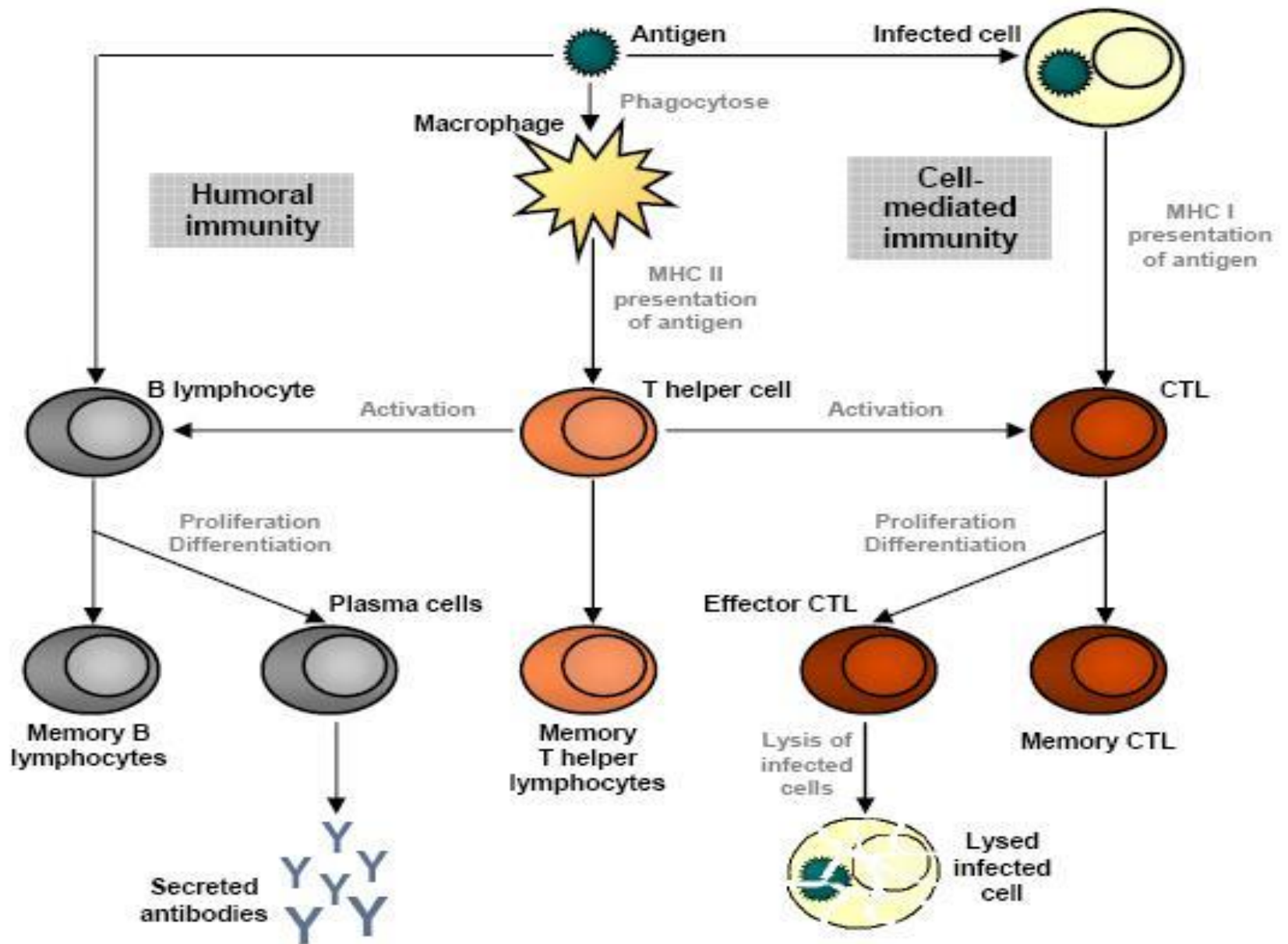
1- a cellular adaptive response

(effected by cytotoxic T cells) and

2-a humoral adaptive response (effected by B cells)

Two subtypes of **helper T cells (Th1 and Th2)** have been identified as being responsible

for guiding adaptive responses towards either a **cellular profile (Th1)** or a **humoral profile (Th2)**



The cellular adaptive response

Body cells are continuously processing protein derived from the internal cellular environment and presenting it in association with **MHC class I receptors**.

