The Immune System: A Tutorial

Modeling and Simulation of Biological Systems 21-366B

Shlomo Ta’asan

Images taken from

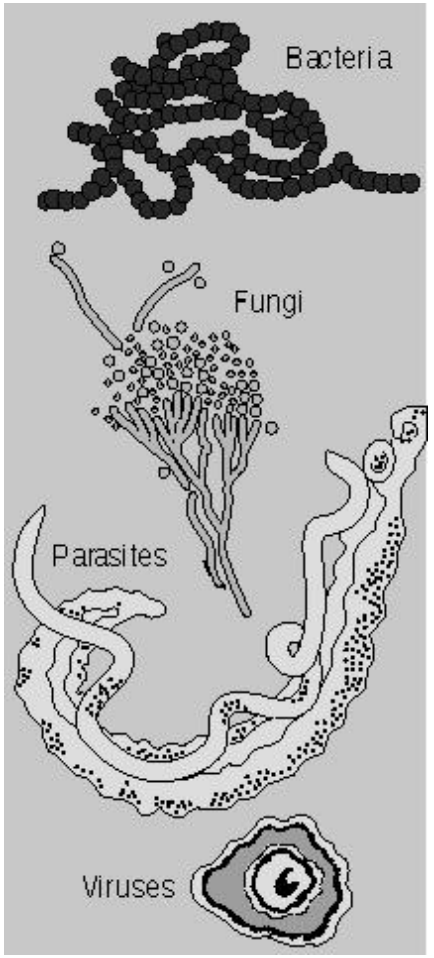
http://rex.nci.nih.gov/behindthenews/uis/uisframe.htm

http://copewithcytokines.de/

The Immune System

The immune system is a body-wide network of molecules, cells and organs that has evolved to defend the body against attacks by "foreign" invaders.

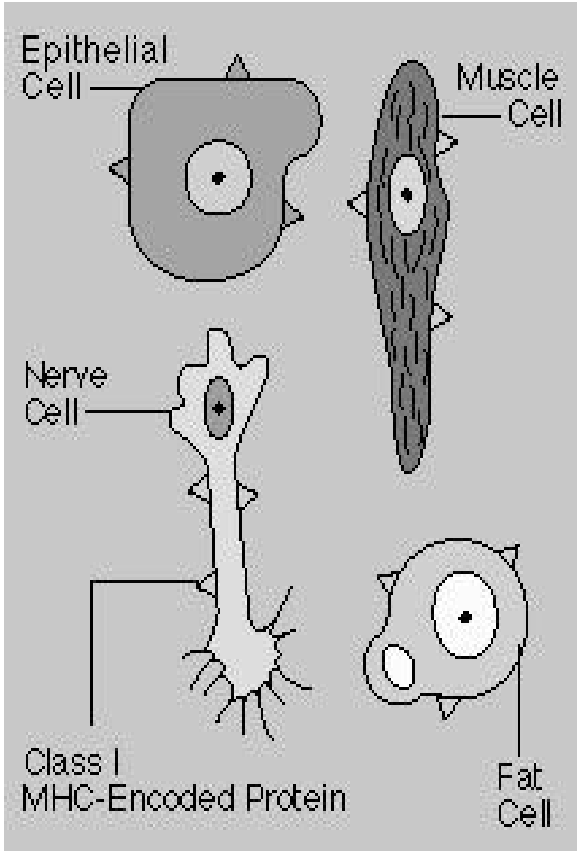
The targets of the immune defenses are infectious organisms including: Bacteria, Fungi, Parasites, and Viruses



Markers of Self

At the heart of the immune response is the ability to distinguish between self and nonself.

Every body cell carries distinctive molecules that distinguish it as "self." Normally the body's defenses do not attack tissues that carry a self marker; rather, immune cells coexist peacefully with other body cells in a state known as self-tolerance.

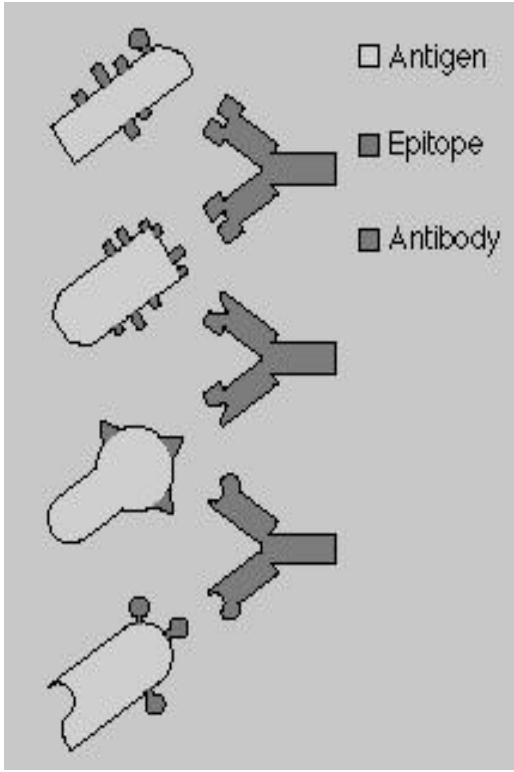


Markers of Non-Self

Most foreign molecules carry distinctive markers.

The immune system is able to recognize many millions of distinctive non-self molecules, and to respond in different ways.

An antigen: a substance capable of triggering an immune response is called an antigen (e.g., bacterium, virus, cells from another individual)



A Huge Network

Interacting:

Organs

Thymus, Spleen, Lymph node, Bone marrow,…

Cells

Macrophages, Neutrophils, Dendritic cells, B cells, T cells, ..

Molecules

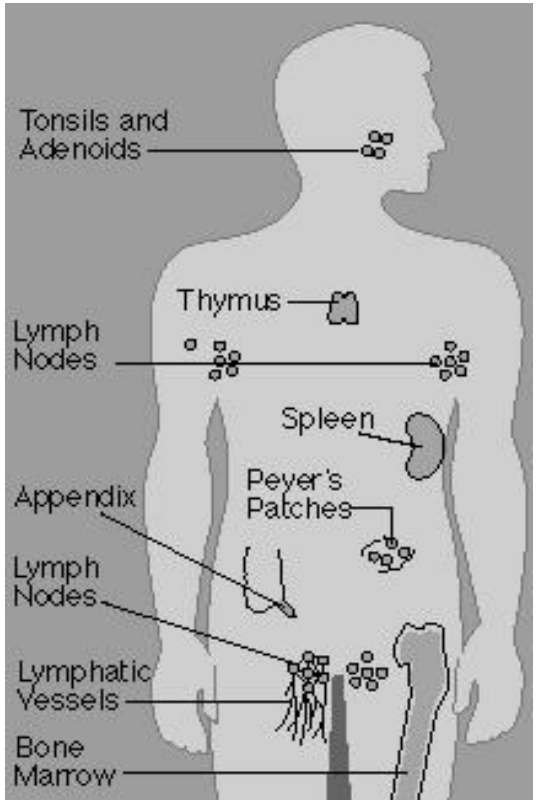
Complement system, Cytokines,…

(Weakly?) Coupling with the nervous system

Organs of the Immune System

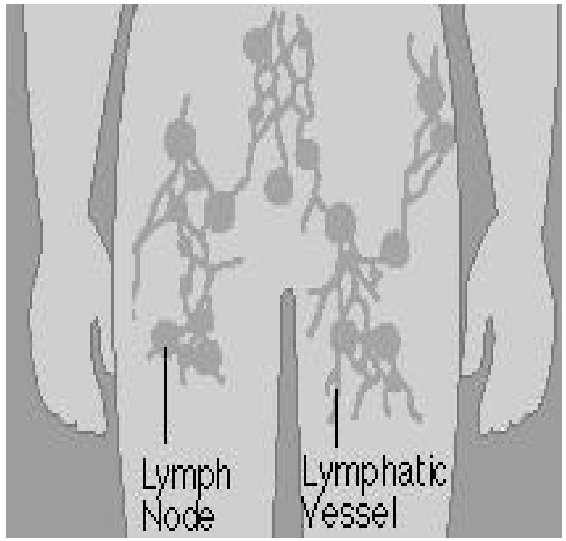
The organs of the immune system are stationed throughout the body.

