



Medical Virology Immunology

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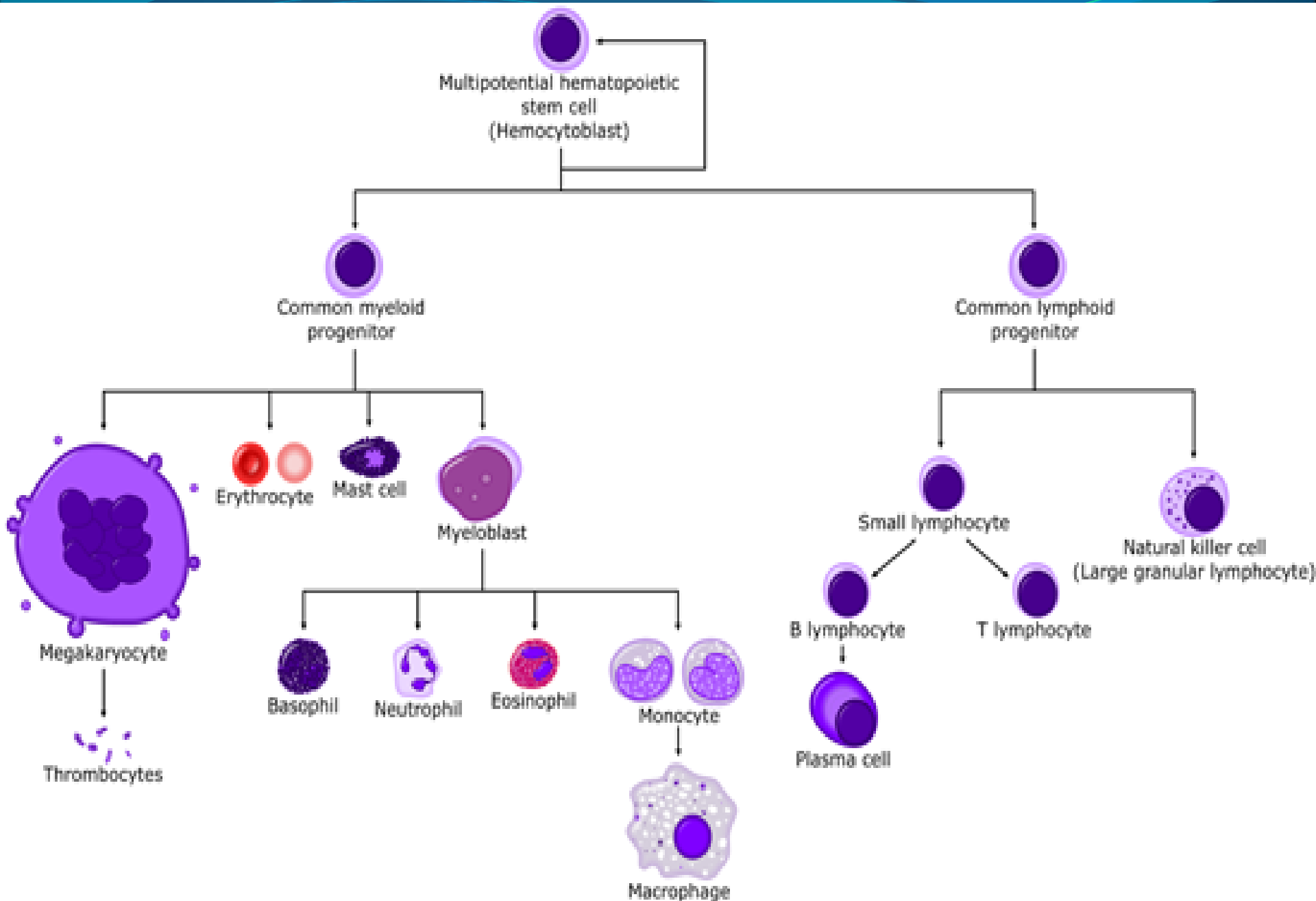
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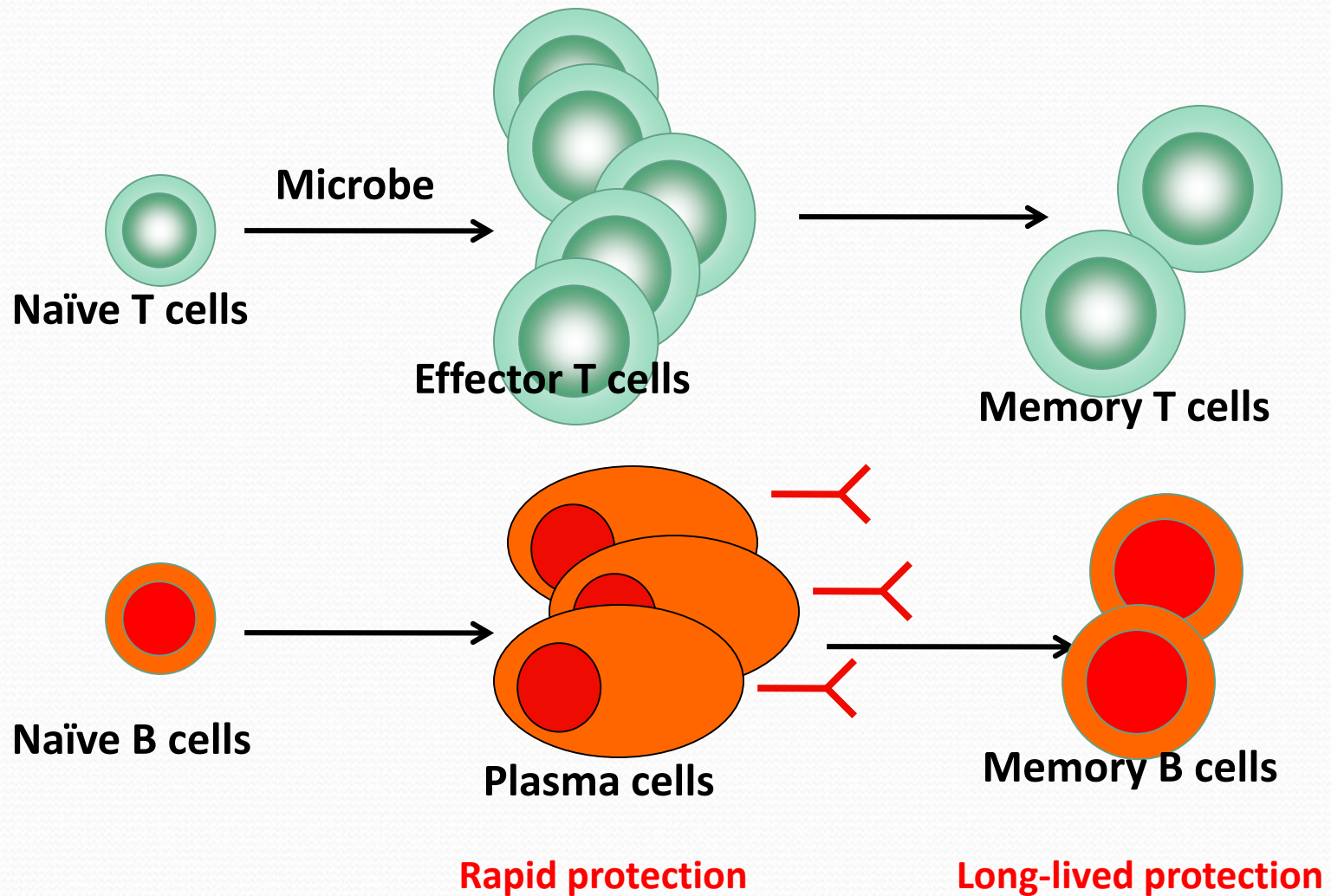
Faculty of Medicine