This will typically

‘self’ antigen (that is ignored by the immune system), but can also be peptides derived from infecting viruses or bacteria, or aberrant cancer peptides. Activated **cytotoxic T cells** of a given specificity

proliferate in the lymph and then migrate to sites of infection where they monitor body cells for signs of intracellular infection or aberrant self proteins associated with cancer – presented

on MHC class I molecules – using **their TCRs**. If they encounter antigen that they recognise, this indicates infection or malignancy, and they are then able to induce apoptosis (autodestruction) of targeted body cells. This constitutes the **cellular adaptive response**.

The humoral adaptive response

B cells can recognise antigen via their **BCRs**, without the need for prior processing or presentation via a receptor – so they are key to identifying extracellular pathogens (e.g. bacteria in the lymph). Once activated,

B cells differentiate into **plasma cells** that are capable of secreting antibody molecules

Once bound to a target, antibody **molecules can activate the classical pathway of the complement system**, thereby directing it to neutralise its targets with great specificity. Binding of antibody also enhances phagocytosis.

1 Antigen recognition
Immunocompetent B cells exposed to antigen. Antigen binds only to B cells with complementary receptors.

2 Antigen presentation
B cell internalizes antigen and displays processed epitope. Helper T cell binds to B cell and secretes interleukin.

3 Clonal selection
Interleukin stimulates B cell to divide repeatedly and form a clone.

4 Differentiation
Some cells of the clone become memory B cells. Most differentiate into plasma cells.

5 Attack
Plasma cells synthesize and secrete antibody. Antibody employs various means to render antigen harmless.

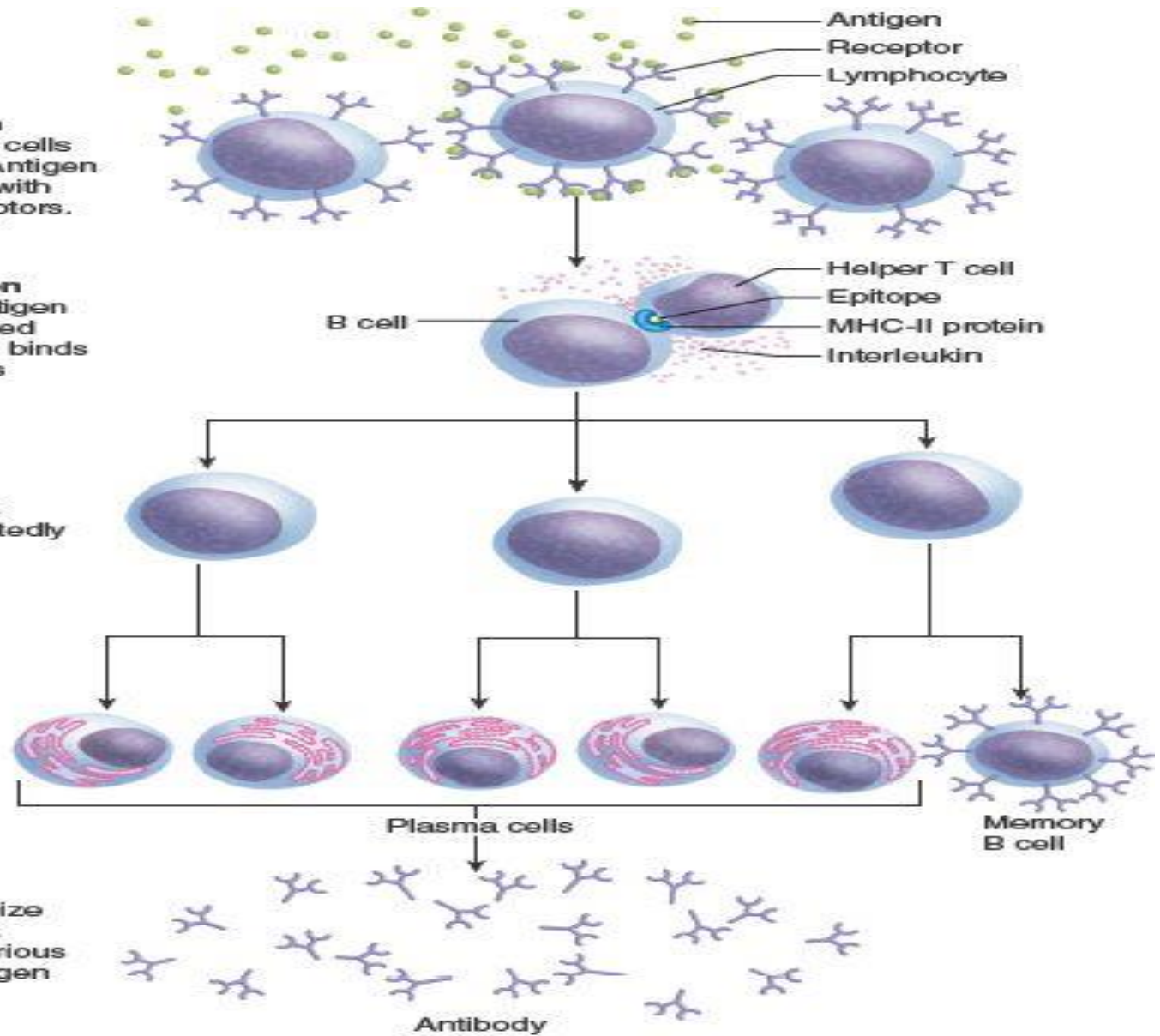


FIGURE 21.25 Clonal Selection and Ensuing Events of the Humoral Immune Response.

Immune memory

It is important to note that an effective primary adaptive) takes some time to develop,

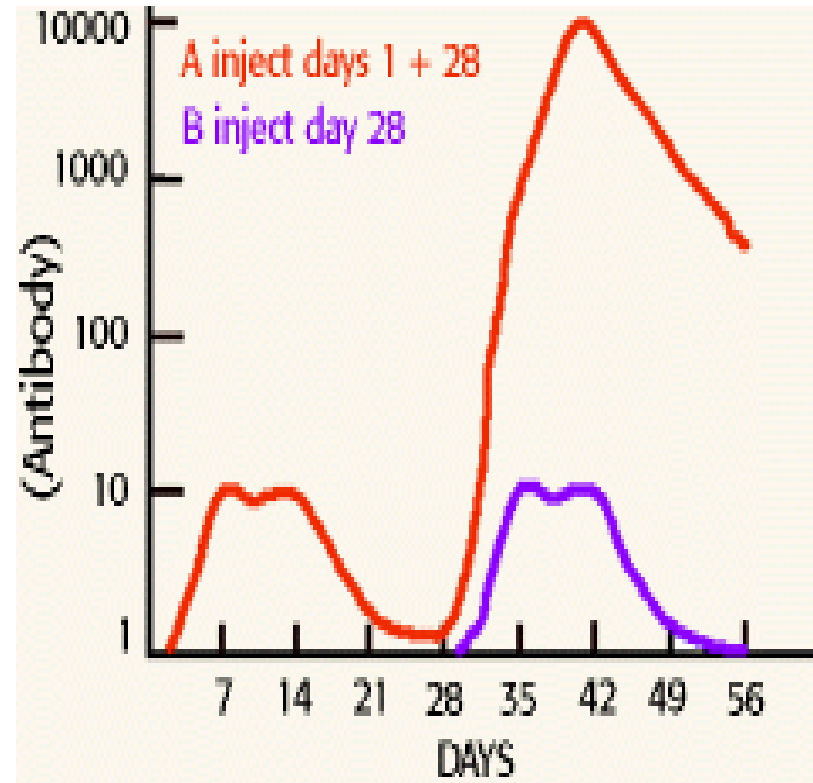
since only small numbers of target-specific B- and T cells are present initially and, once activated, they must first proliferate through a process known as **clonal selection**

to form **effector cells**. A proportion of these effector cells go on to form a stock of

long-lived memory cells ensuring that if a particular pathogen is encountered again, any subsequent develops more quickly and is thus **secondary adaptive response (or 'memory response')** more effective