They are known as lymphoid organs because they are concerned with the growth, development, and deployment of lymphocytes—white blood cells that are key operatives of the immune system.



Lymphatic System

The organs of the immune system are connected with one another and with other organs of the body by a network of lymphatic vessels similar to blood vessels.

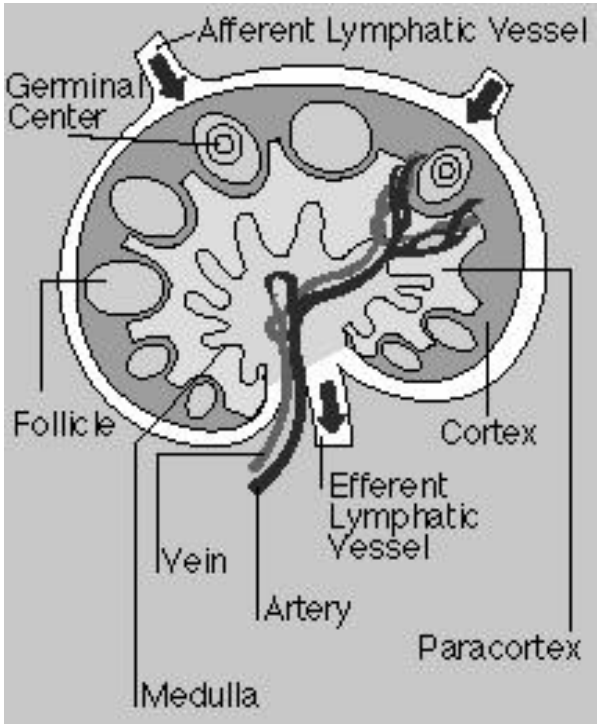


Immune cells and foreign particles are conveyed through the lymphatics in lymph, a clear fluid that bathes the body's tissues.

Lymph Node

Lymph nodes are small, bean-shaped structures that are laced throughout the body along the lymphatic routes.

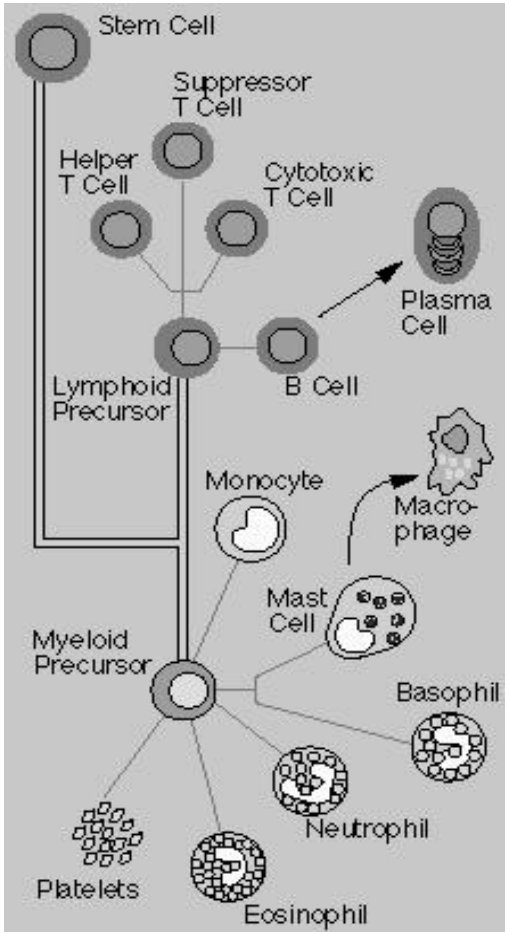
Lymph nodes contain specialized compartments where immune cells congregate, and where they can encounter antigens.

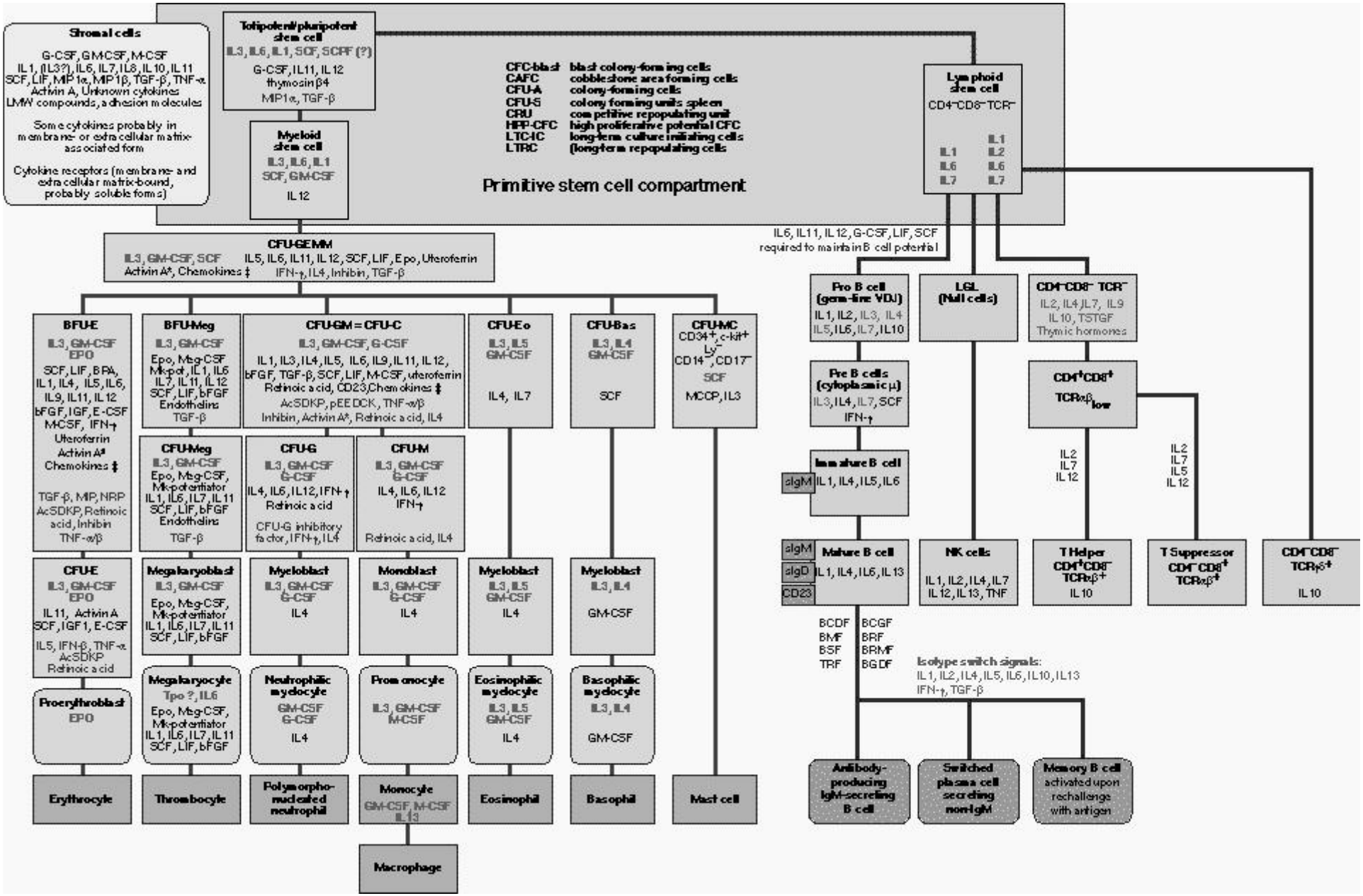


Cells of the Immune System

Cells of the immune system arise in the bone marrow from stem cells.

