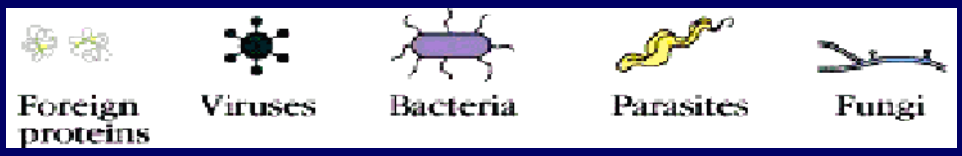
Infectious microbes



Foreign protiens, virus, bacteria, parasite, fungi

↓

Infection

Abnormal → Kill the host

Normal → Short-lived
little permanent damage

Why?

Immune system

- What is immune system?
- What does immune system do?
- How does immune system work?

Immunology

Immunology Department
Tianjin Medical University

Wenyan Niu

Aug, 2013

Chapter 1

Overview of Immunology

Key points

Master

The concept and the function of immunity
Features of innate and adaptive immunity
The components of immune system

Familiar

Key points of clonal selection theory

Understand

The history of immunology

What is immunity?

- Historically, **immunity** meant protection from diseases and, more specifically, infectious diseases.

- The molecules, cells and organs responsible for immunity constitute the **immune system**, and their collective and coordinated response to the foreign substances is called **immune response**.

- More inclusive definition of immunity is a reaction to foreign substances (Antigen), including microbes and macromolecules such as proteins and polysaccharides.

- **Immunology** is the study of the ways in which the body defends itself from infectious agents and other foreign substances in its environment.

The history of immunology

1. Experience immunology (17^{th}-19^{th} century)
2. Experimental immunology (19^{th} -1950’)
3. Modern immunology (1950’-)

1. Experience immunology (17^{th}-19^{th} century)

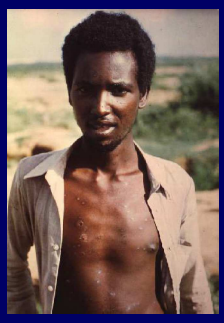
The ancient Chinese (Song dynasty): resistant to smallpox by inhaling powder made from the skin lesions of patients recovering from the disease.

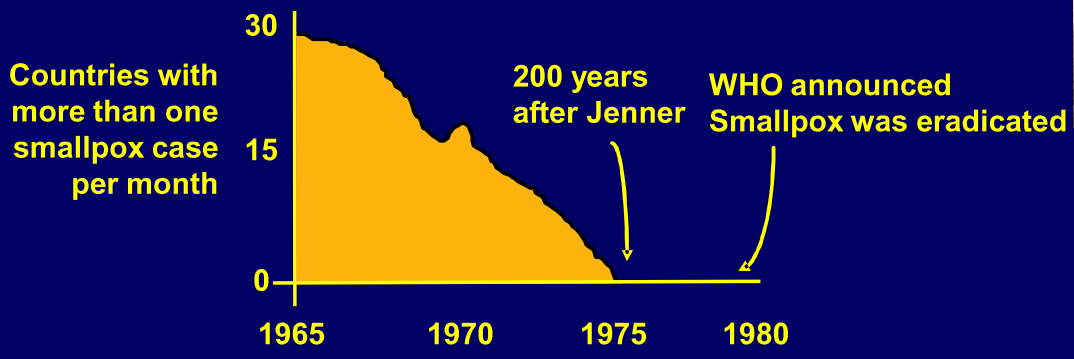
1717 England: Lady Mary Montagu

"The smallpox, so fatal, so general amongst us, is entirely harmless here by the invention of engrafting….I am patriot enough to bring this invention into fashion in England.

English physician, Edward Jenner (1749-1823): injected the material from a cowpox pustule into the arm of an 8-year-old boy.
(vaccination against smallpox)

Smallpox was the first disease that had been eliminated worldwide by a program of vaccination (1980).





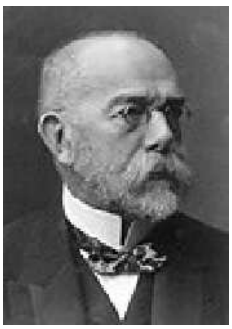
2. Experimental immunology (19th -1950’)

More pathogen were found

Invention of vaccine

Active immunity, Passive immunity

Cellular immunity, Humoral immunity



发现结核杆菌；提出病原菌致病的概念

Mycobacterium tuberculosis

Robert Koch
(1843-1910)

发现抗毒素并治愈一名白喉患者

Diphtheria

Emil von Behring

(1845-1917)

发现细胞吞噬作用，提出细胞免疫理论

Phagocytose

Eli Metchnikoff

(1845-1916)

提出体液免疫理论和抗体生成的侧链学说

Antibody

Paul Ehrilich

(1854-1915)

3. Modern immunology (1950’-)

Immunue system

Antibody

Mechanism of immunity

1957, Burnet clonal selection postulate

Since 1960's, there has been a remarkable transformation in understanding of the immune system and its functions.

Advances in cell culture techniques, immunochemistry, recombinant DNA methodology, x-ray crystallography and creation of genetically modified animals (especially transgenic and knockout mice) have changed immunology from a largely descriptive science into one in which diverse immune phenomena can be explained in structural and biochemical terms.

- **What is the immune system?**
- What does immune system do?
- How does immune system work?

Immune system

Organs	Cells	Molecules
1. primary lymphoid organs	Macrophage	Ig
Bone marrow	T cells	Complements
Thymus	B cells	Cytokines
2. secondary lymphoid organs	NK cells	
Spleen	Mast cells	MHC
Lymph nodes	Neutrophils	CD
Skin or mucosal associated lymphoid tissues	etc.	etc.

Human Lymphoid Organs

Approximately
2×10^{12} lymphocytes
in human body

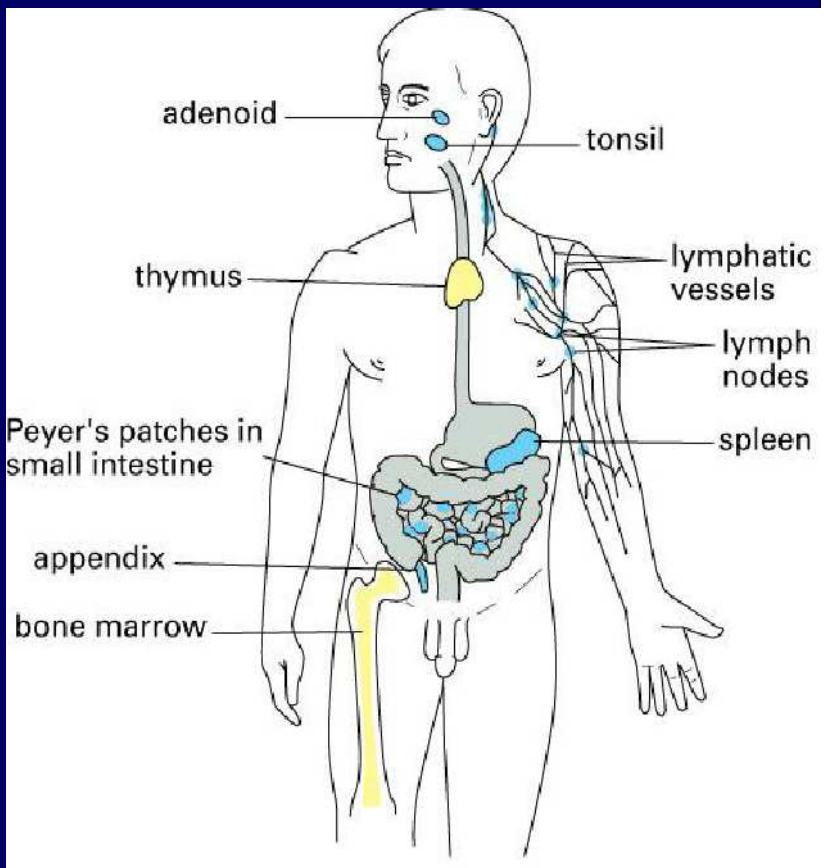
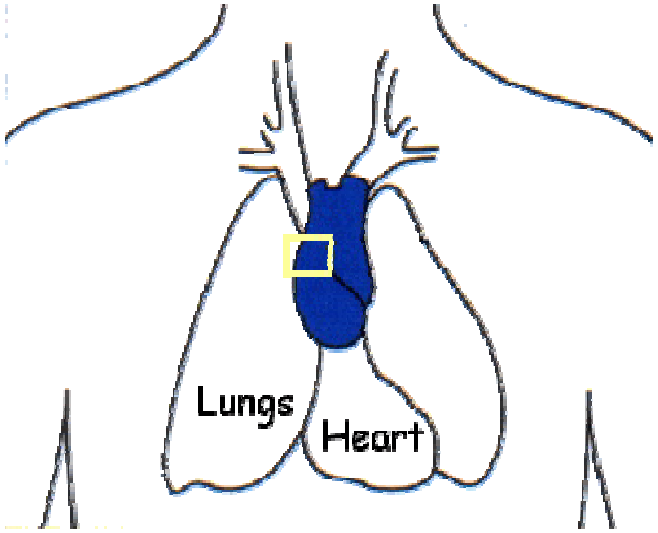
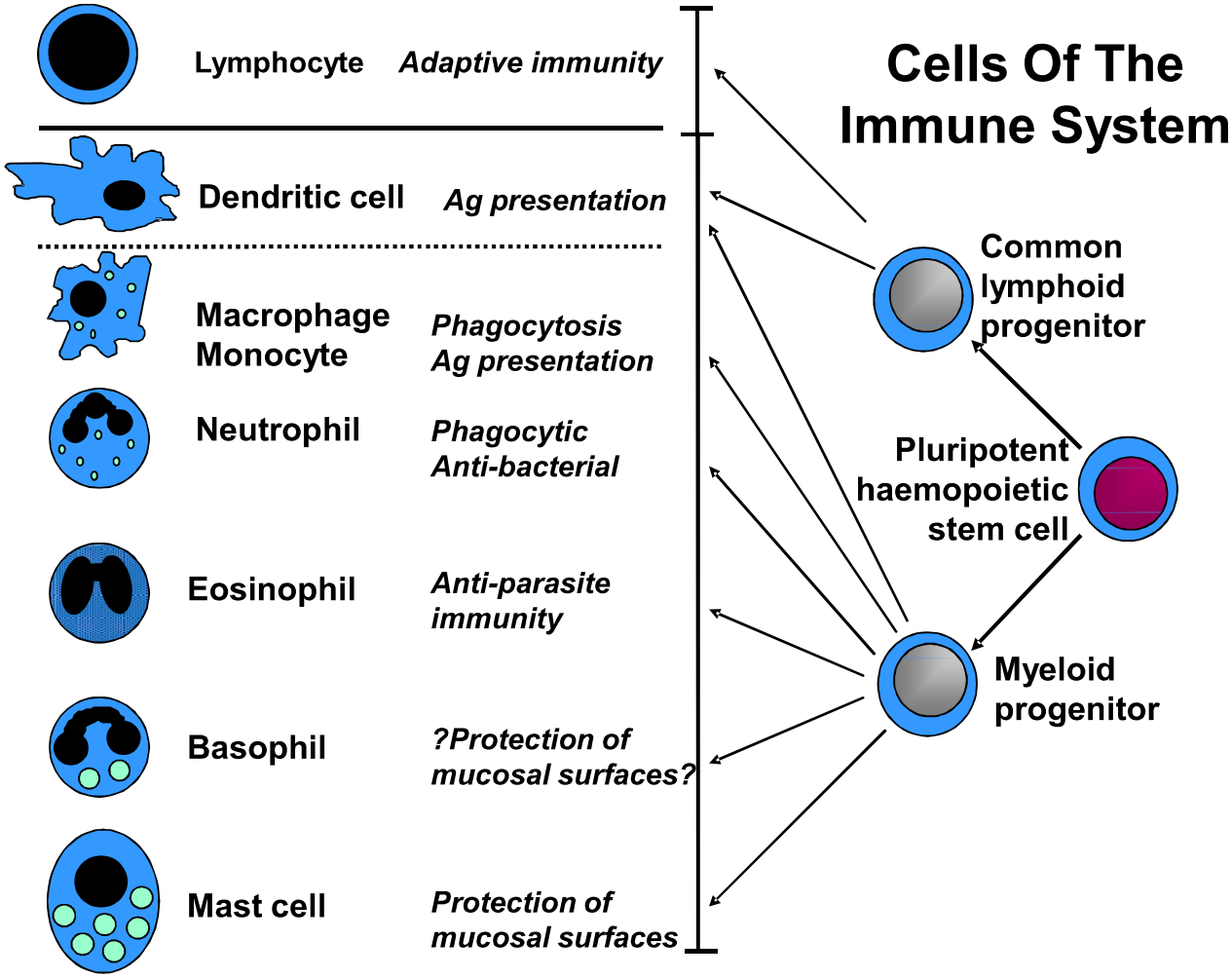