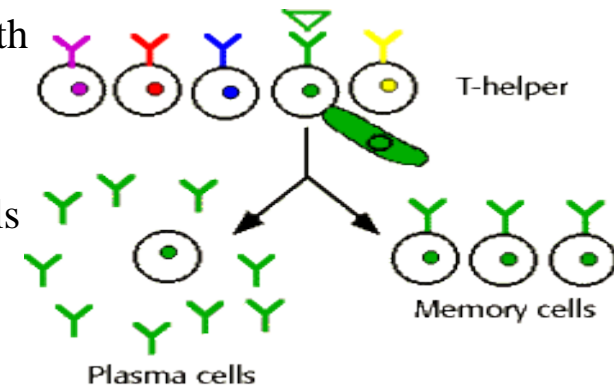
The graph shows a very important feature of the immune response. When first exposed to antigen "A", we begin to make low levels of antibody in about a week. However, a second exposure to antigen "A" produces a much faster response, and several orders of magnitude higher levels of antibody. The ability of antibody to bind antigen also increases dramatically in the secondary response. Injecting a new antigen "B" with "A" shows that a memory or prior exposure is required for the accelerated response. The memory of antigen and the stimulated response is the basis for success in vaccination programs. We explain memory by the clonal selection theory of the immune response.

Immunological response



The Clonal Selection Theory

- The immune system produces Billions of kinds of B-cells each making one kind of antibody receptor.
- The presence of antigen leads to the proliferation and differentiation of clones that have antibody capable of binding the antigen. In the diagram the "green" antigen binds to the green antibody on a B-cell. The color code means that only this antibody receptor on the cell binds free antigen.
- The "green" helper T-cell must give a stimulatory signal to allow a particular B-cell to be selected. This step allows a regulation or control of the process.
- The antigen driven selection produces memory cells and plasma cells secreting antibody capable of binding the original selecting antigen with high affinity..
- If antigen appears in the organism a second time, then the memory cells are already present at high levels, and produce a more rapid and much stronger immune response.



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Both of these receptor types interact with **TCRs**.

The Lymph System

Lymph is an alkaline (pH > 7.0) fluid that is usually clear, transparent, and colorless. It flows in the lymphatic vessels and bathes **tissues** and organs in its protective covering. it has a lower protein content than blood. Like blood, it is slightly heavier than water (density = 1.019 ± .003).

The human lymphoid system has the following:

- **primary organs:** **bone marrow** and the **thymus** gland (located behind the breastbone above the heart), and
- **secondary organs** at or near possible portals of entry for pathogens:
 - adenoids,
 - tonsils,
 - spleen (located at the upper left of the abdomen),
 - lymph nodes (along the lymphatic vessels with concentrations in the neck, armpits, abdomen, and groin),
 - Peyer's patches (within the intestines), and the appendix.