Two groups of cells are the myleoids and lymphoids. Myeloid cells include monocytes, macrophages, neutrophils, eosinophils and basophils. The two major classes of lymphocytes are B cells and T cells.

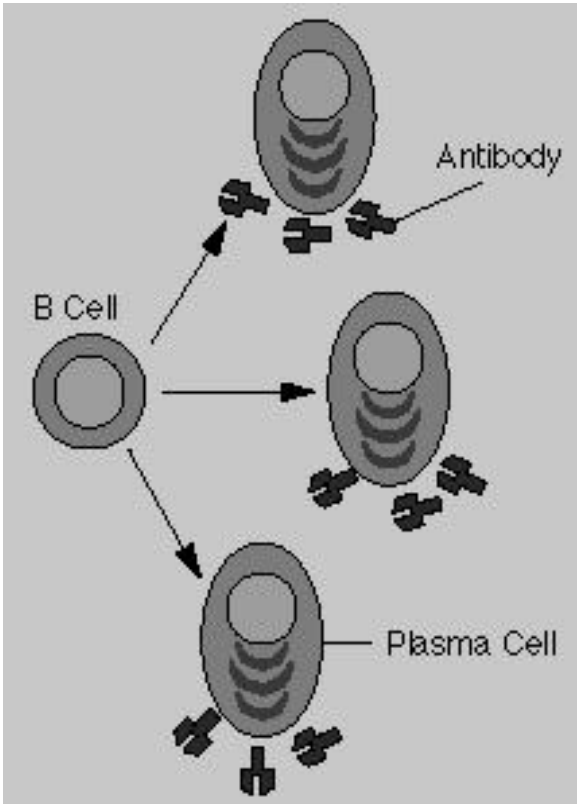



Stromal cells
G-CSF, GM-CSF, M-CSF
IL1, (IL3?), IL6, IL7, IL8, IL10, IL11
SCF, LIF, MIP1α, MIP1β, TGF-β, TNF-α
Activin A, Unknown cytokines
LMW compounds, adhesion molecules
Some cytokines probably in membrane- or extracellular matrix-associated form
Cytokine receptors (membrane- and extracellular matrix-bound, probably soluble forms)
Totipotent/pluripotent stem cell
IL3, IL6, IL1, SCF, SCPF (?)
G-CSF, IL11, IL12
thymosin β4
MIP1α, TGF-β
Myeloid stem cell
IL3, IL6, IL1
SCF, GM-CSF
IL12
CFC-blast blast colony-forming cells
CAFC cobblestone area forming cells
CFU-A colony-forming cells
CFU-S colony forming units spleen
CRU competitive repopulating unit
HPP-CFC high proliferative potential CFC
LTC-IC long-term culture initiating cells
LTRC (long-term repopulating cells
Primitive stem cell compartment
Lymphoid stem cell
CD4-CD8-TCR-
IL1
IL6
IL7
IL1
IL2
IL6
IL7
IL6, IL11, IL12, G-CSF, LIF, SCF required to maintain B cell potential
CFU-GEMM
IL3, GM-CSF, SCF
Activin A*, Chemokines ‡
IL5, IL6, IL11, IL12, SCF, LIF, Epo, Uteroferrin
IFN-γ, IL4, Inhibin, TGF-β
BFU-E
IL3, GM-CSF
EPO
SCF, LIF, BPA, IL1, IL4, IL5, IL6, IL9, IL11, IL12
bFGF, IGF, E-CSF
M-CSF, IFN-γ
Uteroferrin
Activin A*
Chemokines ‡
TGF-β, MIP, NRP
AcSDKP, Retinoic acid, Inhibin
TNF-α/β
BFU-Meg
IL3, GM-CSF
Epo, Meg-CSF
Mk-pot, IL1, IL6
IL7, IL11, IL12
SCF, LIF, bFGF
Endothelins
TGF-β
CFU-GM = CFU-C
IL3, GM-CSF, G-CSF
IL1, IL3, IL4, IL5, IL6, IL9, IL11, IL12,
bFGF, TGF-β, SCF, LIF, M-CSF, uteroferrin
Retinoic acid, CD23, Chemokines ‡
AcSDKP, pEEDCK, TNF-α/β
Inhibin, Activin A*, Retinoic acid, IL4
CFU-Eo
IL3, IL5
GM-CSF
IL4, IL7
CFU-Bas
IL3, IL4
GM-CSF
SCF
CFU-MC
CD34+, c-kit+
Ly-
CD14-, CD17-
SCF
MCCP, IL3
CFU-Meg
IL3, GM-CSF
Epo, Meg-CSF, Mk-potentiator
IL1, IL6, IL7, IL11
SCF, LIF, bFGF
Endothelins
TGF-β
CFU-G
IL3, GM-CSF
G-CSF
IL4, IL6, IL12, IFN-γ
Retinoic acid
CFU-G inhibitory factor, IFN-γ, IL4
CFU-M
IL3, GM-CSF
G-CSF
IL4, IL6, IL12
IFN-γ
Retinoic acid, IL4
CFU-E
IL3, GM-CSF
EPO
IL11, Activin A
SCF, IGF1, E-CSF
IL5, IFN-β, TNF-α
AcSDKP
Retinoic acid
Megakaryoblast
IL3, GM-CSF
Epo, Meg-CSF, Mk-potentiator
IL1, IL6, IL7, IL11
SCF, LIF, bFGF
Myeloblast
IL3, GM-CSF
G-CSF
IL4
Monoblast
IL3, GM-CSF
G-CSF
IL4
Myeloblast
IL3, IL5
GM-CSF
IL4
Myeloblast
IL3, IL4
GM-CSF
Proerythroblast
EPO
Megakaryocyte
Tpo ?, IL6
Epo, Meg-CSF, Mk-potentiator
IL1, IL6, IL7, IL11
SCF, LIF, bFGF
Neutrophilic myelocyte
GM-CSF
G-CSF
IL4
Promonocyte
IL3, GM-CSF
M-CSF
Eosinophilic myelocyte
IL3, IL5
GM-CSF
IL4
Basophilic myelocyte
IL3, IL4
GM-CSF
Erythrocyte
Thrombocyte
Polymorpho-nucleated neutrophil
Monocyte
GM-CSF, M-CSF
IL13
Eosinophil
Basophil
Mast cell
Macrophage
Pro B cell (germ-line VDJ)
IL1, IL2, IL3, IL4
IL5, IL6, IL7, IL10
Pre B cells (cytoplasmic μ)
IL3, IL4, IL7, SCF
IFN-γ
Immature B cell
sIgM IL1, IL4, IL5, IL6
sIgM
sIgD
CD23
Mature B cell
IL1, IL4, IL6, IL13
BCDF
BMF
BSF
TRF
BCGF
BRF
BRMF
BGDF
Isotype switch signals:
IL1, IL2, IL4, IL5, IL6, IL10, IL13
IFN-γ, TGF-β
Antibody-producing IgM-secreting B cell
Switched plasma cell secreting non-IgM
Memory B cell activated upon rechallenge with antigen
LGL (Null cells)
NK cells
IL1, IL2, IL4, IL7
IL12, IL13, TNF
CD4-CD8- TCR-
IL2, IL4 IL7, IL9
IL10, TSTGF
Thymic hormones
CD4+CD8+
TCRαβlow
IL2
IL7
IL12
IL2
IL7
IL5
IL12
T Helper
CD4+CD8-
TCRαβ+
IL10
T Suppressor
CD4-CD8+
TCRαβ+
CD4-CD8-
TCRγδ+
IL10

B Cells

B cells work chiefly by secreting soluble substances known as antibodies.