Figure 24–3. Molecular Biology of the Cell, 4th Edition.

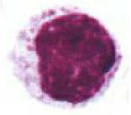
The Thymus




Cells Of The Immune System
Lymphocyte
Adaptive immunity
Dendritic cell
Ag presentation
Macrophage
Monocyte
Phagocytosis
Ag presentation
Neutrophil
Phagocytic
Anti-bacterial
Eosinophil
Anti-parasite immunity
Basophil
?Protection of mucosal surfaces?
Mast cell
Protection of mucosal surfaces
Common lymphoid progenitor
Pluripotent haemopoietic stem cell
Myeloid progenitor

淋巴细胞(T、B细胞)

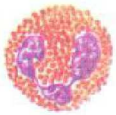
树突状细胞



NK细胞

单核细胞/巨噬细胞

中性粒细胞



嗜酸粒细胞

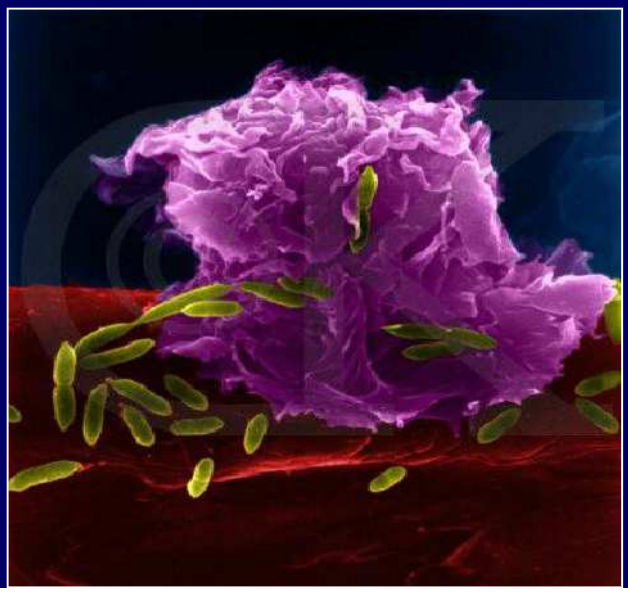
嗜碱粒细胞

肥大细胞

红细胞

血小板

免疫细胞种类



macrophages in lung phagocytose E. coli

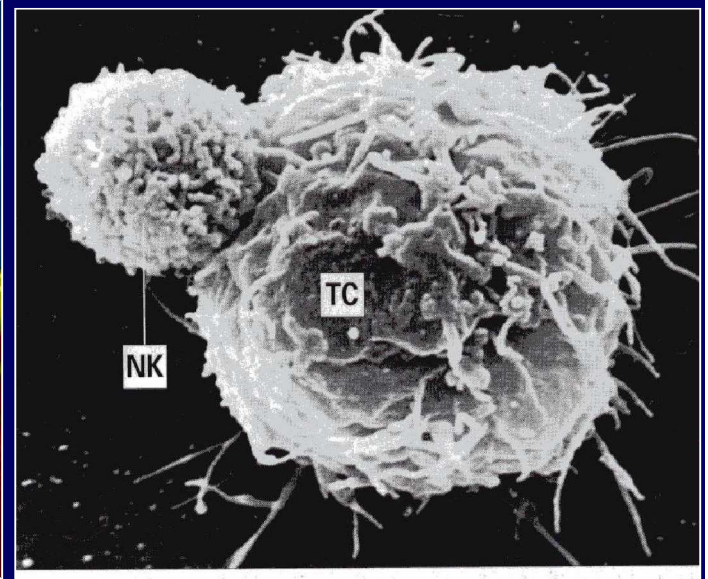


Fig. 2.17 An NK cell (NK) attached to a target cell (TC). ×4500.

- What is the immune system?
- **What does immune system do?**
- How does immune system work?

- Exclusion of non-self from self (e.g. physical barrier)
- Separate self from non-self

  self: our normal constituents (not antigens, but sometimes can become self antigens)

  non-self: foreign material (non-self antigens)

- Removal of non-self if self is penetrated

- What is the immune system?
- What does immune system do?
- **How does immune system work?**

Immune Responses

All viruses, some bacteria and some protozoan parasites replicate inside host cells. In order to clear infection, immune system must recognize and destroy these infected cells.

Many bacteria and larger parasites live in tissues, body fluids or other extracellular spaces, and the responses to these pathogens are quite different.

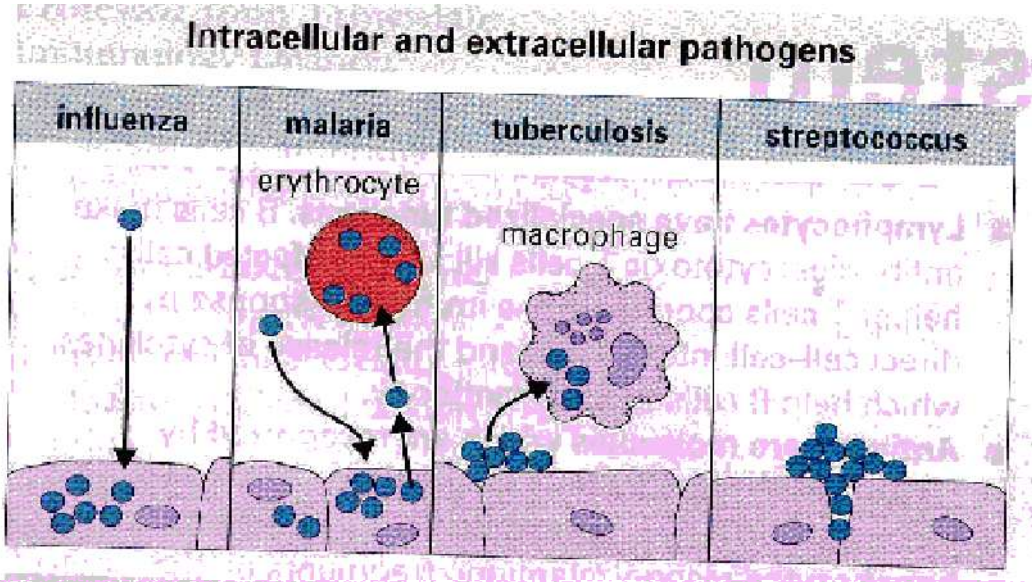


Fig. 1.2 All infectious agents spread to infect new cells by passing through the body fluids or tissues, but many pathogens must infect cells of the body to divide. For example, viruses such as influenza must invade cells to reproduce, while *Plasmodium* spp. (malaria) have two separate phases of division, either in cells of the liver or in erythrocytes. The mycobacteria which cause tuberculosis can divide extracellularly or within macrophages. Some bacteria such as the streptococci, which produce sore throats and wound infections, generally divide outside cells.

During the course of an infection, however, even intracellular pathogens must reach their target cells by moving through the blood and tissue fluid. At this time they are susceptible to elements of the immune system, which normally counter extracellular pathogens.

immune response involves:

- recognition of the pathogen or other foreign material.
- reaction to eliminate it.

Broadly, the different types of immune response fall into two categories:

1. innate (or non-adaptive) immune responses
2. adaptive immune responses

Innate and adaptive immunity

1. Innate immunity (**natural** or **native immunity**) consists of mechanisms that exist before infection, are capable of rapid responses to microbes, and react in essentially the same way to repeated infections.