The Hashemite University

Human blood cells



Phases of immune responses



Immunity to microbes: general principles

Host response to virus infection:

The body's defense mechanisms to virus infection are of two types: 1) Non specific 2) Specific

- Defense against infections is mediated by the early reactions of innate immunity and the later responses of adaptive immunity
 - The innate immune response controls infection long enough for adaptive responses to kick in, and can often eradicate the infection
 - Many pathogenic microbes resist innate immunity
 - Adaptive immunity is able to combat these microbes -- the lymphocyte expansion that is characteristic of adaptive immunity helps to keep pace with rapidly dividing microbes; specialized immune responses are better able to deal with diverse microbes

Immunity to microbes: general principles

- The immune system is specialized to generate different effector mechanisms for different types of microbes
 - Extracellular microbes: antibodies, phagocytes; TH1
 - Intracellular microbes: phagocytes + TH1; CTLs

Body Defense Mechanisms

Non specific defense mechanisms (Innate immunity):

The body has defenses which are not specifically directed at particular infectious agents, but which serve as non-immunological barriers to infection:

- 1) **Skin**- an effective and impermeable barrier unless breached by injury, disease, etc...
- 2) **Respiratory tract**- upwards flow of mucus by ciliated epithelium removes virus particles, to prevent invasion of the lower respiratory tract.
- 3) **Gastrointestinal tract**- stomach acid inactivates acid-labile viruses. Bile (lyses enveloped viruses), movement of intestinal contents and uptake of virus by lymphoid tissue all aid elimination of ingested viruses.
- 4) **Urinary tract**- flow of urine exerts a protective flushing effect.
- 5) **Conjunctiva**- tears flush viruses from the eye.

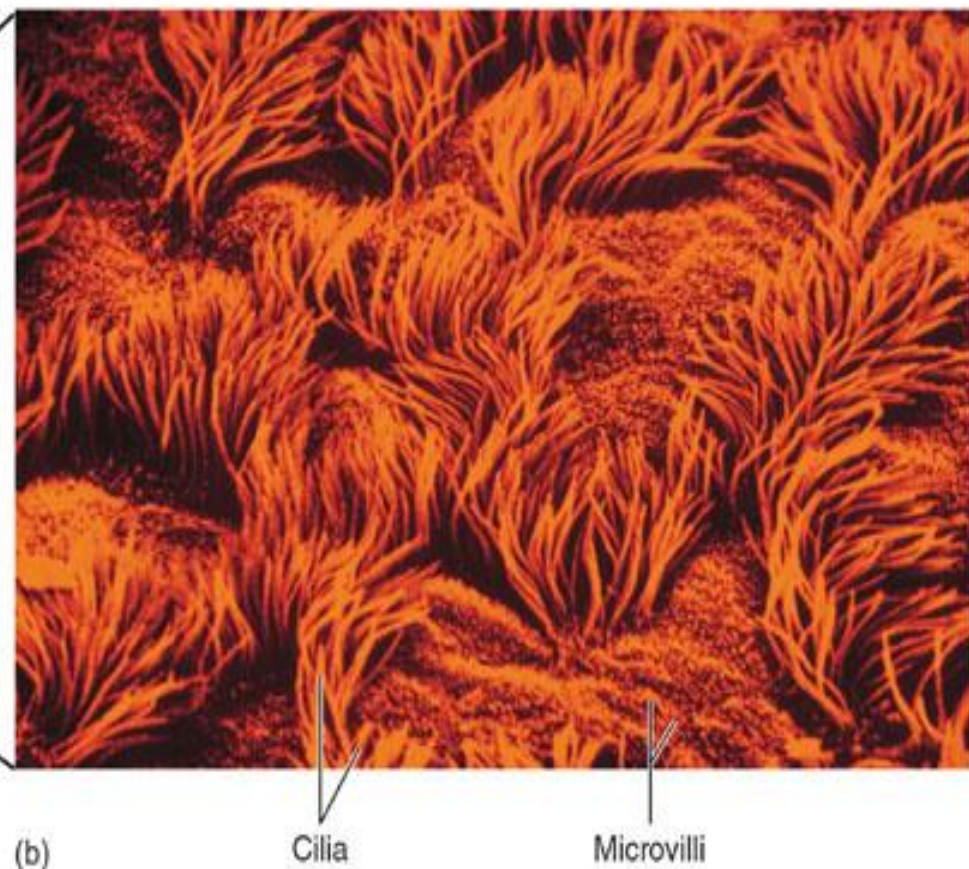
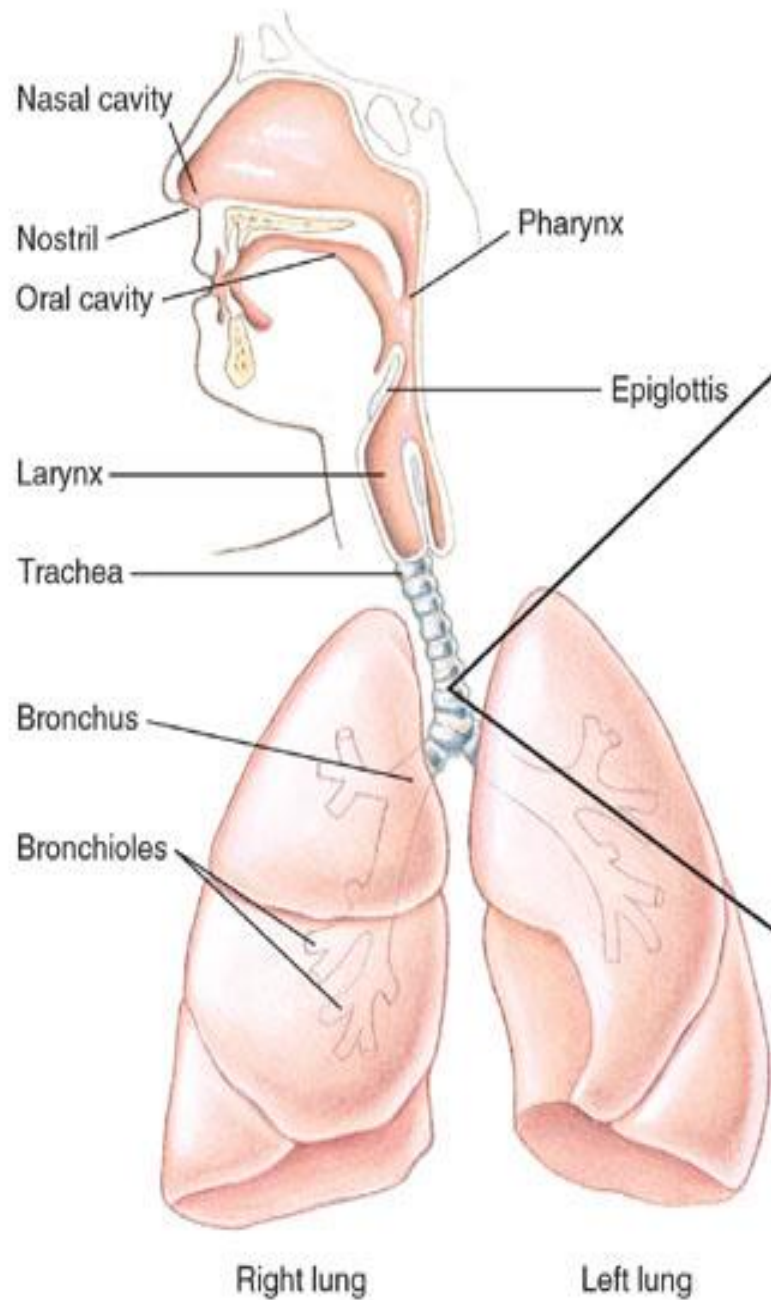
Body Defense Mechanisms