Each B cell is programmed to make one specific antibody. When a B cell encounters its triggering antigen (along with various accessory cells), it gives rise to many large plasma cells. Each plasma cell is essentially a factory for producing that one specific antibody.



Antibody

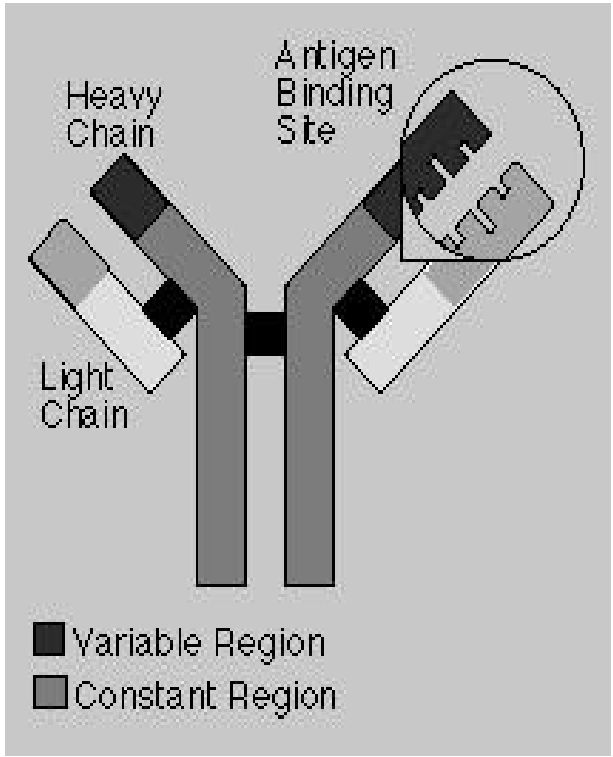
Each antibody is made up of two identical heavy chains and two identical light chains.

The tips of the Y: recognition sites.

The stem of the Y: link to other participants in the immune defenses.

Many tips, and only a few stems.

Antibodies belong to a family of large protein molecules known as immunoglobulins



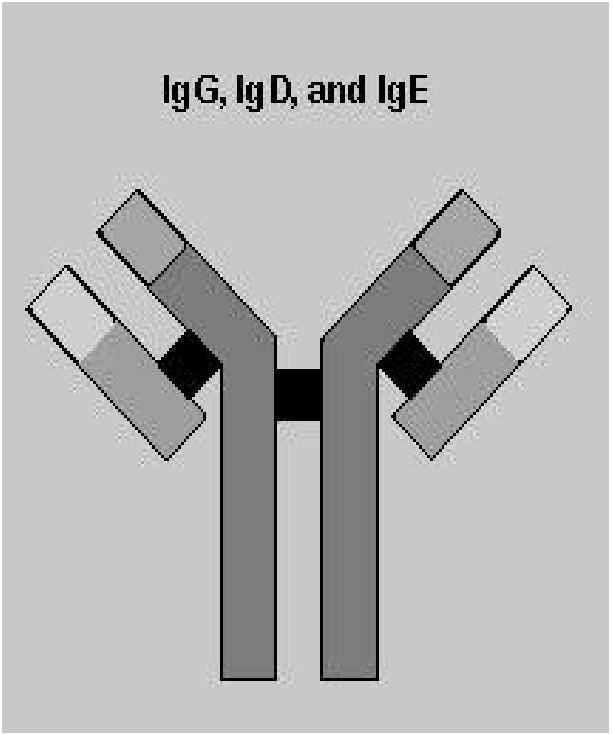
IgG, IgD, and IgE

There are nine chemically distinct classes of human immunoglobulins, IgG and two kinds of IgA, plus IgM, IgE, and IgD.

IgG: able to enter tissue spaces;

IgD mostly the membrane of B cells, (regulates the cell's activation).

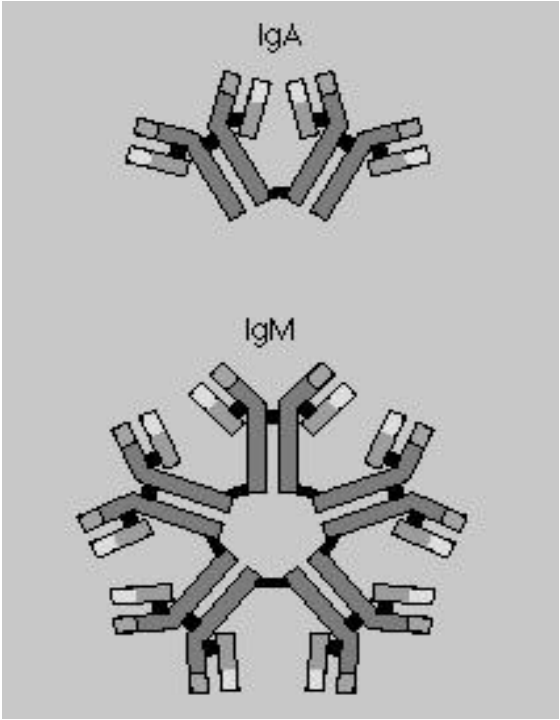
IgE is responsible for the symptoms of allergy



IgA and IgM

IgA—a doublet, exists in tears, saliva, and the secretions of the respiratory and gastrointestinal tracts. guard the entrances to the body.

IgM usually in star-shaped clusters. It tends to remain in the bloodstream.



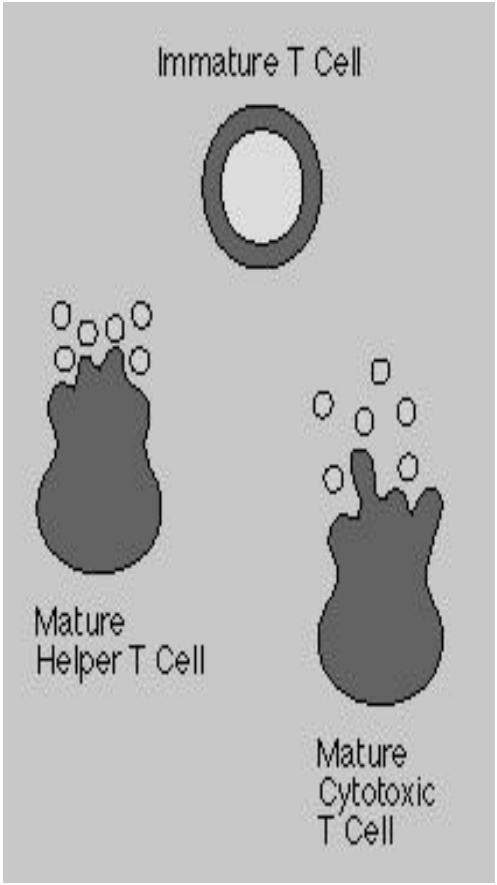
T Cells

T cells are of three main classes

(i) regulate the complex workings of the immune system.

(ii) directly contact infected cells and destroy them.