Features of innate immunity

1. exist before infection
2. rapid responses
3. non-specific
4. no memory

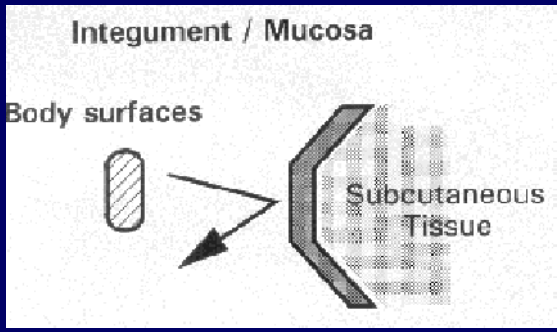
Components:

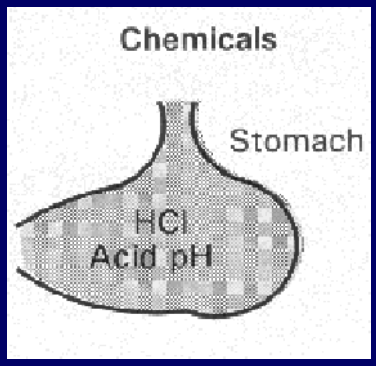
physical and chemical barriers

blood proteins

cytokines

phagocytic cells (phagocytes)





Components:

physical and chemical barriers

blood proteins (complements, etc.)

cytokines

phagocytic cells (phagocytes)

Components:

physical and chemical barriers

blood proteins

Cytokines (IL, TNF, etc.)

phagocytic cells

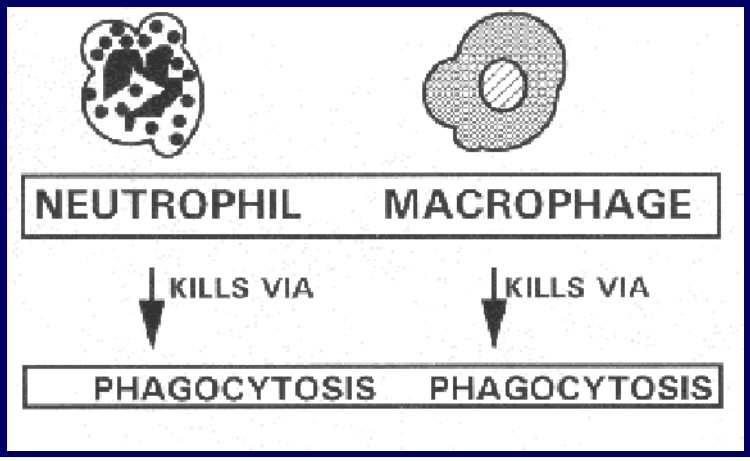
Components:

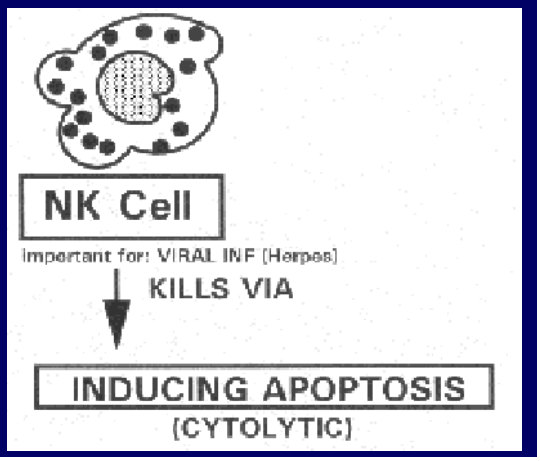
physical and chemical barriers

blood proteins

Cytokines

phagocytic cells (macrophage, neutrophil)





In contrast to innate immunity, more highly developed defense mechanisms are stimulated by exposure to infectious agents and increase in magnitude and defensive capabilities with each successive exposure to a particular microbes.

Because this form of immunity develops as a response to infection and adapts to the infection, it is called adaptive immunity.

2. Adaptive immunity
(specific immunity or acquired immunity)

specificity for foreign substances (**antigen**) and an ability to remember and respond more vigorously to repeated exposures to the same antigen.

Components: mainly **lymphocytes** and their products

Features of adaptive immunity

1. acquired
2. response slowly but stronger
3. specific
4. memory

3. The differences and the links between innate immunity and adaptive immunity

The differences:

The important difference between these is that an adaptive immune response is highly specific for a particular pathogen.

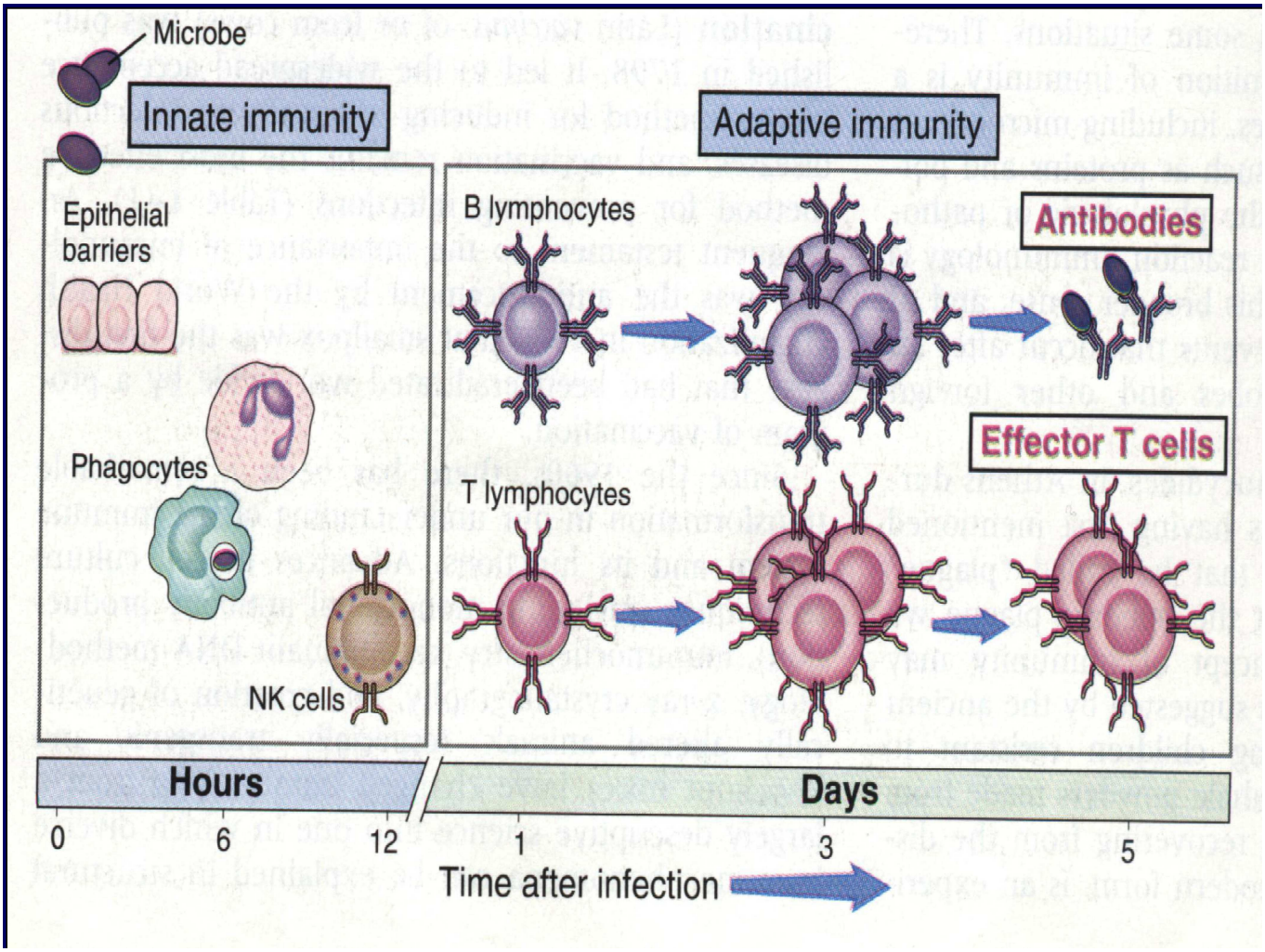
Moreover, the innate response does not alter on repeated exposure to a given infectious agent, but the adaptive response improves with each successive encounter with the same pathogen.

In fact the adaptive immune system "remembers" the infectious agent and can prevent it from causing disease later.

The links:

innate immune response → adaptive immune response

adaptive immune responses use many of
the effector mechanisms of innate immunity
to eliminate microbes.


Microbe
Innate immunity
Adaptive immunity
Epithelial barriers
Phagocytes
NK cells
B lymphocytes
Antibodies
Effector T cells
T lymphocytes
Hours
Days
0
6
12
1
3
5
Time after infection

Type of adaptive immune responses

1. **Humoral immunity**

2. **Cell-mediated immunity or cellular immunity**

Humoral immunity

- Mediated by antibodies in the blood, that are produced by B lymphocytes. Antibodies specifically recognize microbial antigens, neutralize the infectivity of the microbes, and target microbes for elimination by various effector mechanisms.

- It is the principal defense mechanism against extracellular microbes and their toxins, because antibodies can bind to these microbes and toxins to assist in their elimination.

Cellular immunity

- Mediated by T lymphocytes.
- Intracellular microbes, such as viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell-mediate immunity, which promotes the destruction of microbes residing in phagocytes or the lysis of infected cells.