6) **Phagocytosis**- an important defense mechanism in bacterial infection and in virus infections also: invading viruses- like bacteria- are ingested by two types of scavenger cell:

- a) neutrophil polymorphonuclear leukocytes (PMN).
- b) macrophages (or mononuclear cells of the reticuloendothelial system)- of two types:
 - 1) free macrophages in lung alveoli, peritoneum.
 - 2) fixed macrophages in lymph nodes, spleen, liver (Kupffer cells), connective tissue (histiocytes) and CNS (microglia).

Phagocytosis is enhanced by antibody (a specific immune mechanism) and complement: this effect is known as *opsonization*.

Macrophages 'activated' by cytokines released by T lymphocytes (a specific immune mechanism) have increased phagocytic activity and are attracted by chemotaxis to the site of infection.



Body Defense Mechanisms

Cytokines

Cytokines are small protein molecules released by many cells, including lymphocytes and macrophages: they function as signals or mediators to activate, modulate and control the immune responses (and other activities) of cells.

There are numerous cytokines, e.g. interferons, interleukins and tumour necrosis factor: many act sequentially and interact with other cytokines.

In addition to their role in the immune response, some have physiological functions such as tissue repair, differentiation and signaling activity in the CNS.

Interferon as Body Defense Mechanism

- Small protein produced by certain cells
 - Alpha interferon- lymphocytes & macrophages
 - Beta interferon – fibroblasts & epithelial cells
 - [Gamma interferon – T cells (specific immunity)]
- Produced in response to viruses, RNA, immune products, and various antigens
- Bind to cell surfaces and induce expression of antiviral proteins
- Inhibit expression of cancer genes

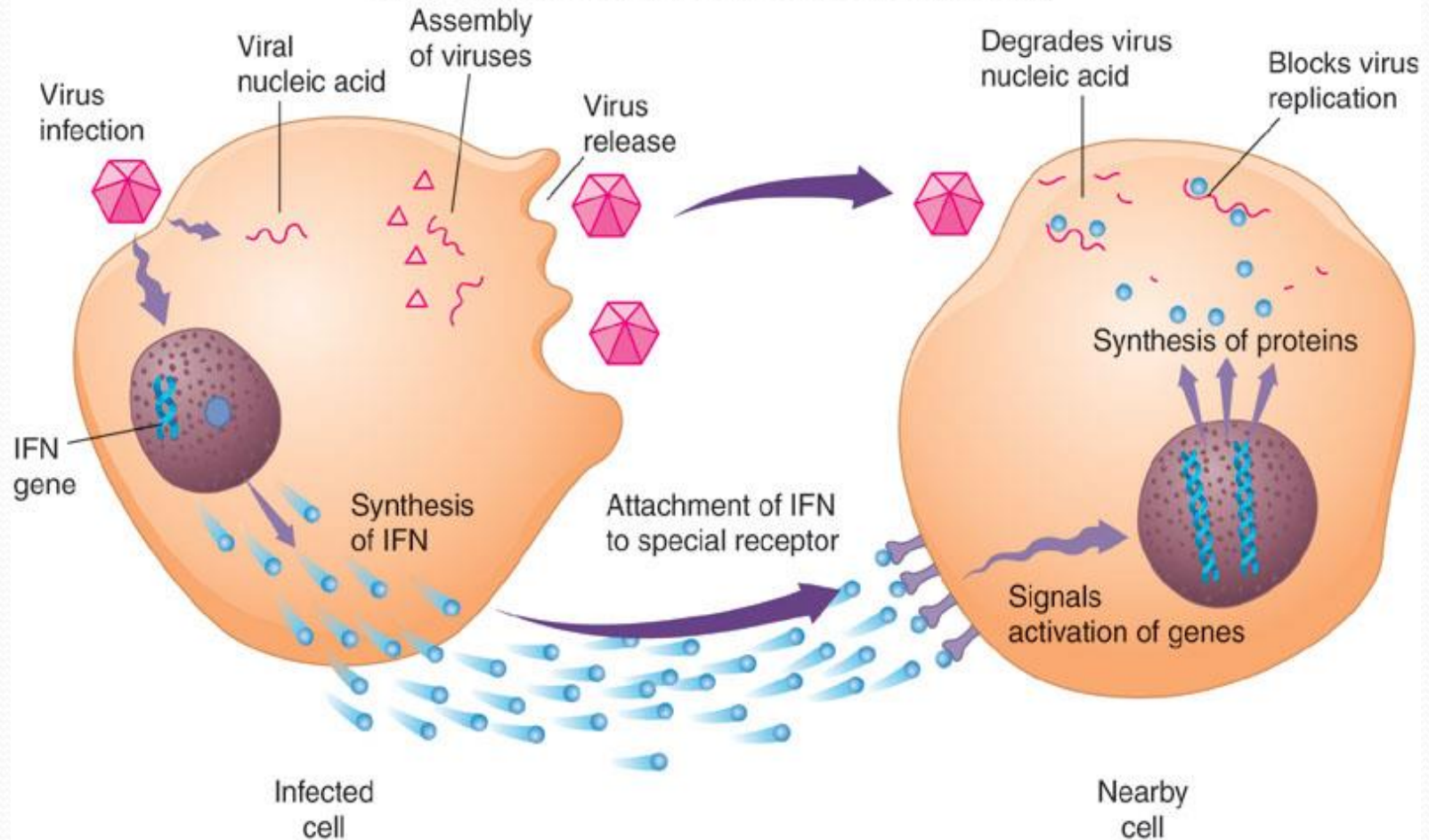
Mechanism of action of Interferons :

- **Induction** of the following enzymes:
 - 1) a *protein kinase* which inhibits protein synthesis
 - 2) an *oligo-adenylate synthase* which leads to degradation of viral mRNA
 - 3) a *phosphodiesterase* which inhibit t-RNA

The action of these enzymes leads to an **inhibition of translation**

Interferon

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Body Defense Mechanisms

Specific (Adaptive immunity) defense mechanisms:

Immunological responses are of two types:

- 1) Humoral- main effect is neutralization of viruses:
responsible for protective immunity.
- 2) cellular- main effect is localization of lesions:
kills virus-infected cells.