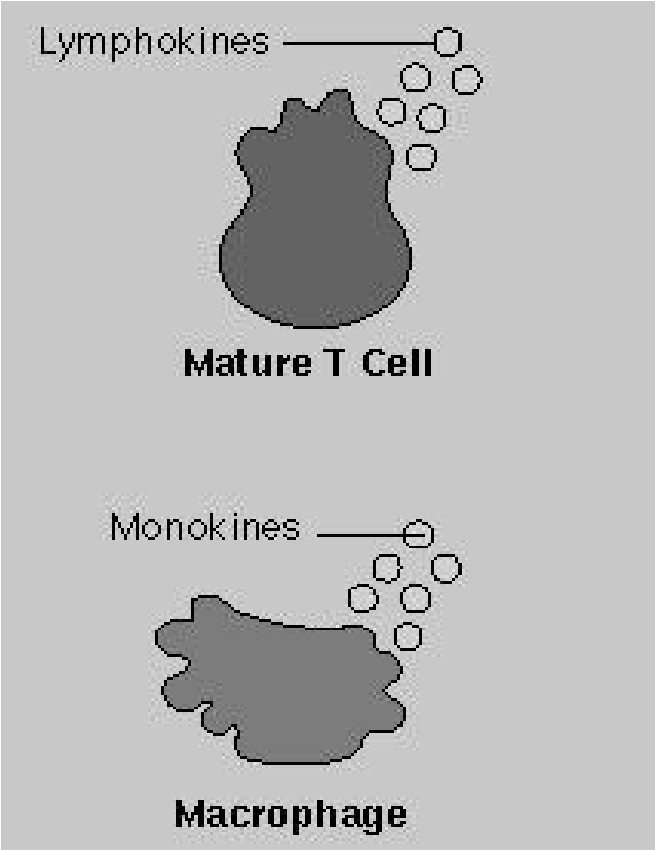
(iii) turn off or suppress immune cells.



Cytokines

A diverse and potent chemical messengers secreted by the cells of the immune

Cytokines encourage cell growth, promote cell activation, direct cellular traffic, and destroy target cells—including cancer cells.

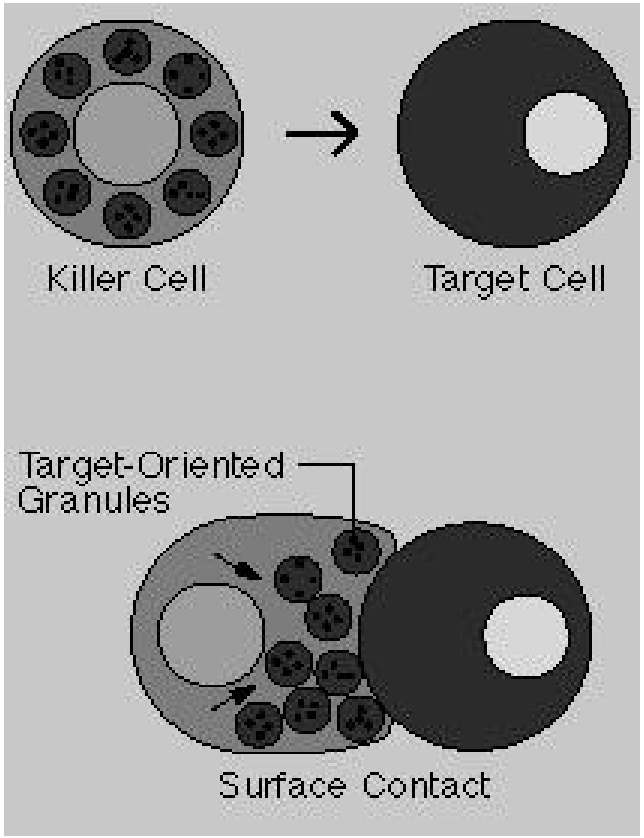


Natural Killer Cells

NK cells do not have a specific recognition.

Both Killer T cells and NK cells types contain granules filled with potent chemicals, and kill on contact.

The killer binds to its target, aims its weapons, and delivers a burst of lethal chemicals.



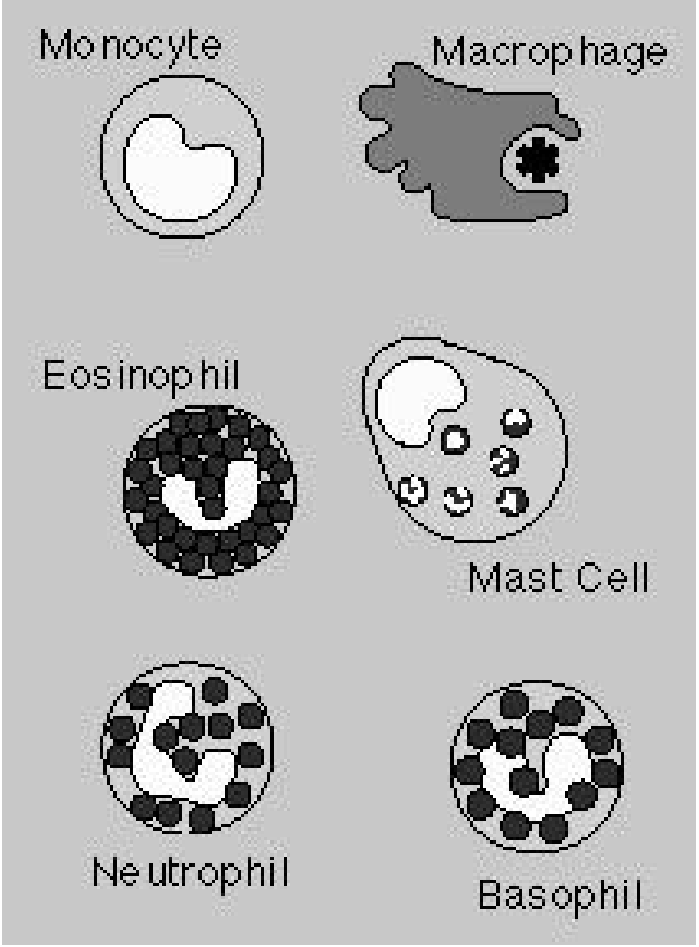
Phagocytes and Granulocytes

Phagocytes: large white cells that can engulf and digest foreign invaders.

Monocytes: circulate in the blood,

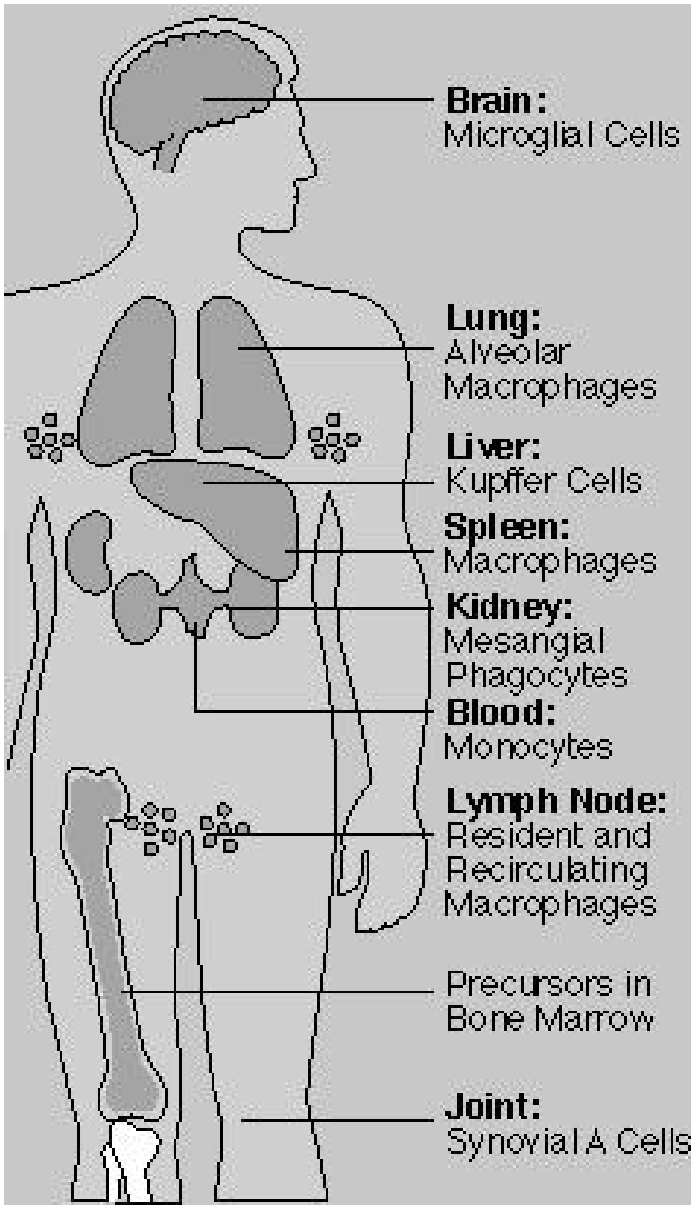
Macrophages: in tissues throughout the body,

Neutrophils: circulate in the blood, but move into tissues when needed.