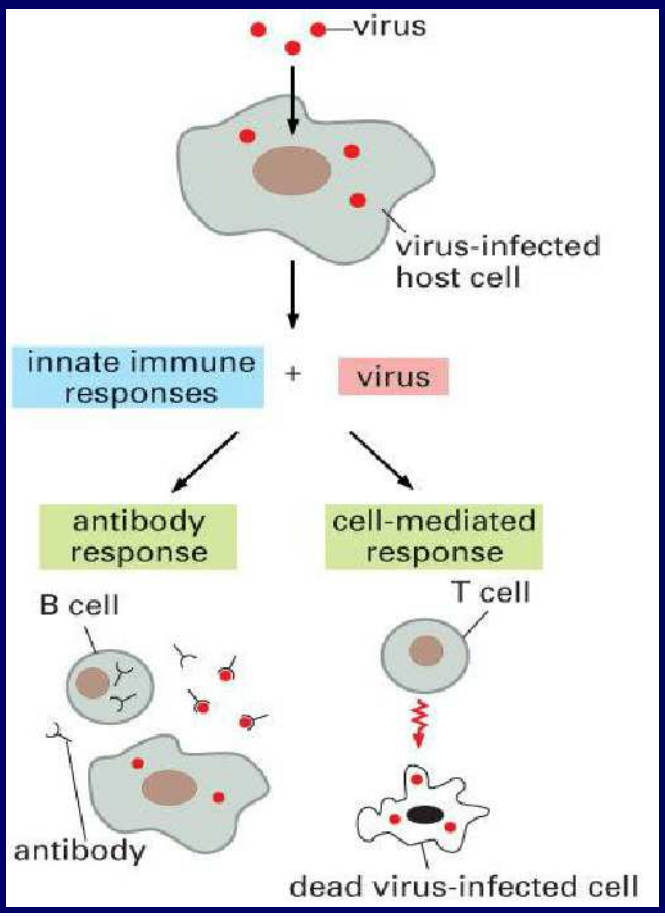
Adaptive immune response

Antibody Responses
(B-cells responses)
Humoral Immunity

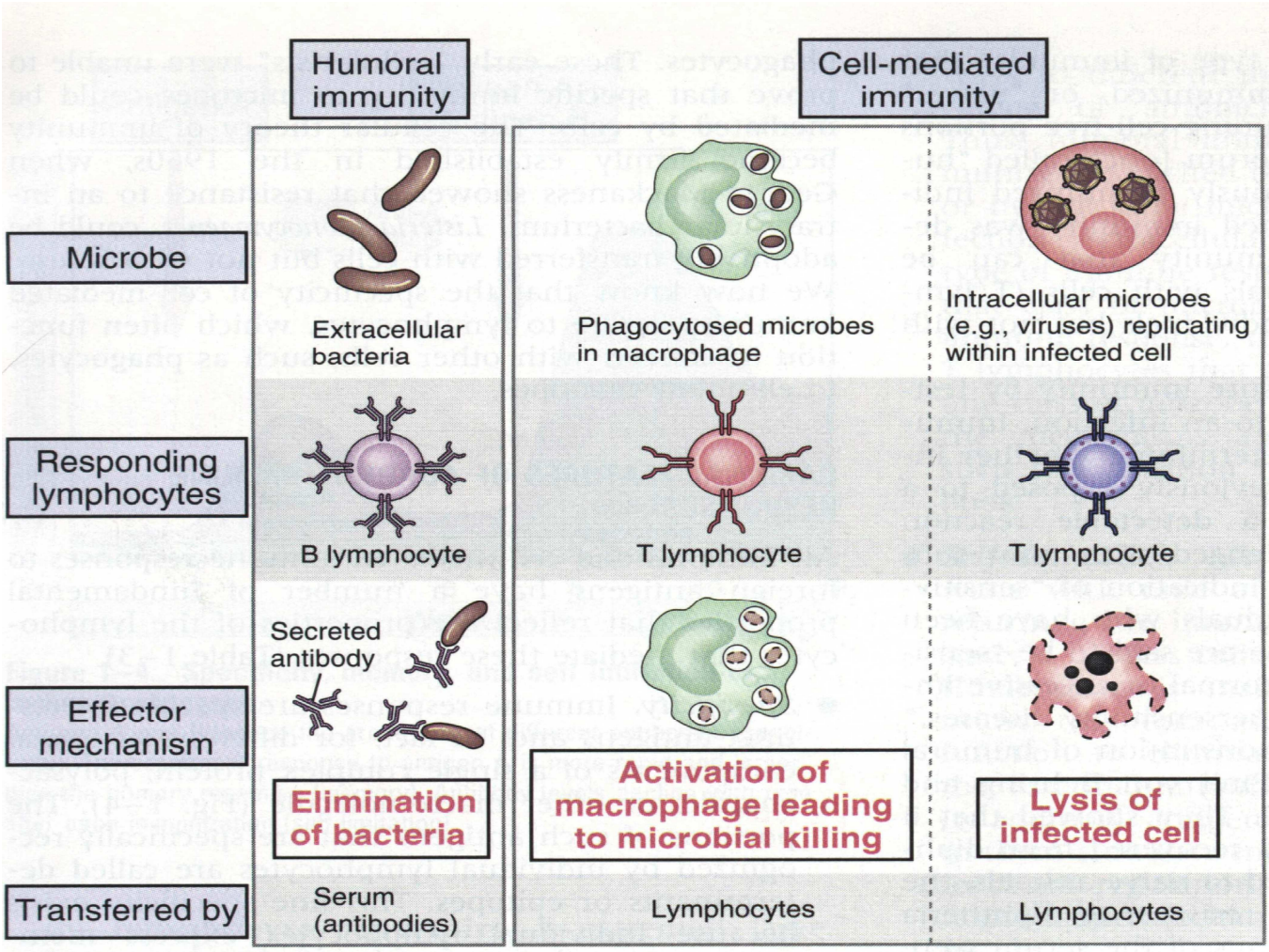
Cell-mediated Responses
(T-cell responses)
Cellular immunity

adaptive immune responses

Called a B-cell response as the cells are derived from bone marrow



Called a T-cell response as the cells are derived from the thymus


Humoral immunity
Cell-mediated immunity
Microbe
Responding lymphocytes
Effector mechanism
Transferred by
Extracellular bacteria
Phagocytosed microbes in macrophage
Intracellular microbes (e.g., viruses) replicating within infected cell
B lymphocyte
T lymphocyte
T lymphocyte
Secreted antibody
Elimination of bacteria
Activation of macrophage leading to microbial killing
Lysis of infected cell
Serum (antibodies)
Lymphocytes
Lymphocytes

The classic experiment showing that lymphocytes are required for adaptive immune responses to foreign antigens

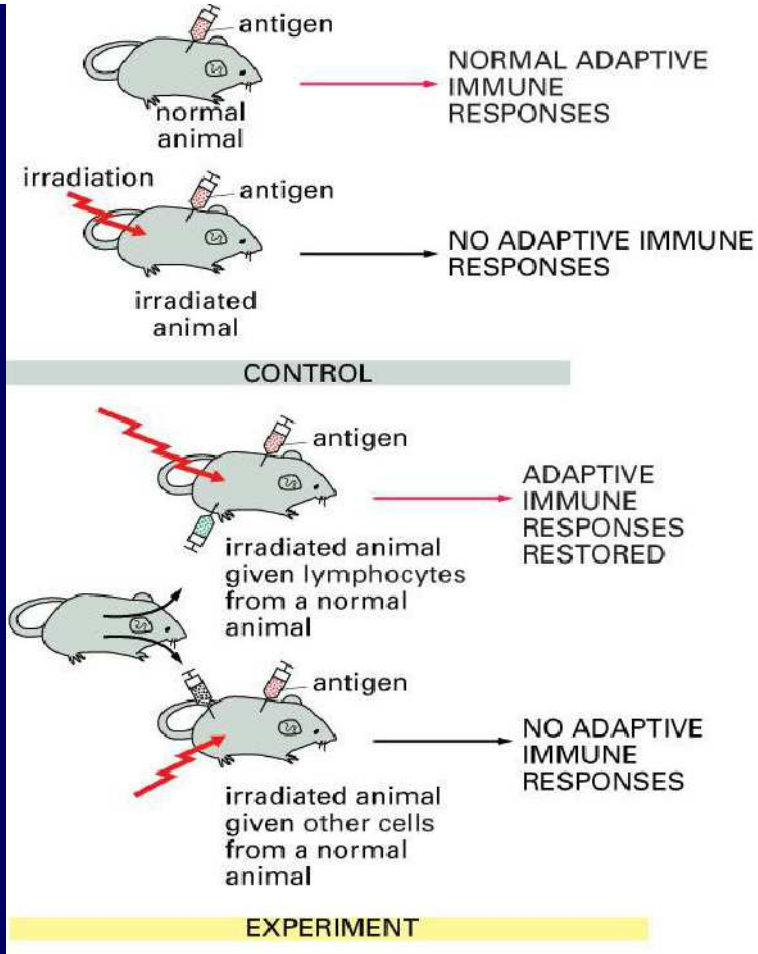


Figure 24–4. Molecular Biology of the Cell, 4th Edition.

Humoral immunity can be transferred to naïve individuals by antibody-containing cell-free portions of the blood (plasma or serum) obtained from immunized individuals.

Cellular immunity can be transferred to naïve individuals with cells (T lymphocytes) from immunized individuals.

This type of protective immunity is called passive immunity.

There is another type of protective immunity called active immunity.

Active immunity: induced by exposure to antigen.