cellular adaptive immunity

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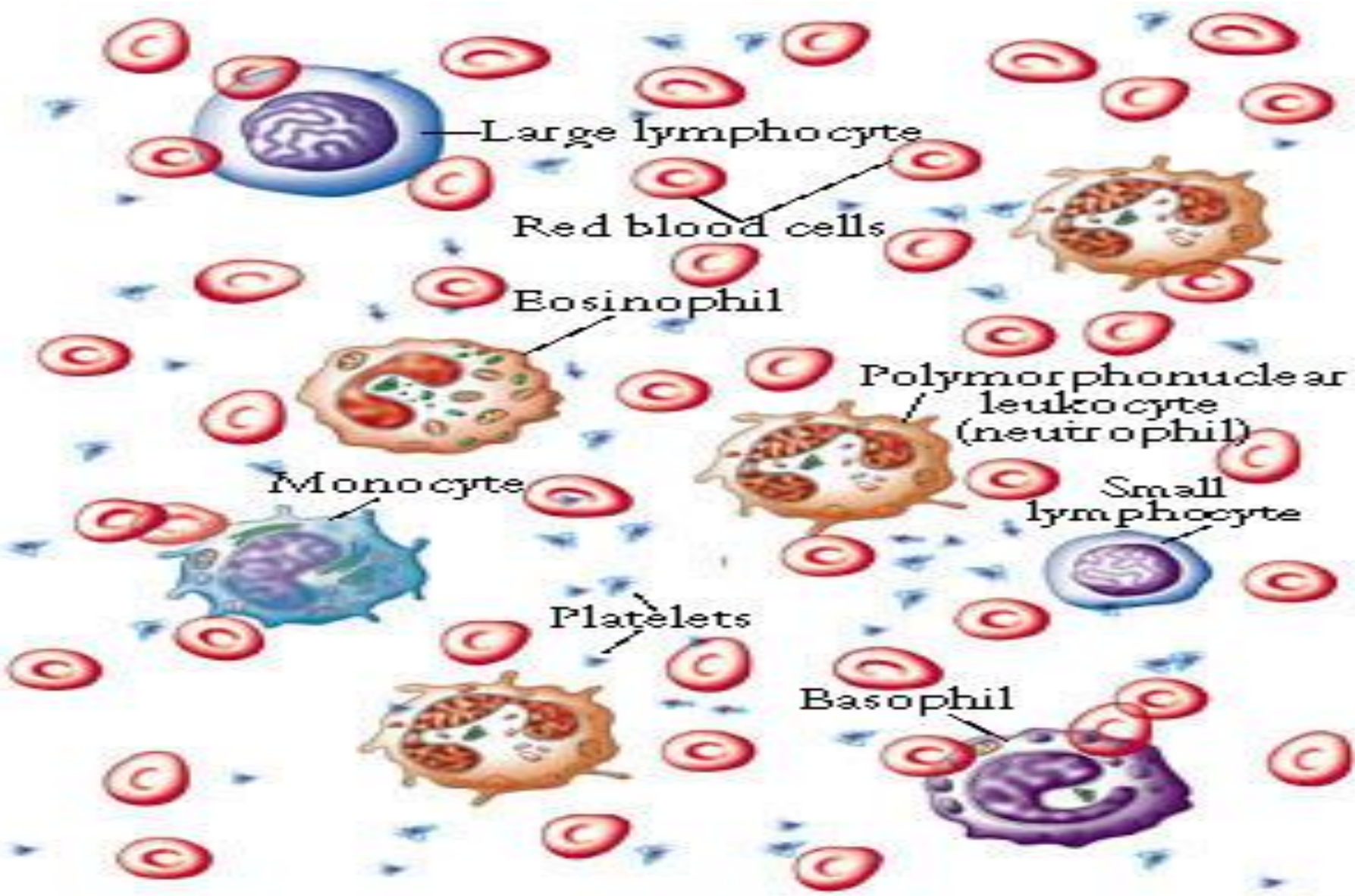
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Innate Immunity

The innate immunity system is what we are born with and it is nonspecific; all antigens are attacked pretty much equally. It is genetically based and we pass it on to our offspring.



Large lymphocyte

Red blood cells

Eosinophil

Monocyte

Polymorphonuclear leukocyte (neutrophil)

Small lymphocyte

Platelets

Basophil



1-Surface Barriers or Mucosal Immunity

- The first and, arguably, most important barrier is the **skin**. The skin cannot be penetrated by most organisms unless it already has an opening, such as a nick, scratch, or cut.
- Mechanically**, pathogens are expelled from the lungs by **ciliary** action as the tiny hairs move in an upward motion; **coughing and sneezing**; the **flushing** action of **tears, saliva, and urine** also force out pathogens.
- Sticky mucus** in respiratory and gastrointestinal tracts traps many microorganisms.
- Acid pH (< 7.0)** of skin secretions inhibits bacterial growth.
- **Hair follicles** secrete sebum that contains **lactic acid and fatty acids** both of which inhibit the growth of some (pathogenic bacteria and fungi. Areas of the skin not covered with hair, such as the palms and soles of the feet, are most susceptible to fungal infections. Think athlete's foot.)

- **Saliva, tears, nasal secretions,** and perspiration contain **lysozyme**, an enzyme that destroys Gram positive bacterial cell walls causing cell lysis. **Vaginal secretions** are also slightly).
- **Spermine and zinc** in **semen** destroy some pathogens.
- **Lactoperoxidase** is a powerful enzyme found in **mother's milk**.
- **The stomach** is a formidable obstacle insofar as its mucosa secrete hydrochloric acid (**HCl**) ($0.9 < \text{pH} < 3.0$, very acidic that kill many pathogens).

10-Normal flora are the microbes, mostly bacteria, that live in and on the body with, usually, no harmful effects to us.

- There are 10^3 – 10^4 microbes per cm^2 on the skin (*Staphylococcus aureus*, *Staph. epidermidis*, diphtheroids, streptococci, *Candida*, etc.).

-Various bacteria live in the **nose and mouth**.

- **Lactobacilli** live in the stomach and small intestine.