Body Defense Mechanisms

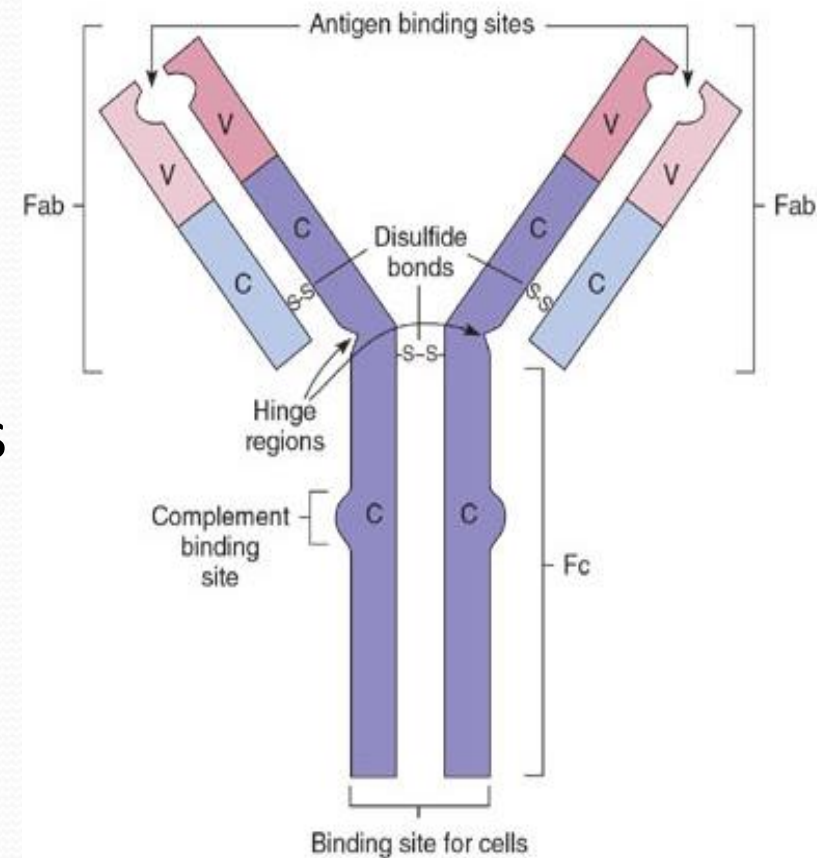
Humoral (antibody) response:

Like other infectious agents, viruses induce production of antibodies in the blood. Antibodies are:

- 1) Immunoglobulins- proteins which react specifically with antigens- which are also usually proteins and of which the most important in protective immunity are those on the surface of virus particles.
- 2) Plasma cells- formed when B-lymphocytes are activated by encounter with antigen. B-lymphocytes have immunoglobulin on their surface, which acts as receptors for virus antigen. Helper T cells contribute to the differentiation of B- cells into plasma cells.

Antibodies

- **Immunoglobulin (Ig)**
- A large Y-shaped protein
- Consists of 4 polypeptide chains
- Contains 2 identical fragments (Fab) with ends that bind to specific antigen
- Fc binds to self



(a)

Body Defense Mechanisms

Humoral (antibody) response:

Three immunoglobulins are mainly responsible for humoral immunity in virus infections:

- 1) IgM-** the earliest antibody produced: appears at a variable interval after exposure, depending on the virus, incubation period, dose and route of transmission; persists for about 4-6 weeks, sometimes longer; a pentamer of five IgG molecules.
- 2) IgG-** formed later than IgM but persists long term, often for years: responsible for immunity to reinfection.
- 3) IgA-** a dimeric molecule, found in body secretions (as well as blood), i.e. saliva, respiratory secretions, tears and intestinal contents; the main antibody involved in immunity to respiratory viruses and in gut immunity associated with enteric virus infection; secretory IgA acquires a carbohydrate 'transport piece' in extracellular fluids that is absent from serum IgA.

Body Defense Mechanisms

Cell-mediated immunity:

Cellular immunity plays an important part in the response of the body to viruses.

Children with congenital deficiency of cellular immunity are abnormally susceptible to virus infection and often (although not always) develop unusually severe disease: those with humoral immune deficiency, on the other hand, respond normally to virus infections.

Cell-mediated immunity is the mechanism for the elimination of virus-infected cells- and therefore virus- from the body.

T- or thymus-dependent lymphocytes are the principal cells involved in this.

There are two main types:

1) CD4-positive helper T-cells 2) CD8-positive cytotoxic T-cells

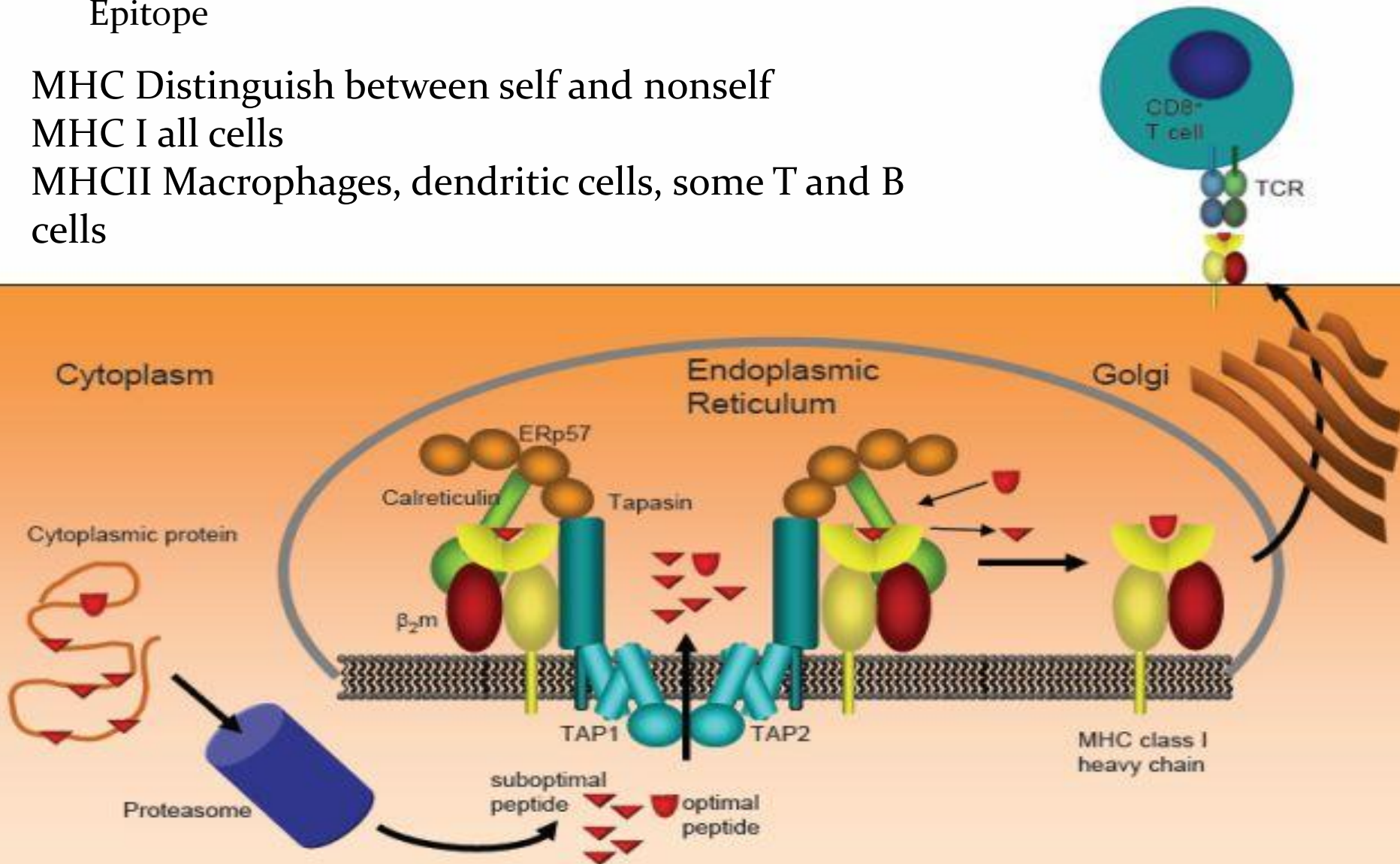
Antigen processing and presentation

Epitope

MHC Distinguish between self and nonself

MHC I all cells

MHCII Macrophages, dendritic cells, some T and B cells



Body Defense Mechanisms

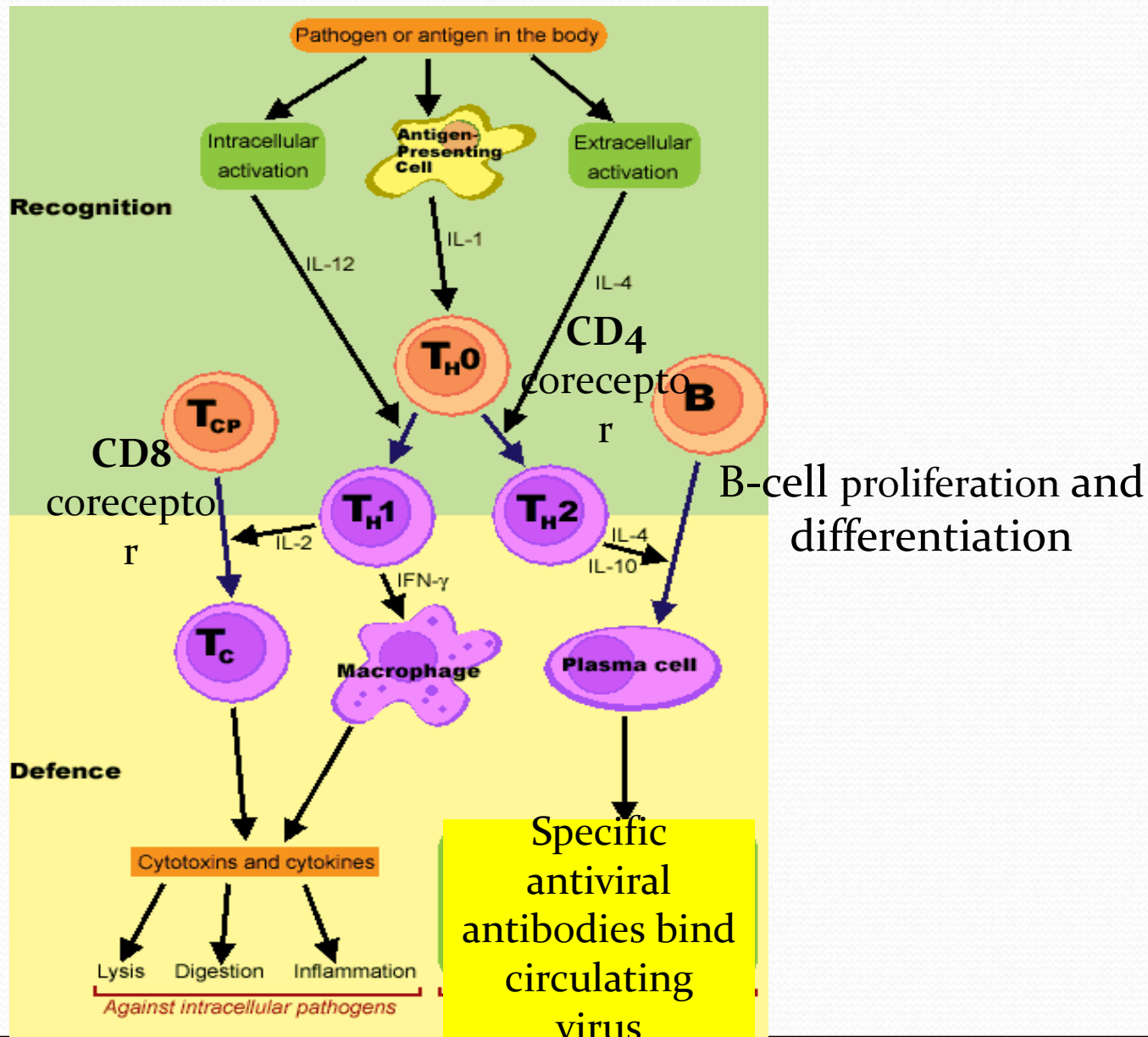
Cell-mediated immunity:(continue)

- 1) CD4-positive helper T-cells- carry CD4 receptors as markers on the their surface. The most important cells in the cellular response, they liberate *cytokines* that activate and modulate cellular immune responses. They require MHC (Major Histocompatibility Complex) class II antigens to be presented in association with the target antigen for their activation. They also interact with B-lymphocytes for antibody production.
- 2) CD8-positive cytotoxic T-cells- carry the marker CD8 receptor on their surface and are MHC Class I antigen-restricted. They lyse target cells such as virus-infected cells and tumour cells; the main mechanism for elimination of virus-infected cells from the body; also release cytokines.