Passive immunity: acquired by transferring serum or lymphocytes from a specifically immunized individual (adoptive transfer). *Rapidly*

1879 Louis Pasteur

Pasteurella multocida

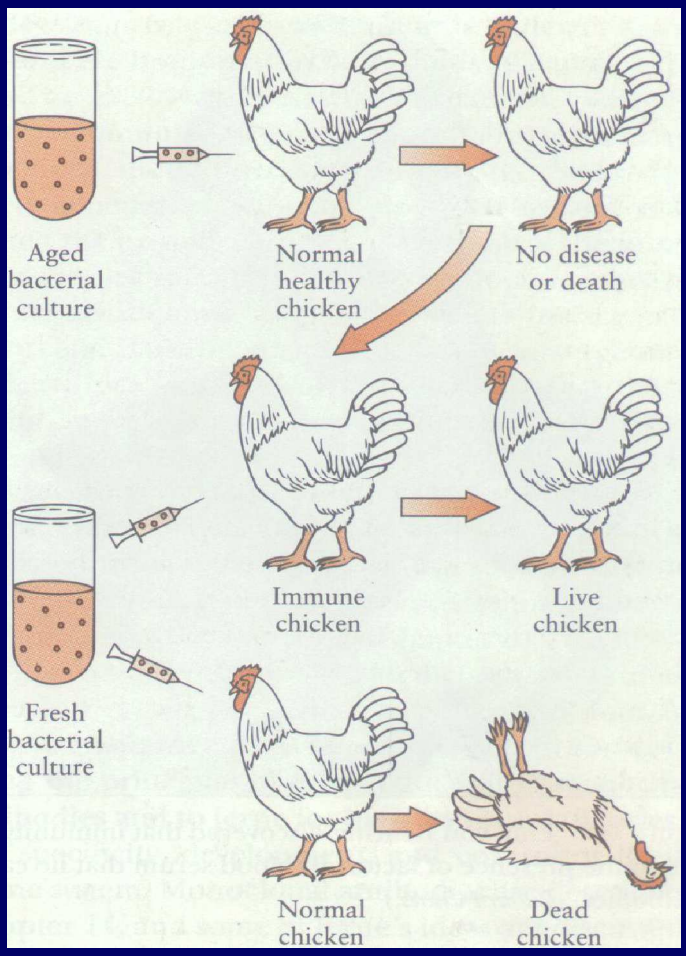
Fowl cholera

Pasteurella multocida

rabies vaccine

anthracnose vaccine

vaccine



BEHRING.

KITASATO.

Emil Von Behring

Kitasato

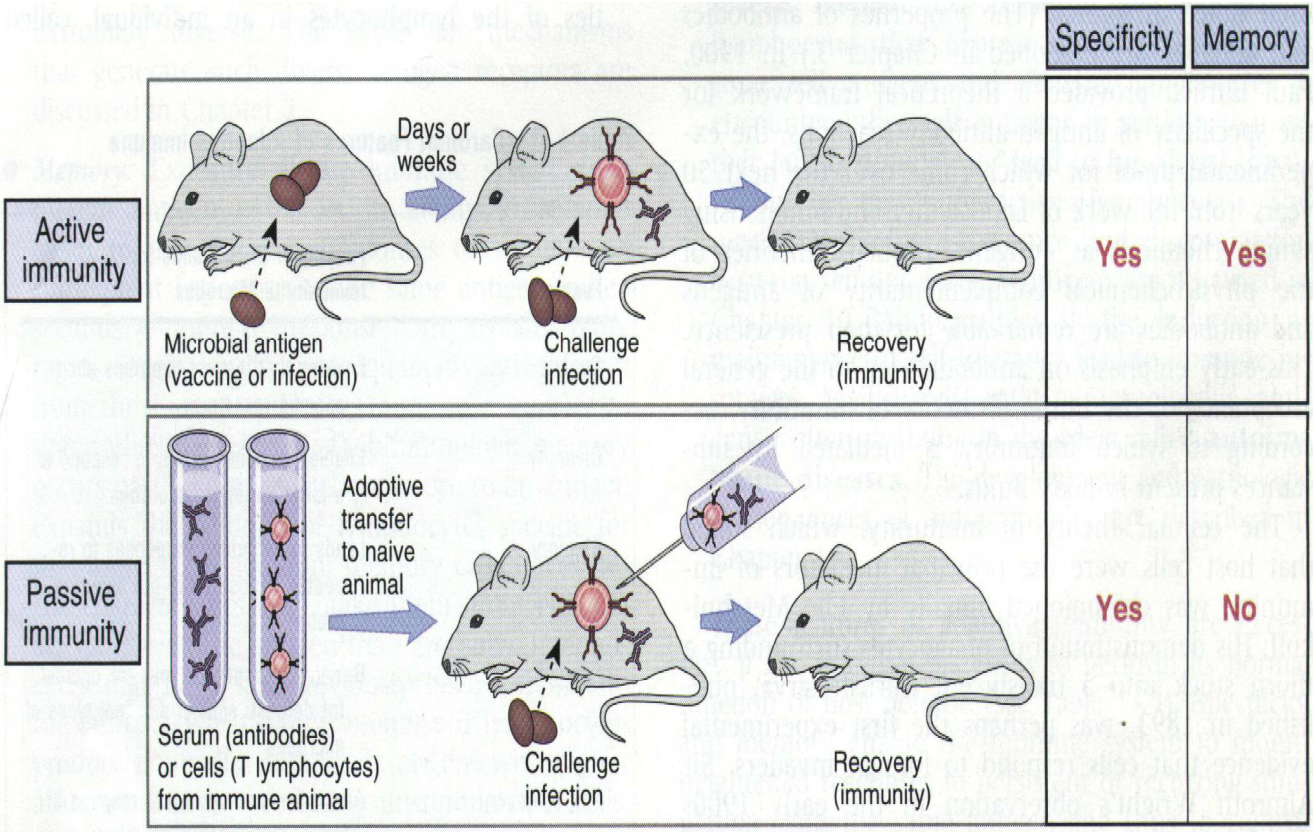
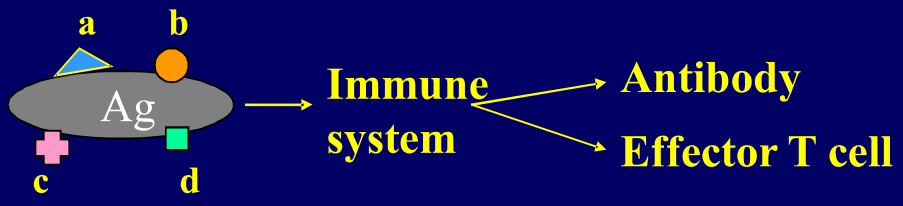


Figure 1–3 Active and passive immunity.

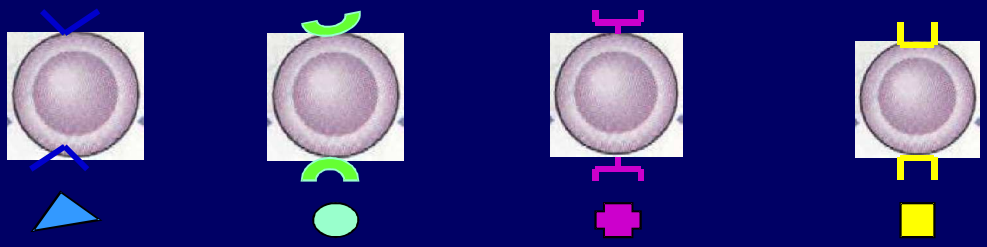
Active immunity is conferred by a host response to a microbe, whereas passive immunity is conferred by adoptive transfer of antibodies or T lymphocytes specific for the microbe. Both forms of immunity provide resistance to infection and are specific for microbial antigens, but only active immune responses generate immunologic memory.

Features of adaptive immune responses

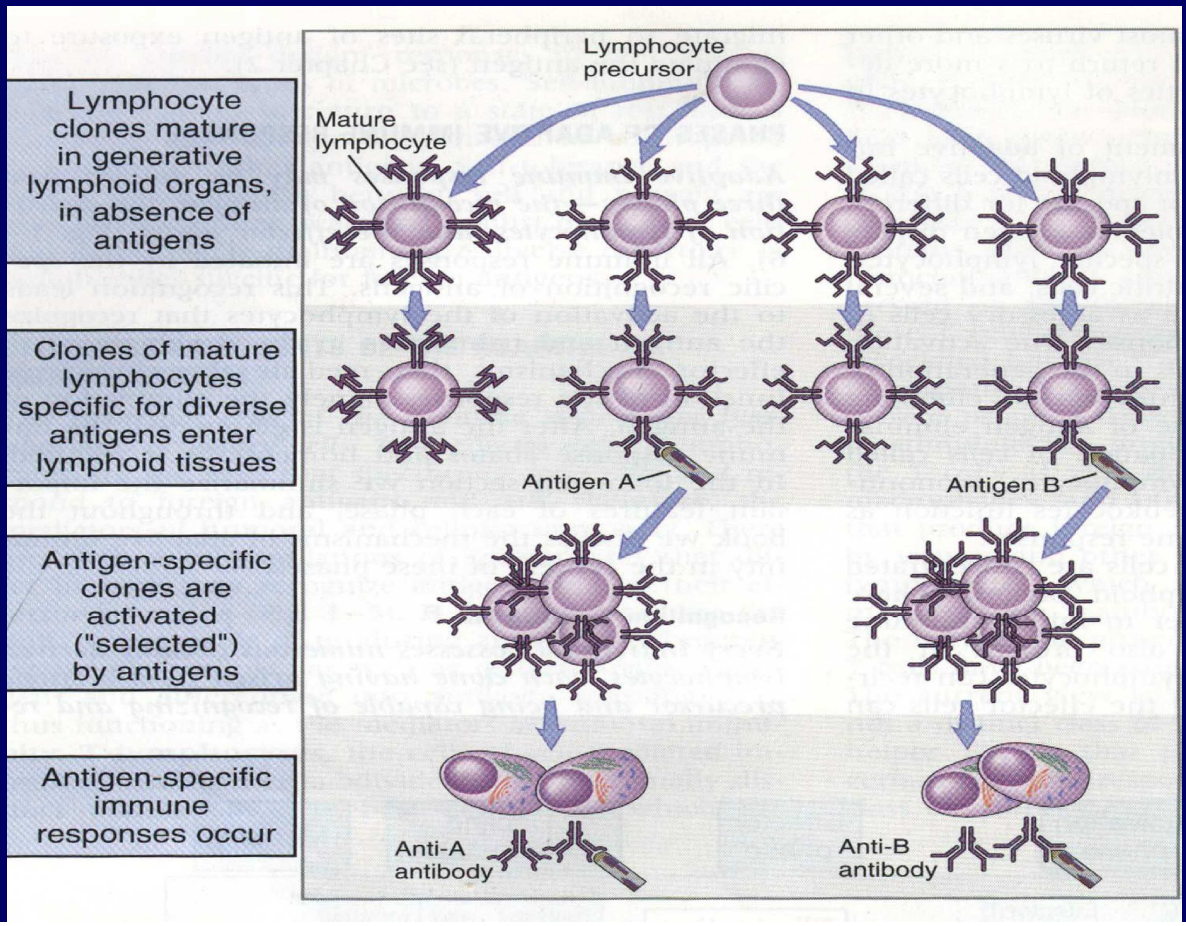
1. Specificity. Immune responses are specific for distinct antigens and in fact, for different structural components of an antigen (called determinants or epitopes)