Phagocytes in the Body

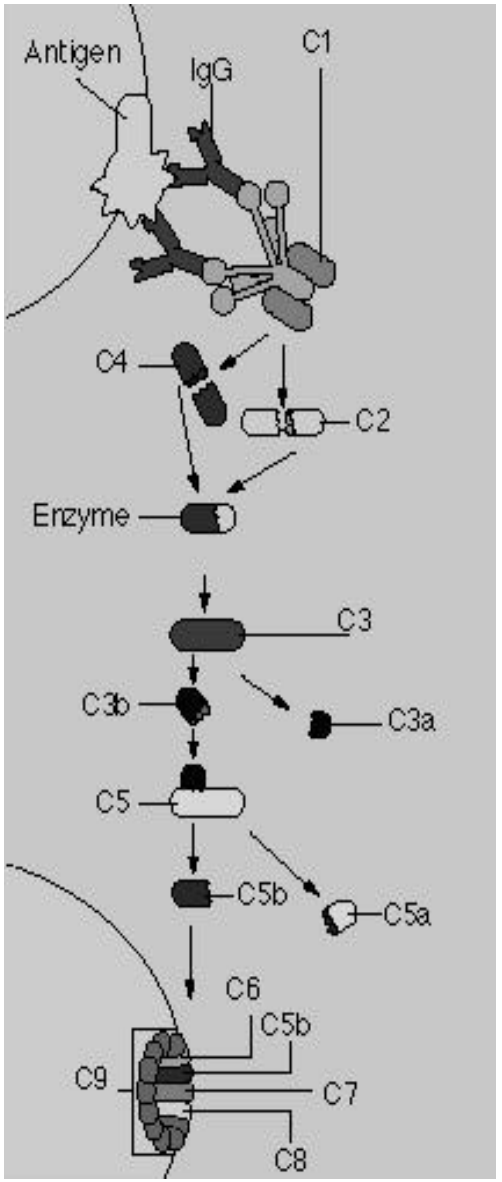
Specialized phagocytes are found in organs throughout the body.



The Complement System

The complement system: a series of proteins that work to "complement" the work of antibodies in destroying bacteria.

Complement proteins circulate in the blood in an inactive form.



Antigen Receptors

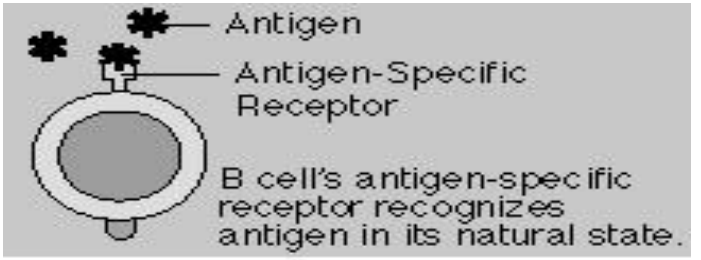
B cells and T have receptors for recognizing and responding to specific targets.

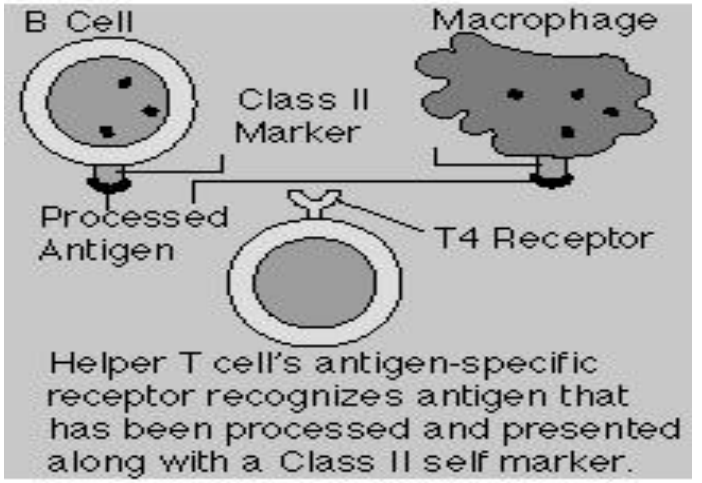
The B cell's antigen-specific receptor = antibody it can manufacture; it recognizes antigen in its natural state.

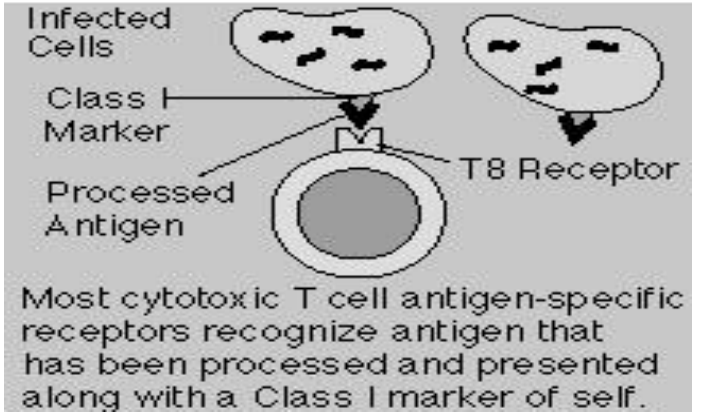
A T cell can recognize an antigen only after the antigen is processed and presented to it by a so-called antigen-presenting cell, in combination with a special type of cell marker (MHC).

CD4 T cell's receptor à MHC II, found on immune system cells (B-cells, Macrophages, D-Cells)

CD8 T cell's receptor à MHC I; found on virtually all body cells.





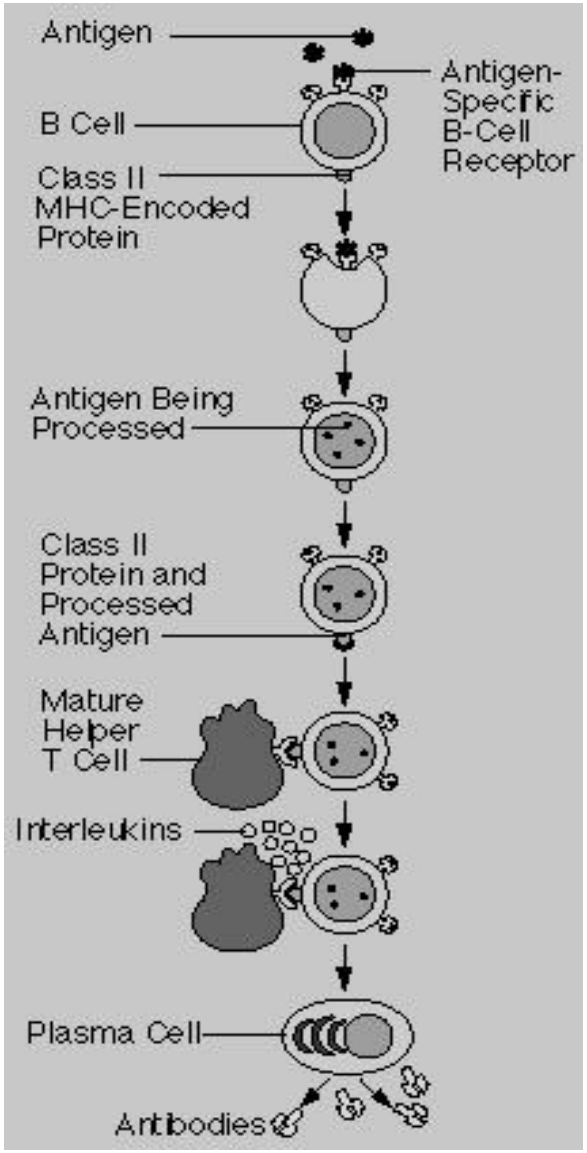


B Cells Activation

The B cell + specific antigen Ł B cell engulf and process antigen.