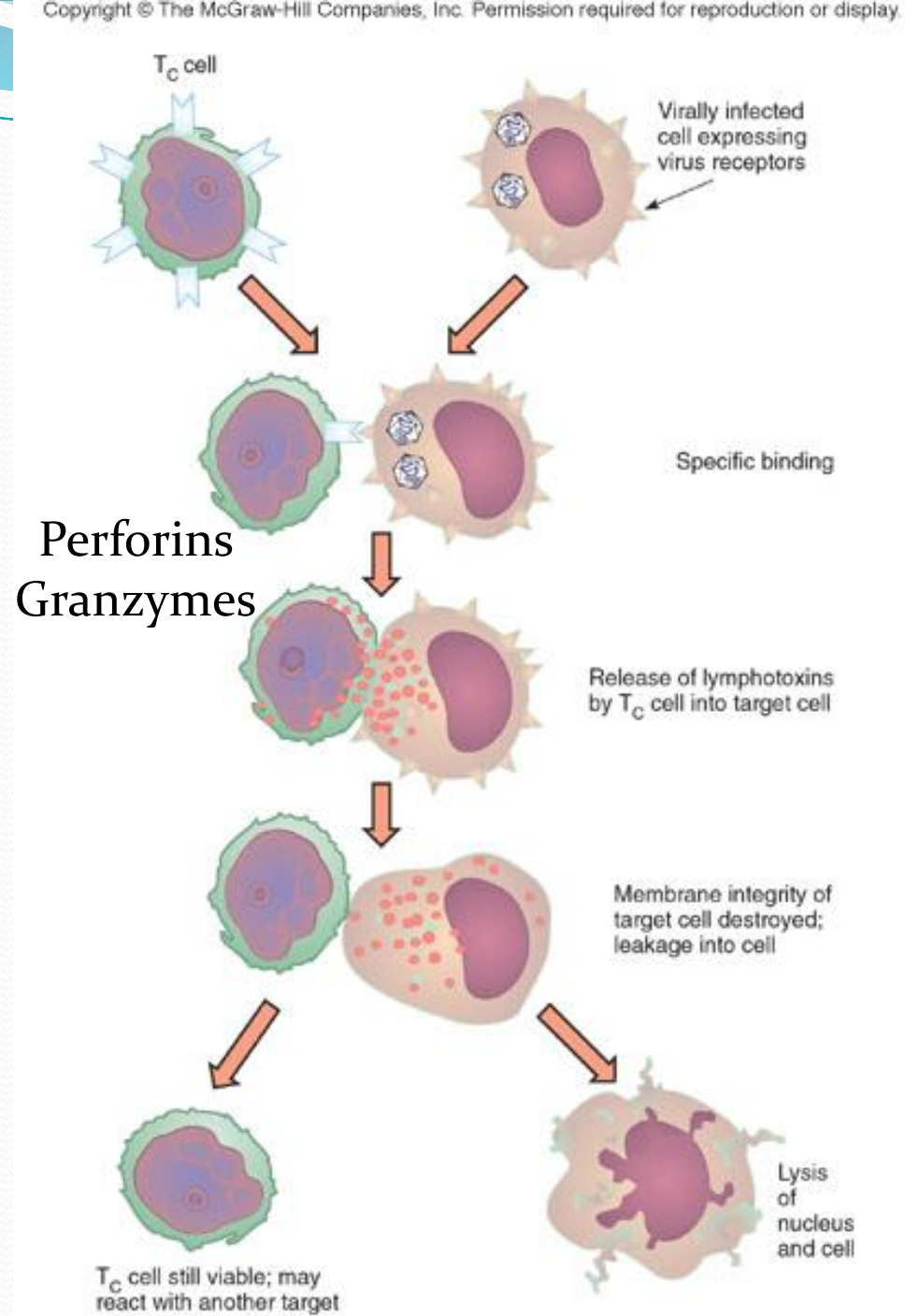
Suppressor function: note that both CD4 and CD8 cells can suppress as well as activate the cellular response.

Virus is recognized as antigen by helper T-cells when presented by a macrophage or dendritic cell (found in lymph nodes and skin) acting as an antigen-presenting cell: recognition is dependent on MHC Class II antigens.

T-cell response



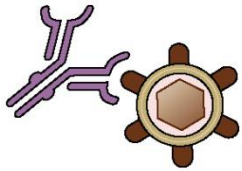
Cytotoxic T cells



Principal mechanisms of defense against microbes

Antibodies

Antibodies block infectivity of microbes



Best way of preventing infection before it takes hold (goal of vaccination)

All microbes

Phagocytes

(may work with antibodies, T cells)

Phagocytosis and intracellular killing of microbes

Antibodies (and complement proteins) coat microbes and promote phagocytosis and intracellular killing

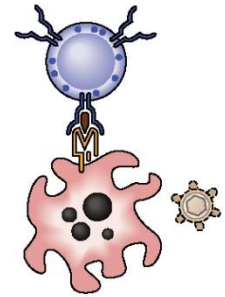
T lymphocytes recognize antigens of ingested microbes and activate phagocytes to become better killers

All microbes



T cells (CTLs)

T lymphocytes kill infected cells



When infection cannot be blocked, or cleared by phagocytes

Intracellular microbes, esp. viruses

Properties and roles of memory cells

- Survive even after infection is cleared
- Numbers more than naïve cells
- Respond to antigen challenge (recall) more rapidly than do naïve cells
- Memory T cells: migrate to tissues, some live in mucosal tissues and skin
- Memory B cells: produce high affinity antibodies
- Provide rapid protection against recurrent or persistent infections
- Goal of vaccination is to induce effective memory

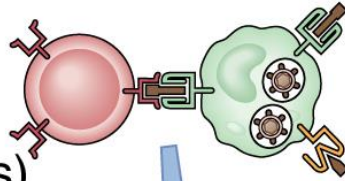
Specialization of immune responses to microbes

<u>Type of microbe</u>	<u>Adaptive immune response</u>	<u>Effector mechanism</u>
Extracellular microbe (bacteria, viruses)	Endocytosed antigen stimulates CD4+ helper T cells (T_H1 , T_H17) --> antibody, inflammation	Neutralization, phagocytosis
Intracellular microbe in phagocytes	Antigen in vesicles or cytosol --> CD4+, CD8+ T cells	IFN- γ activates phagocytes; killing of infected cells
Intracellular microbe in non-phagocytic cell (virus)	Antigen in cytosol --> CD8+ CTLs	Killing of infected cells

Cell-mediated immunity against intracellular microbes

A Phagocytes with ingested microbes; microbial antigens in vesicles

CD4⁺
effector
T cells
(T_H1 cells)



Cytokine secretion



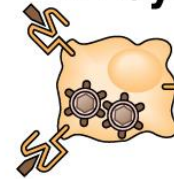
**Macrophage
activation,
killing of
ingested
microbes**