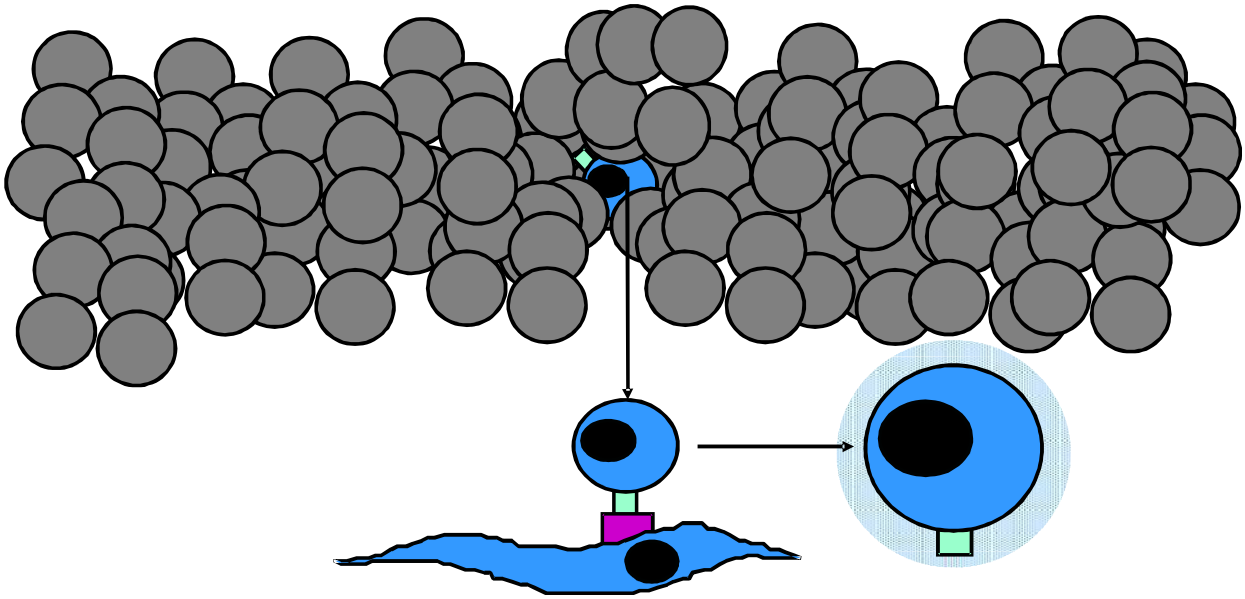
- This fine specificity exists because individual lymphocytes express membrane receptors that are able to distinguish subtle differences in structure between distinct antigens.
- Clones of lymphocytes with different specificities are present in unimmunized individuals and are able to recognize and respond to foreign antigens.



Clonal selection hypothesis



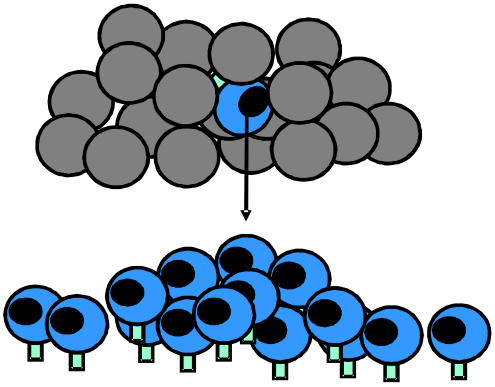
Clonal selection theory



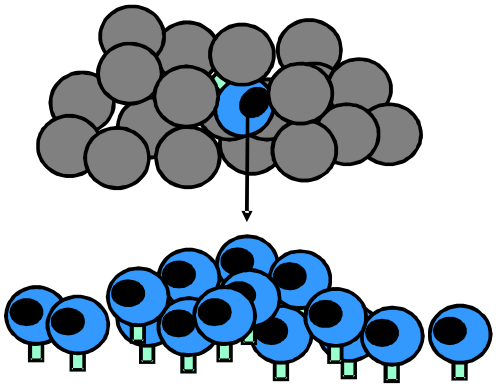
Each lymphocyte bears a single type of receptor of unique specificity.
Antigen interaction leads to lymphocyte activation.

Daughter cells bear identical antigen specificity to the parent cell.

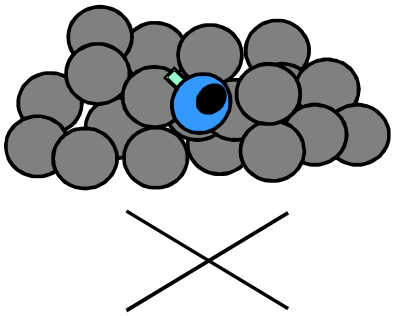
Clonal selection induces proliferation and increases effector cell frequency



Clonal nature of adaptive immune response allows for removal of harmful cells

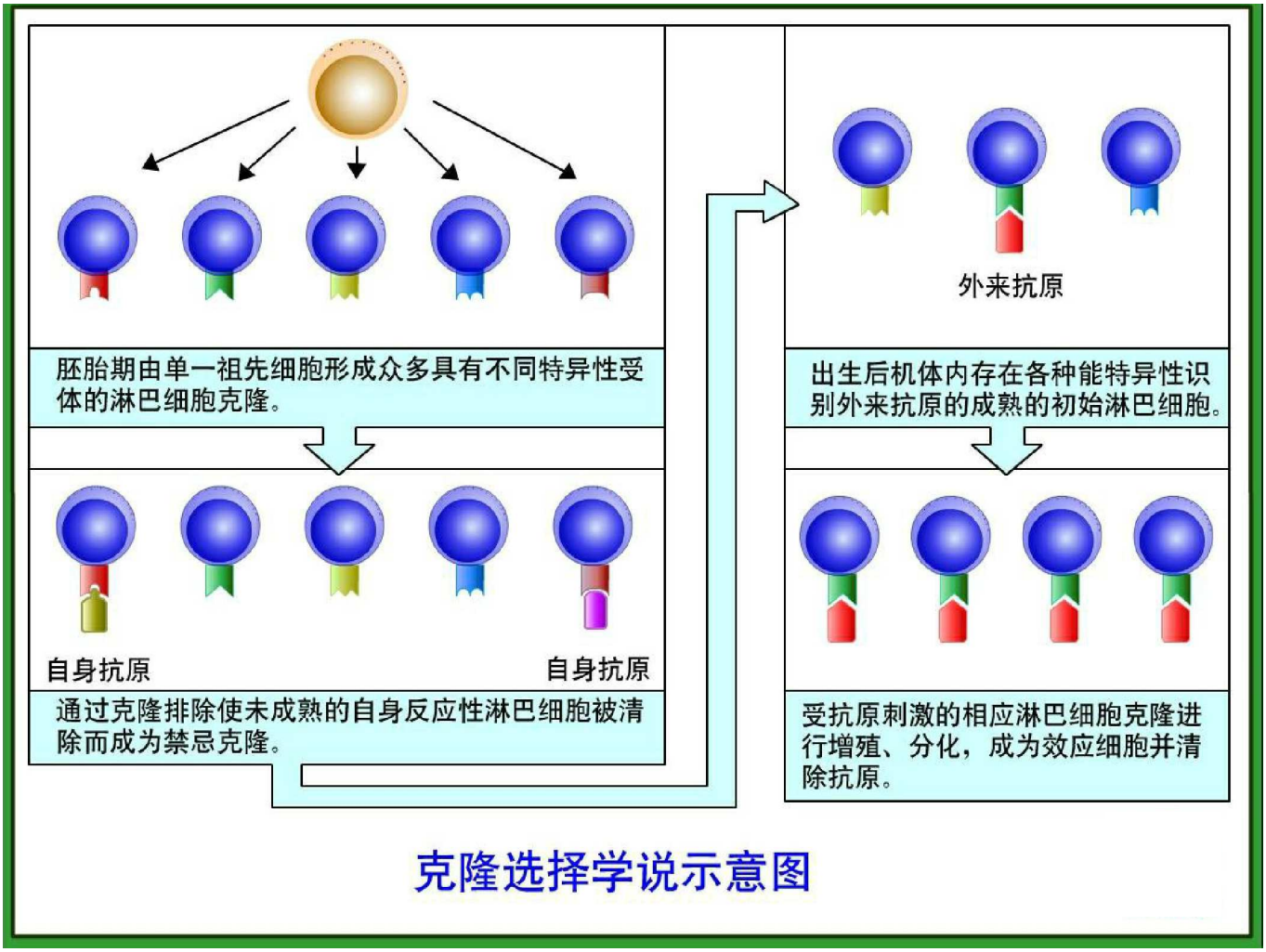


!!!!Cells specific for self antigen!!!!



Opportunity to remove harmful specificity at an early stage of development
IMMUNOLOGICAL TOLERANCE

Antigen receptors recognising self antigens can be individually purged from the antigen receptor REPERTOIRE before clonal expansion


外来抗原
胚胎期由单一祖先细胞形成众多具有不同特异性受体的淋巴细胞克隆。
出生后机体内存在各种能特异性识别外来抗原的成熟的初始淋巴细胞。
自身抗原
自身抗原
通过克隆排除使未成熟的自身反应性淋巴细胞被清除而成为禁忌克隆。
受抗原刺激的相应淋巴细胞克隆进行增殖、分化，成为效应细胞并清除抗原。

克隆选择学说示意图

2. Diversity. The total number of antigenic specificities of the lymphocytes in an individual (**lymphocyte repertoire)** is extremely large.

The mammalian immune system can discriminate 10^9 to 10^{11} distinct antigenic determinants.