- The upper intestine has about **10^4 bacteria per gram** of which 95–99% are anaerobes

The urogenitary tract is lightly colonized by various bacteria

Normal flora produce (**bacteriocidins, defensins, cationic proteins, and lactoferrin**) all of which work to destroy other bacteria

The resident bacteria can become problematic when they invade spaces in which they were not meant to be. As examples:

(a) **staphylococcus** living on the skin can gain entry to the body through small cuts/nicks.

(b) Some **antibiotics**, (clindamycin), kill some of the bacteria in our intestinal tract. This causes an overgrowth of (***Clostridium difficile***,) which results in **colitis**, a rather painful condition wherein the inner lining of the intestine cracks and bleeds

11- **phagocyte** : is a cell that attracts (by chemotaxis), adheres to, engulfs, and ingests foreign bodies.

made in the bone marrow, after which they are released into the blood and called **monocytes**, which mature into **macrophages** .

-Some **macrophages** are concentrated in the lungs, liver (**Kupffer cells**), lining of the lymph nodes and spleen, brain, kidney mesoangial cells,

. They are long-lived,. Once a macrophage phagocytizes a cell, it places some of its proteins, called **epitopes**, on its surface.

These surface markers serve as an alarm to other immune cells that then infer the form of the invader.

All cells that do this are called antigen presenting cells (APCs).

The *wandering macrophages* roam the blood vessels and can even leave them to go to an infection site where they destroy dead tissue and pathogens. Emigration by squeezing through the capillary walls to the tissue is called **diapedesis** or **extravasation**. The presence of histamines at the infection site attract the cells to their source.

- **Natural killer cells** move in the blood and lymph to lyse cancer cells and virus-infected body cells. They are large granular **lymphocyte**.

- **neutrophils**, , are phagocytes that have no mitochondria., short-lived (half-life of 6–8 hours, 1–4 day lifespan), and have a segmented nucleus.

. The neutrophils provide the major defense against pyogenic (pus-forming) bacteria and are the first on the scene to fight infection. They are followed by the wandering macrophages about three to four hours later

Eosinophils are attracted to cells coated with complement C3B, where they release major basic protein (MBP), which work together to burn holes in cells and helminths (worms).

The **complement system** is a major triggered enzyme plasma system. It coats microbes with molecules that make them more susceptible to engulfment by phagocytes

Dendritic cells are covered with a membranous processes that look like **nerve cell dendrites**.

Most of them are highly efficient **antigen presenting cells**. There are four basic types:. Our major concern will be **Langerhans cells**, which are found in the epidermis and mucous membranes, especially in the anal, vaginal, and oral cavities. These cells make a point of attracting antigen and efficiently presenting it to T helper cells for their activation

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Adaptive or Acquired Immunity

. Lymphocytes constitute 20–40% of the body's WBCs. f!)

Lymphocytes come in two major types:

- **1-B cells 15%**, B cells are produced in the **stem cells** of the bone marrow;
- they produce **antibody** and oversee **humoral immunity.** ,
- **2-T cells. 80%** of them ,T cells are **nonantibody-producing** lymphocytes which are also produced in the bone marrow but sensitized in the **thymus** and constitute the basis of
- **cell-mediated immunity**

Humoral immunity

- when an **antigen** binds to its surface receptors in the(**APC**)
- there is a **T helper** cell nearby (to release a **cytokine**)
- . immature **B-lymphocyte** is stimulated to maturity

This **sensitizes** the B cell and it undergoes **clonal selection**, which means it reproduces asexually by mitosis

1-. Most of the family of clones become **plasma cells**. These cells produce highly specific **antibodies** at a rate of as many as 2000 molecules per second for four to five days.

2- The other B cells become long-lived **memory cells**.

Cell-mediated immunity

1-Macrophages engulf antigens, process them internally, then display parts of them on their surface together with some of their own proteins.

2--This sensitizes **the T helper cells** to recognize these antigens.

Helper T cells (CD4+) serve as managers, directing the immune response. They secrete chemicals called **lymphokines** that::

stimulate **cytotoxic T cells and B cells** to grow and divide, attract neutrophils, and enhance the ability of macrophages to engulf and destroy microbes.

Cytotoxic or killer T cells (CD8+) do their work by releasing **lymphotoxins**, which **cause cell lysis**.