Inflammation

*CD4⁺ T cells: make phagocytes
better killers of microbes*

B Infected cell with microbes in cytoplasm



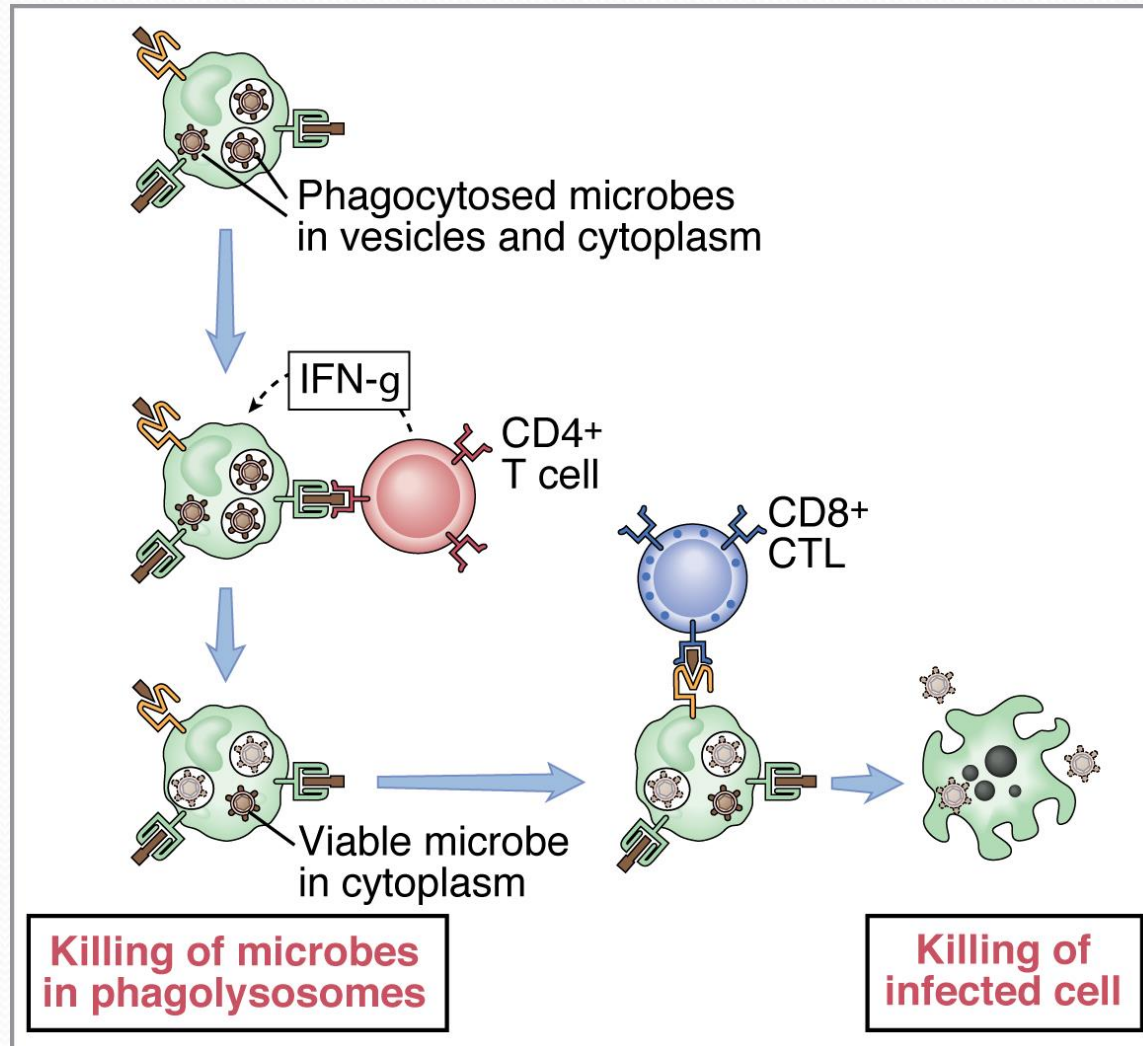
CD8⁺
T cells
(CTLs)



**Killing of
infected cell**

*CTLs: eliminate the
reservoir of infection*

CD4+ and CD8+ T cells cooperate in cell-mediated immunity against intracellular microbes