3. Memory. Exposure of the immune system to a foreign antigen enhances its ability to respond again to that antigen.

primary immune responses: the first exposures to the antigen

secondary immune responses: responses to second and subsequent exposures to the same antigen. Memory cells more rapid, larger, more efficient at eliminating the antigen

B-cell clonal selection

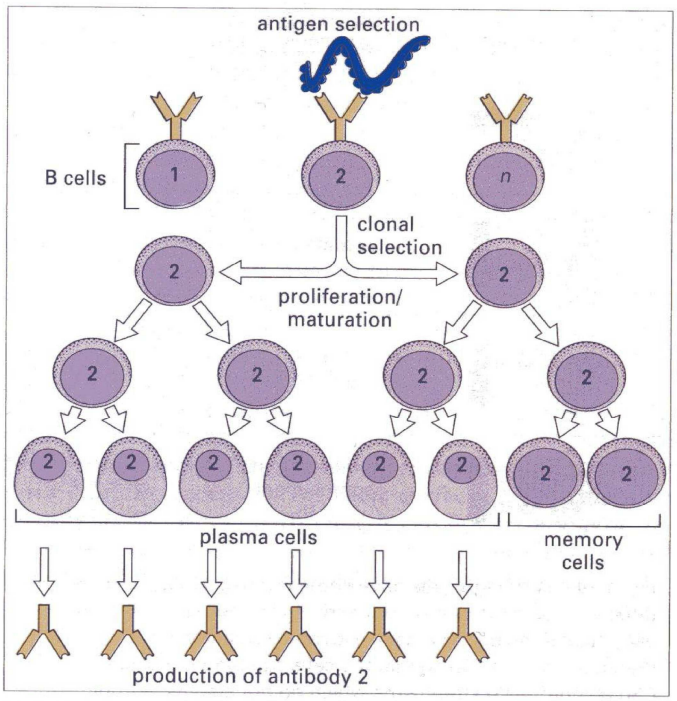


Fig. 1.13 Each antibody-producing cell (B cell) is programmed to make just one antibody, which is placed on its surface as an antigen receptor. Antigen binds to only those B cells with the appropriate surface receptor – B cell 2 in this example. In this way these cells are stimulated to proliferate and mature into antibody-producing cells, and the longer-lived memory cells, all having the same antigen-binding specificity.

4. **Specialization.** The immune system responds in distinct and special ways to different microbes.
5. **Self-limitation.** All normal immune responses wane with time after antigen stimulation, thus returning the immune system to its resting basal state (**homeostasis**).
6. **Nonreactivity to self.** Immune system recognize, respond to, and eliminate many foreign (nonself) antigens while not reacting harmfully to that individual's self substances (**tolerance**). Abnormalities in self-tolerance lead to **autoimmune diseases**.

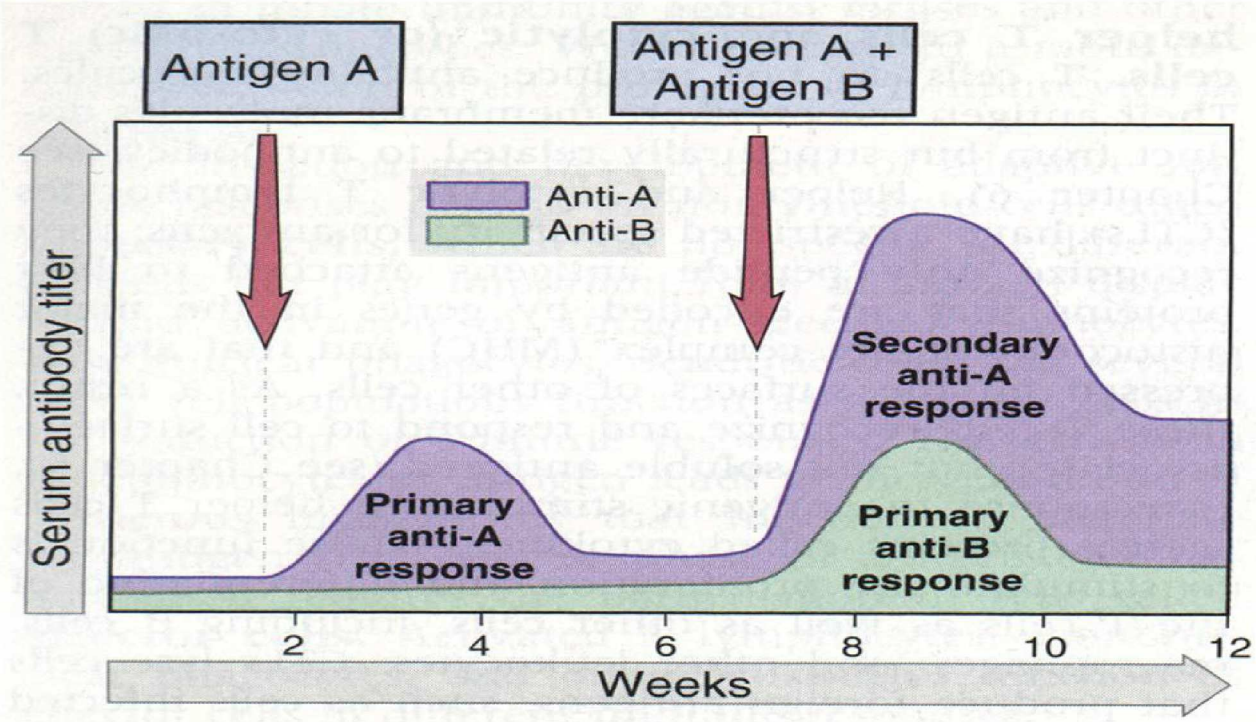


Figure 1–4 Specificity, memory, and self limitation of immune responses.
Antigens A and B induce the production of different antibodies (specificity). The secondary response to antigen A is more rapid and larger than the primary response (memory). Antibody levels decline with time after each immunization (self limitation).

Features of adaptive immune responses

Feature	Functional significance for immunity to microbes
Specificity	Ensures that distinct microbes elicit specific responses
Diversity	Enables immune system to respond to a large variety of microbes
Memory	Leads to enhanced responses to repeated exposures to the same microbe
Specialization	Generates responses that are optimal for defense against different types of microbes
Self-limitation	Allows immune system to respond to newly encountered microbes
Nonreactivity to self	Prevents injury to the host during responses to microbes

Cellular components of the adaptive immune system

1. Lymphocytes:

*B lymphocytes: recognize extracellular antigens
product antibodies
mediate humoral immunity

*T lymphocytes: recognize only peptide antigens
presented on the surface of the other cell by
major histocompatibility complex (MHC)
mediate cellular immunity

helper T cells (Th): Th1, Th2

cytolytic / cytotoxic T cells (CTL/Tc)

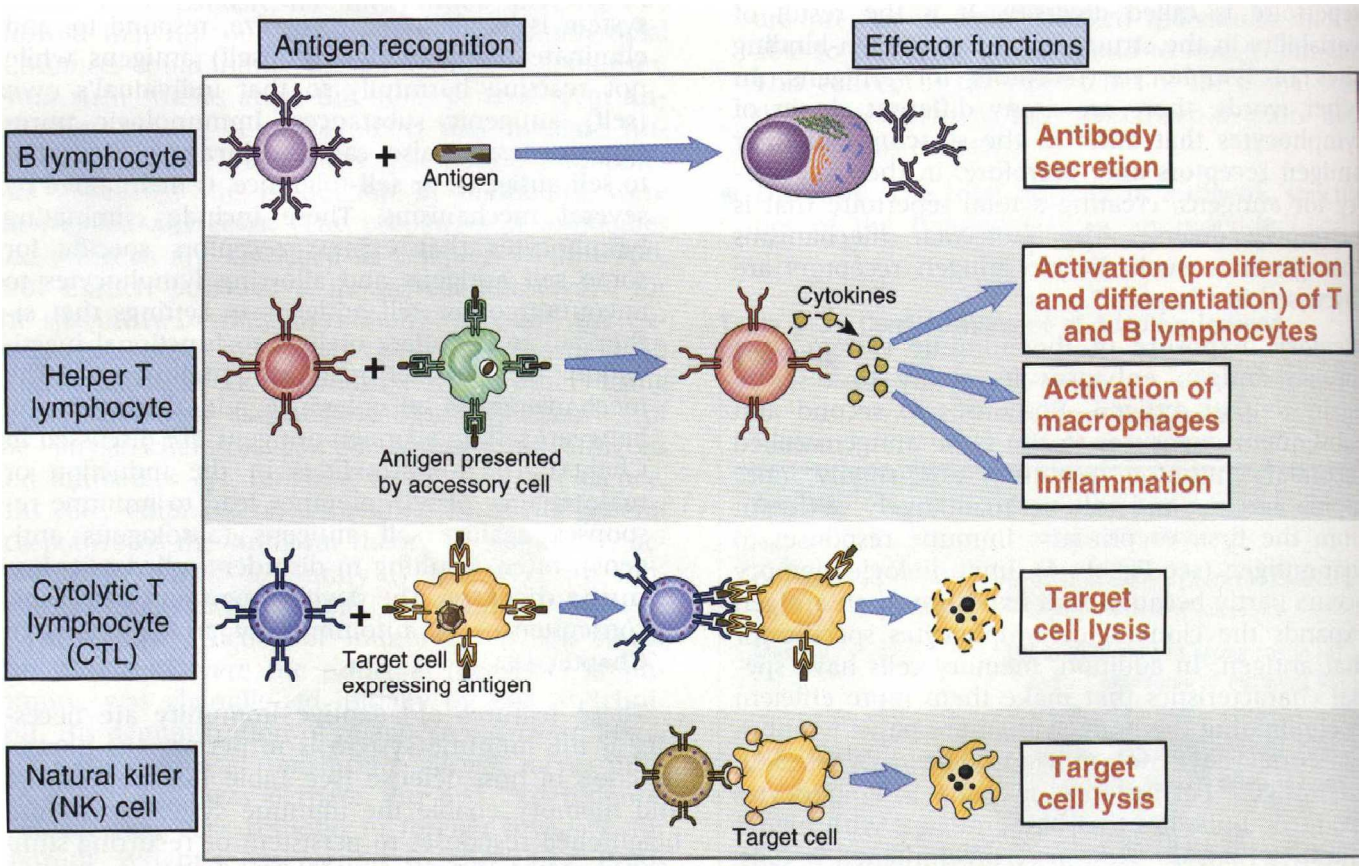


Figure 1–5 Classes of lymphocytes.