Suppressor T cells inhibit the production of cytotoxic T cells once they are unneeded, lest they cause more damage than necessary.

Memory T cells are programmed to recognize and respond to a pathogen once it has invaded and been repelled.

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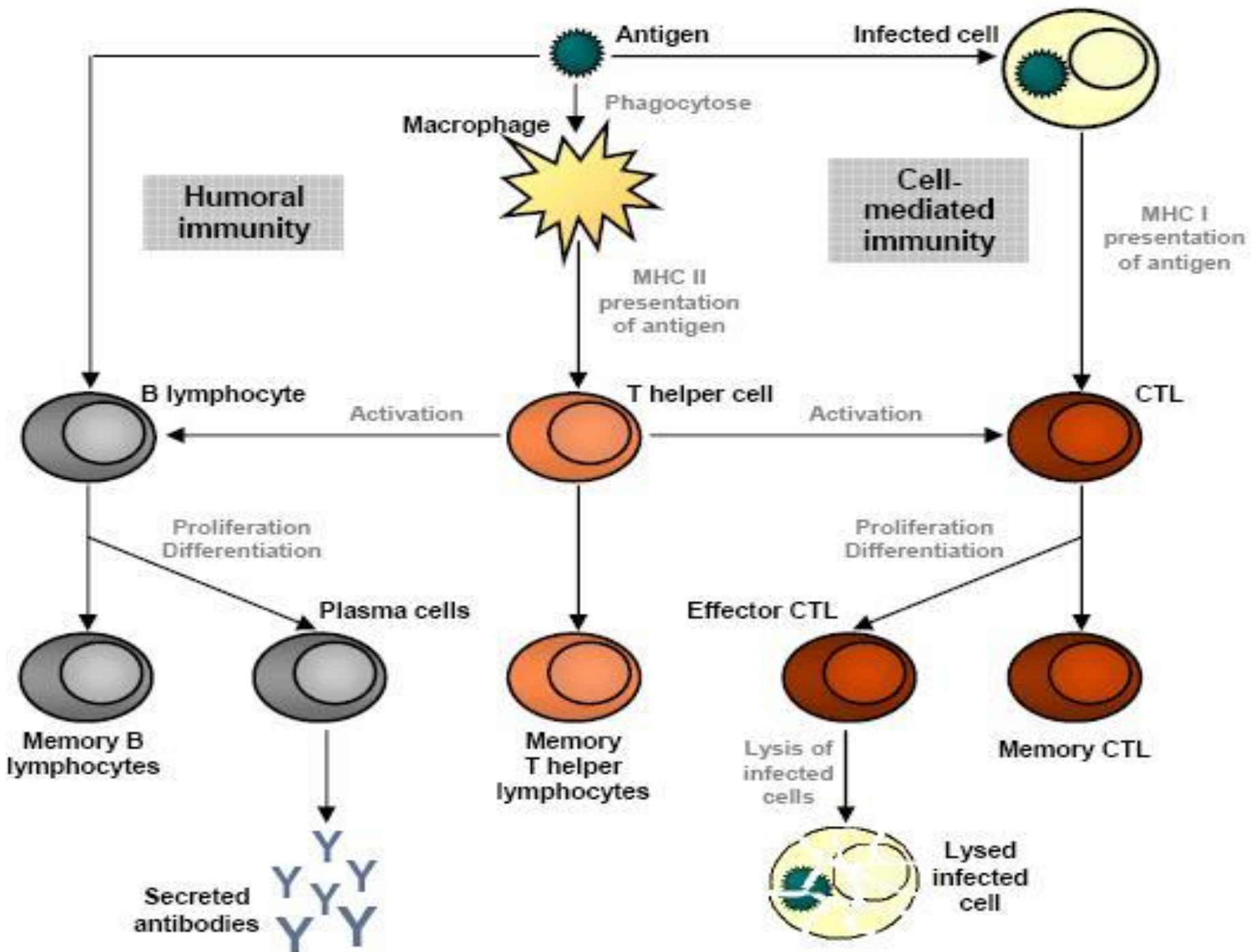


Table 1

innat immunity

Adaptive immunity

Response is antigen-independent

Response is antigen-dependent

There is immediate maximal response

There is a lag time between exposure and maximal response

Not antigen-specific

Antigen-specific

Exposure results in no immunologic memory

Exposure results in immunologic memory