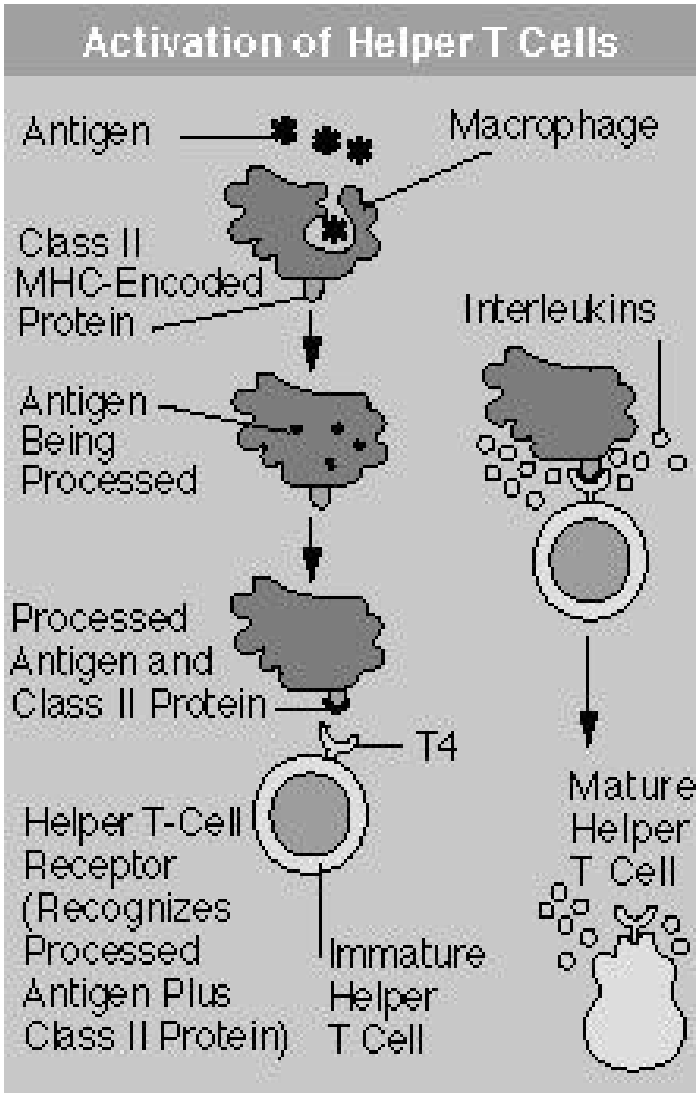
Antigen fragment (peptide) + special marker (MHC II) à B cell surface.

T recognizing peptide+MHC à T cell releases cytokines transforming the B cell into an antibody-secreting cell (plasma cell).

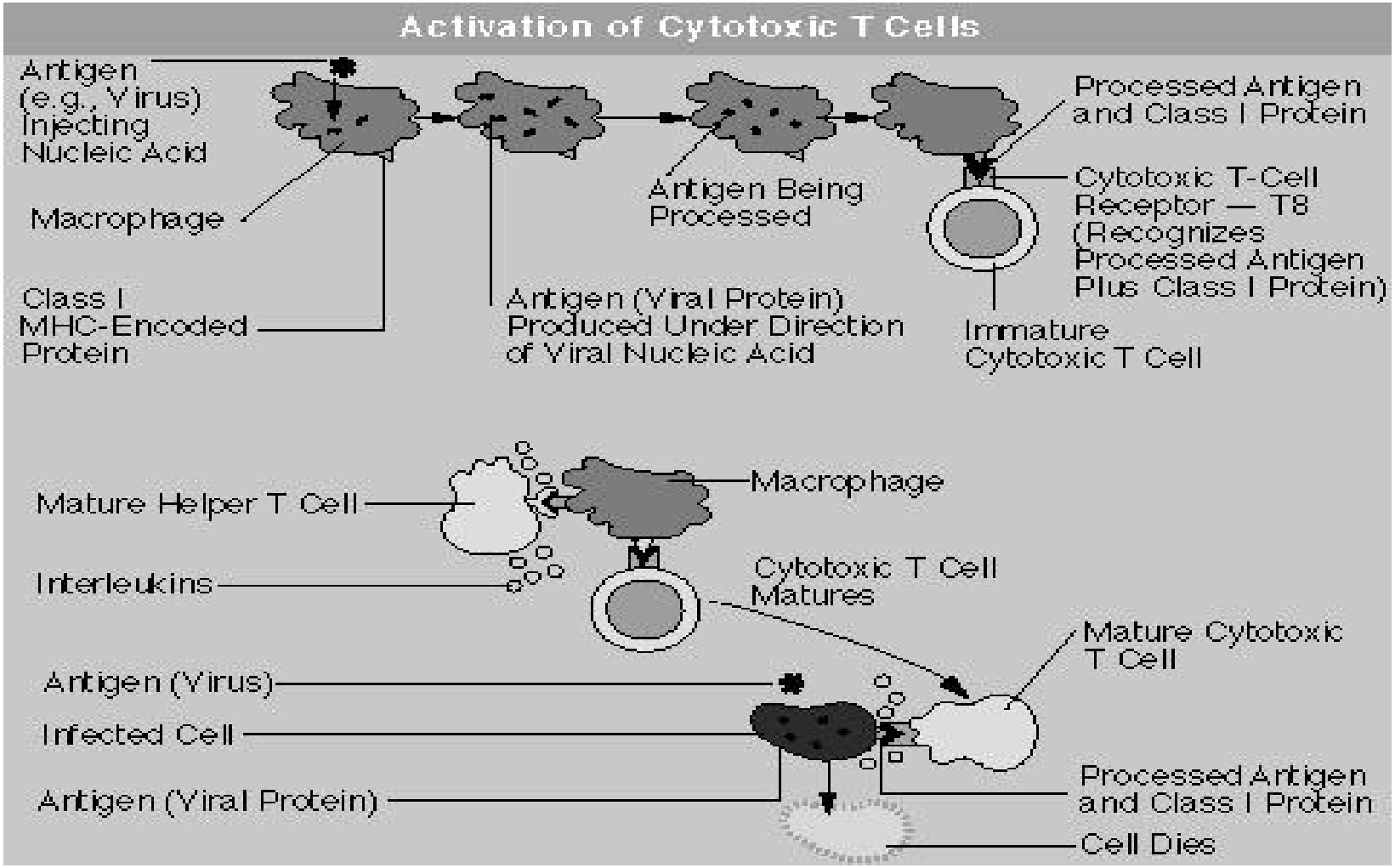


Helper T Cell activation

APC (Antigen presenting cell, (macrophage, B cell, D cell) + specific CD4 T cell à APC releases cytokines à T cell matures à T cell releases cytokines