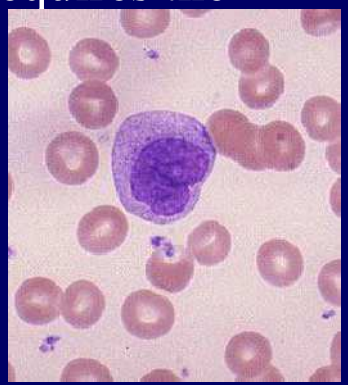
B lymphocytes recognize soluble antigens and develop into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of host accessory cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytolytic T lymphocytes recognize antigens on target cells and lyse these targets. Natural killer cells use receptors that are not fully identified to recognize and lyse targets.

2. accessory cells: mononuclear phagocytes,
dendritic cells, etc.

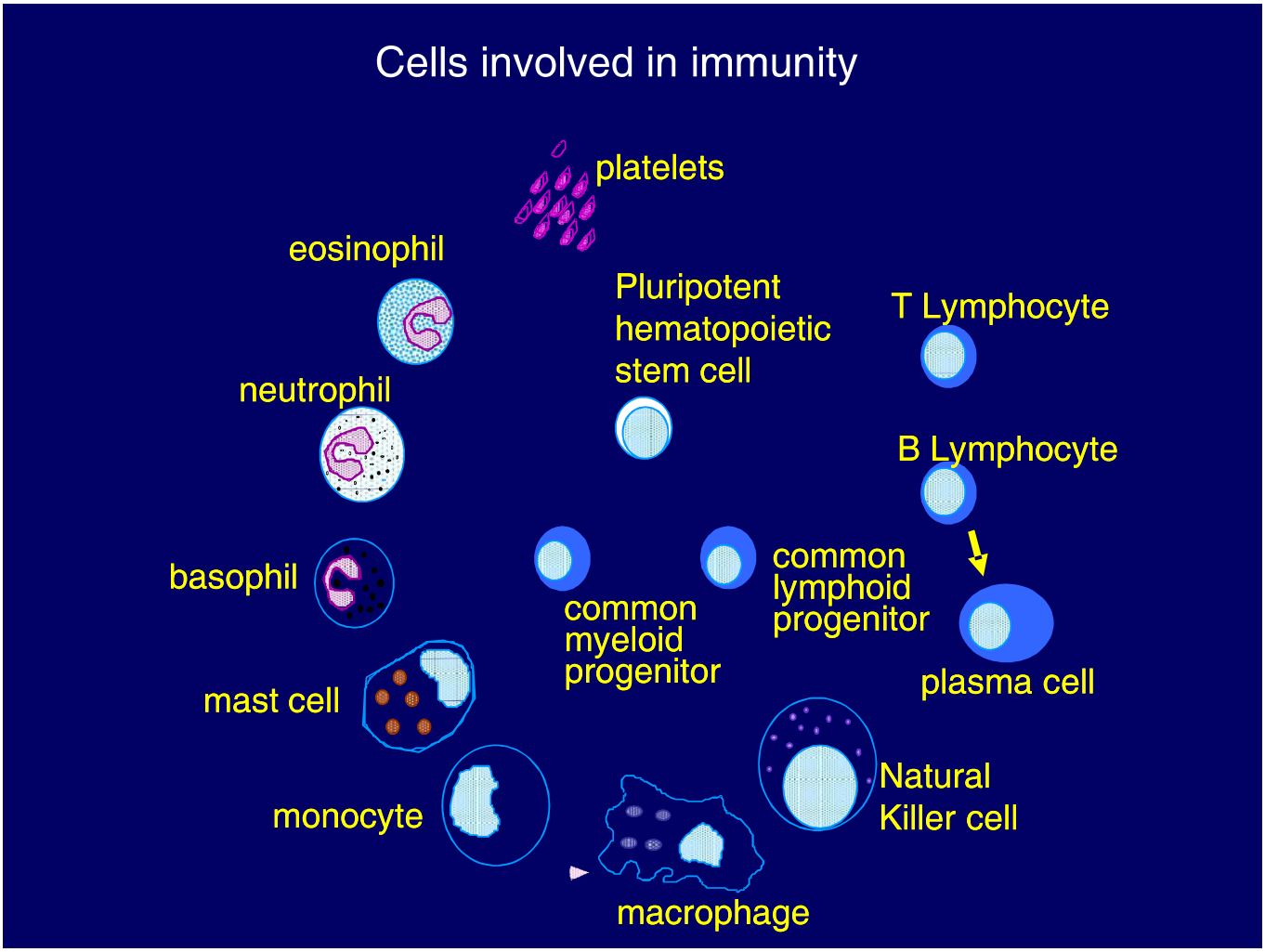
Play important roles in antigen display to and activation of antigen-specific lymphocytes.

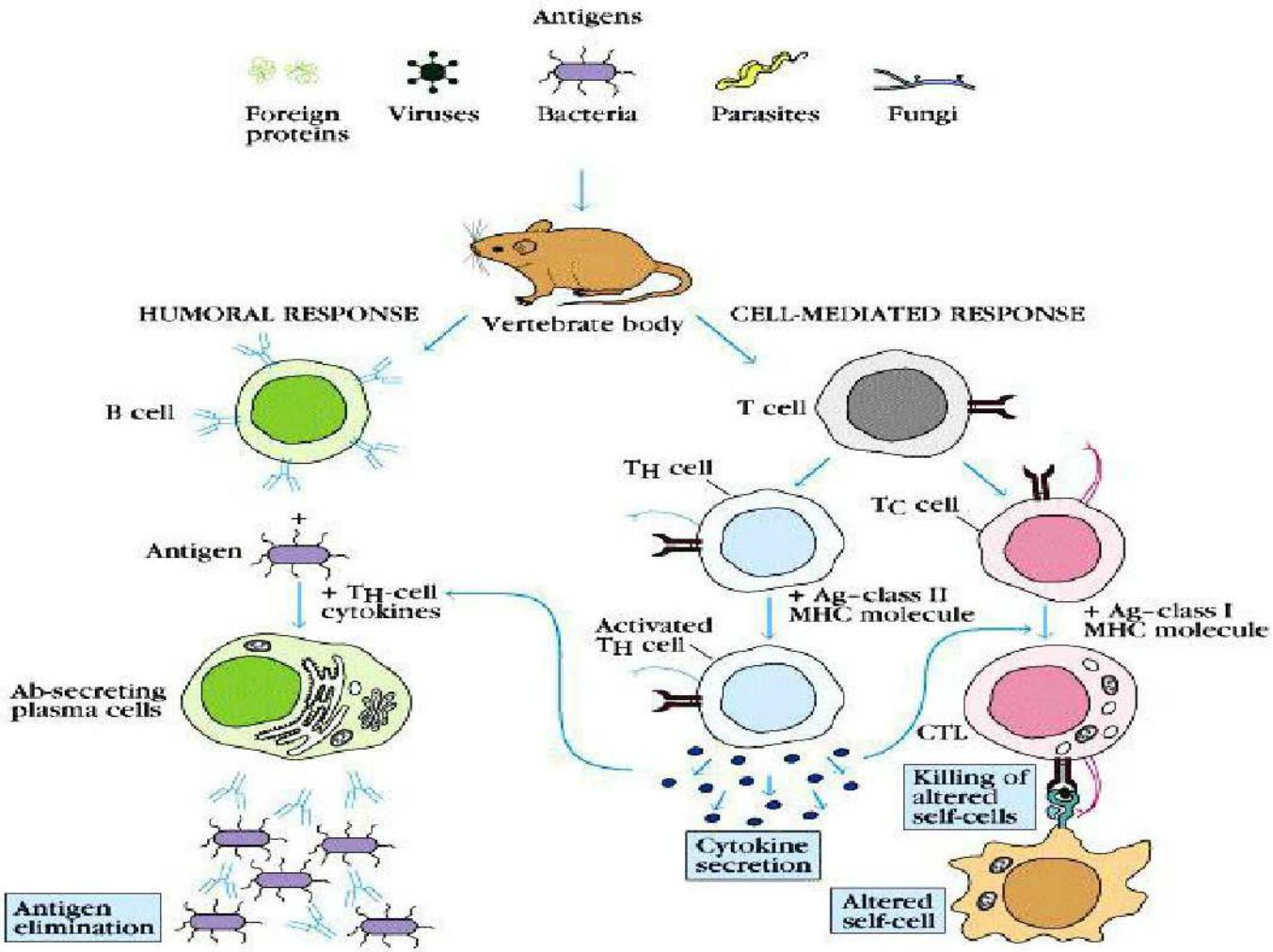
3. effector cells: activated T lymphocytes
mononuclear phagocytes

The effector phase of antigen elimination requires the participation of effector cells.



mononuclear phagocytes


Cells involved in immunity
platelets
eosinophil
Pluripotent
hematopoietic
stem cell
T Lymphocyte
neutrophil
B Lymphocyte
basophil
common
lymphoid
progenitor
common
myeloid
progenitor
plasma cell
mast cell
Natural
Killer cell
monocyte
macrophage


Antigens
Foreign proteins
Viruses
Bacteria
Parasites
Fungi
Vertebrate body
HUMORAL RESPONSE
CELL-MEDIATED RESPONSE
B cell
T cell
TH cell
TC cell
Antigen
+ TH-cell cytokines
+ Ag–class II MHC molecule
+ Ag–class I MHC molecule
Activated TH cell
Ab-secreting plasma cells
CTL
Killing of altered self-cells
Cytokine secretion
Altered self-cell
Antigen elimination

Summary

1. The components of innate immunity and adaptive immunity:

innate immunity: physical and chemical barriers
phagocytic cells (phagocytes)
blood proteins
cytokines

adaptive immunity: lymphocytes and their products

2. The type of adaptive immunity:

type	mediated by	defense against
Humoral immunity	antibodies/ B lymphocytes,	extracellular microbes and their toxins
Cell-mediated immunity	T lymphocytes	intracellular microbes