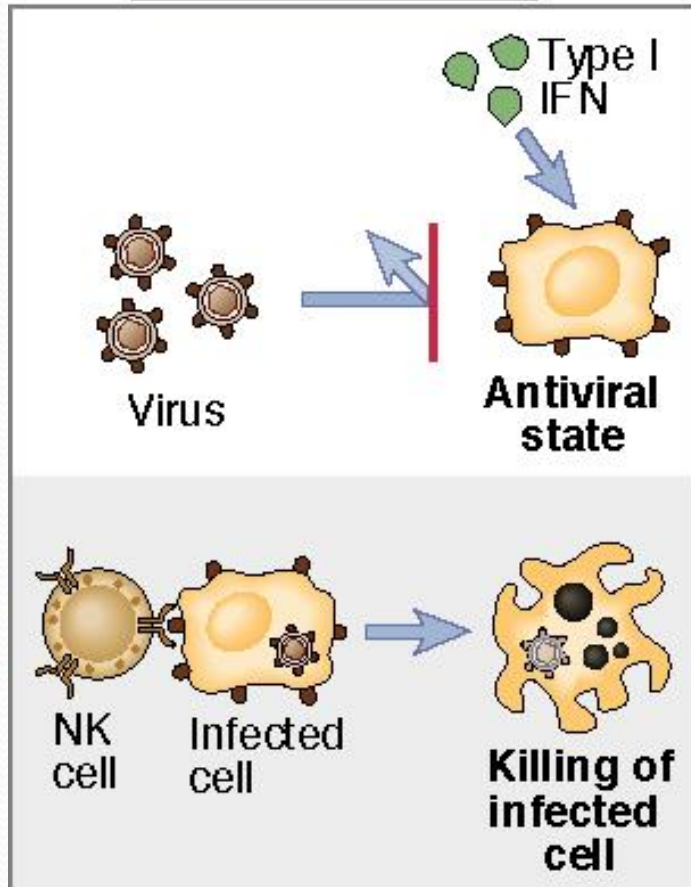


CD4+ T cells: help to kill microbes in vesicles of phagocytes

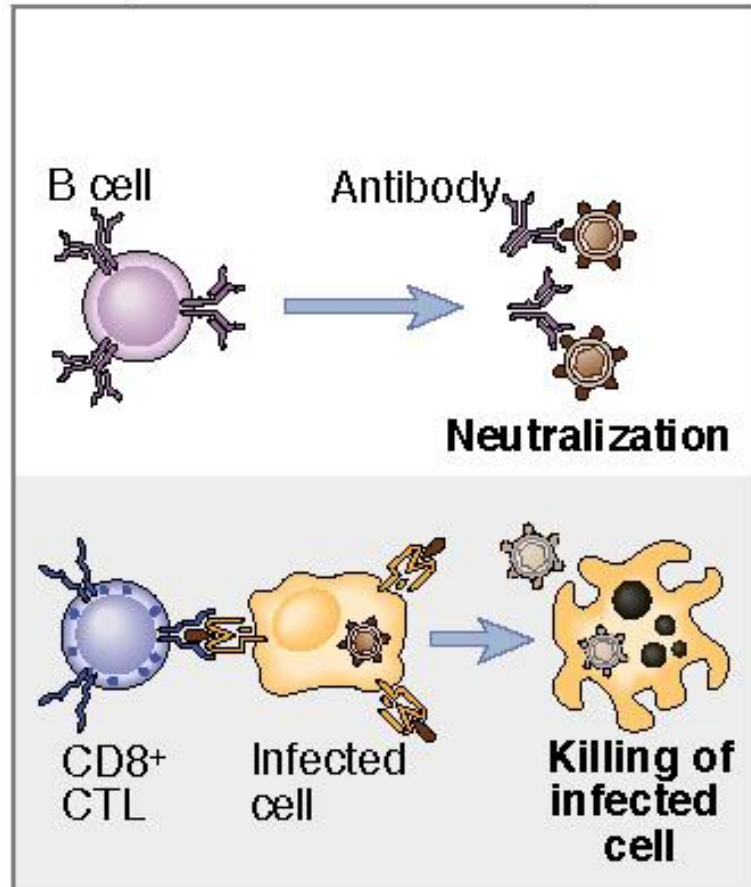
CD8+ CTLs: kill microbes that have escaped into the cytoplasm

Innate and adaptive immunity to viruses

Innate immunity



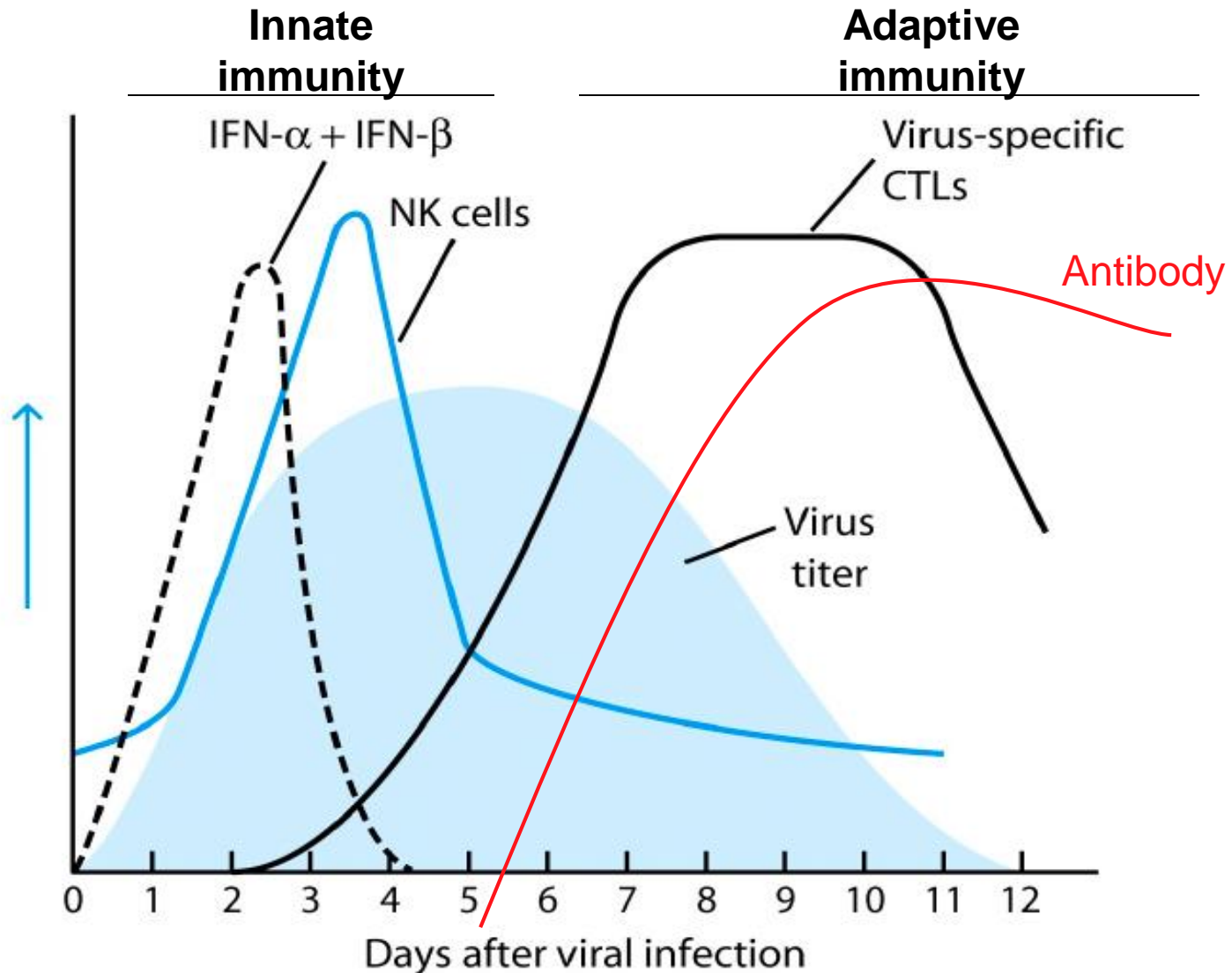
Adaptive immunity



**Protection
against
infection**

**Eradication
of established
infection**

Innate and adaptive immune responses in viral infections



Roles of antibodies and CTLs in adaptive immunity to viruses

- **Antibodies neutralize viruses and prevent infection**
 - Block infectious virus early in course of infection (before entering cells) or after release from infected cells (prevents cell-to-cell spread)
- **CTLs kill infected cells and eradicate reservoirs of established infection**
 - In some latent viral infections (EBV, CMV), CTLs control but do not eradicate the infection; defective T cell immunity leads to reactivation of the virus (in HIV, immunosuppression caused by leukemias, treatment for graft rejection)

Immune evasion by viruses

- Antigenic variation
 - Influenza, HIV, rhinovirus
- Inhibition of the class I MHC antigen processing pathway
 - Different viruses use different mechanisms
 - NK cells are the host adaptation for killing class I MHC-negative infected cells
- Production of immune modulators
 - Soluble cytokine receptors may act as “decoys” and block actions of cytokines (poxviruses)
 - Immunosuppressive cytokines, e.g. IL-10 (EBV)
- Infection of immune cells
 - HIV

Efficacy of vaccines

- Vaccines have been useful for generating protective antibodies, but so far, not for generating effective cell-mediated immunity
- **Vaccines work best against microbes that:**
 - Do not vary their antigens
 - Do not have animal reservoirs
 - Do not establish latent infection within host cells
 - Do not interfere with the host immune response