Cytotoxic T cell activation



When The Immune System Fails

Allergy

Autoimmune diseases

Cancer

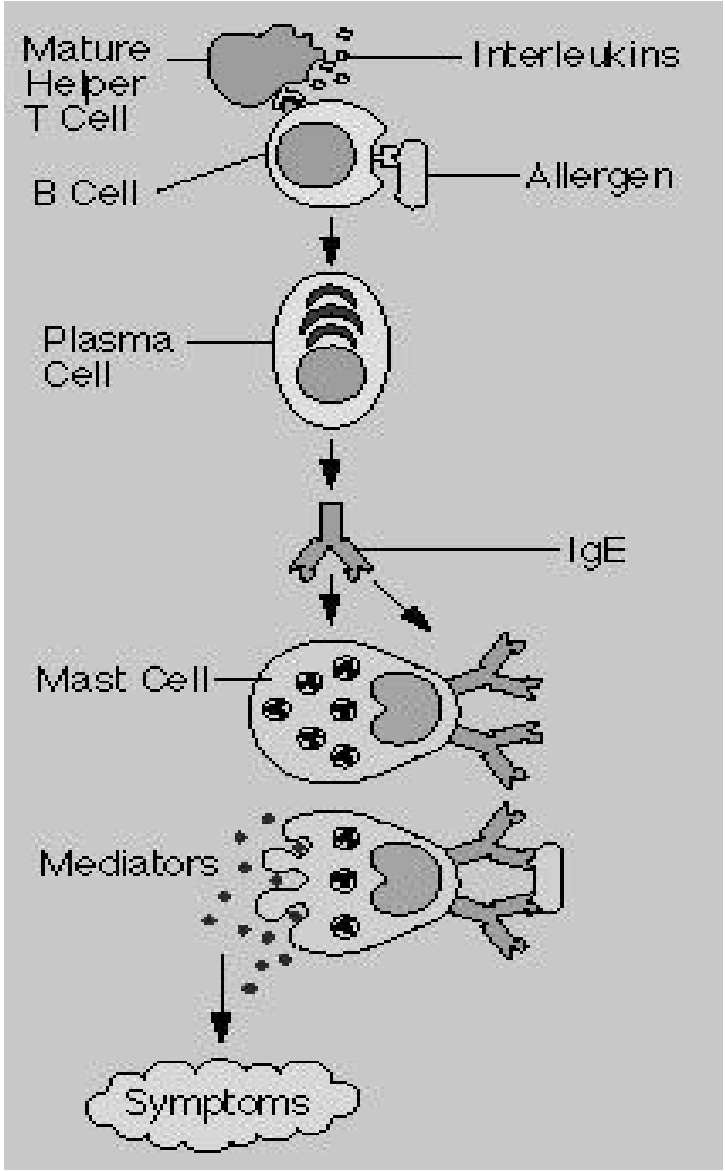
…

Allergy

First exposure to an allergen à B cells make large amounts of IgE antibodies.

These IgE molecules attach to mast cells, (in lungs, skin, tongue, and linings of the nose and gastrointestinal tract)

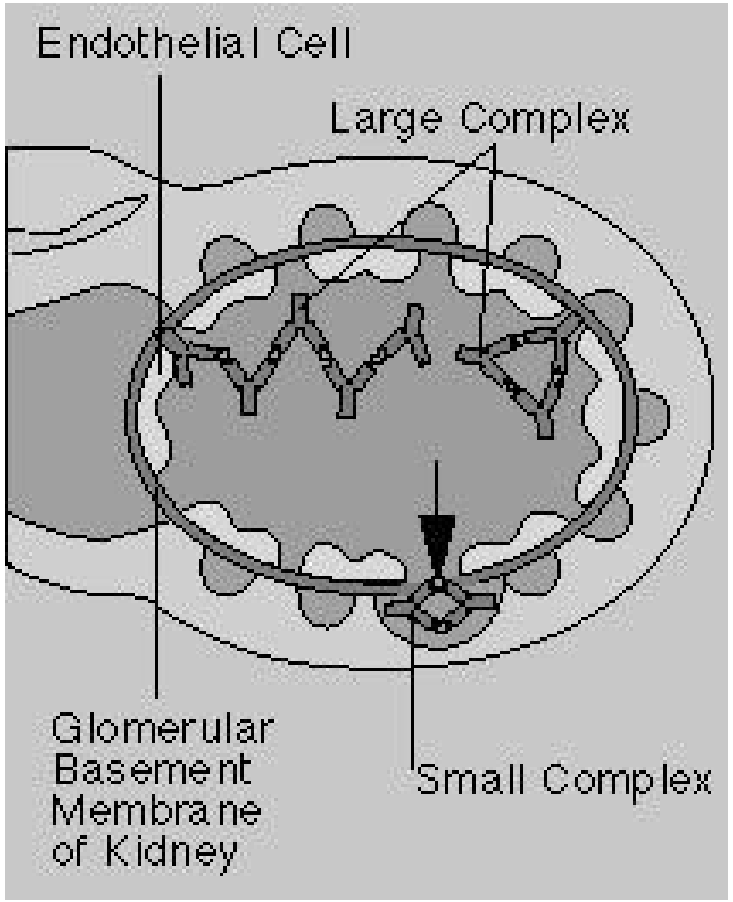
Next exposure to allergen à the IgE-primed mast cell releases chemicals causing wheezing, sneezing, and other symptoms of allergy.



Immune Complex Disease

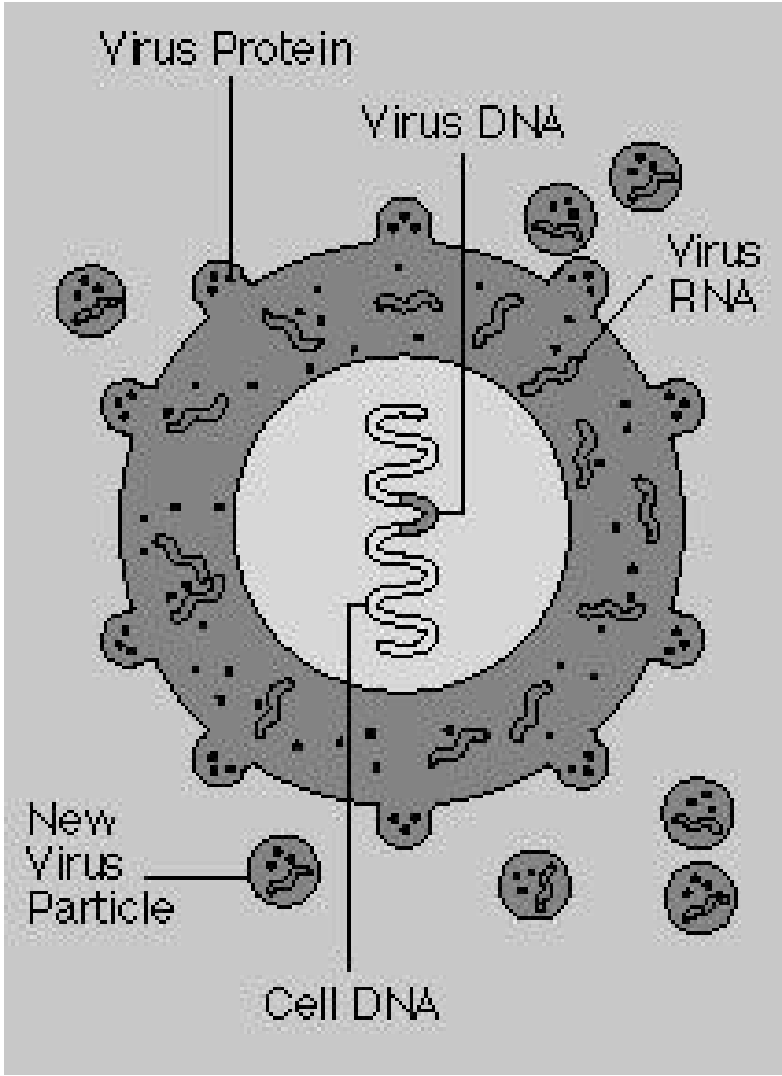
Immune complexes: clusters of interlocking antigens and antibodies.

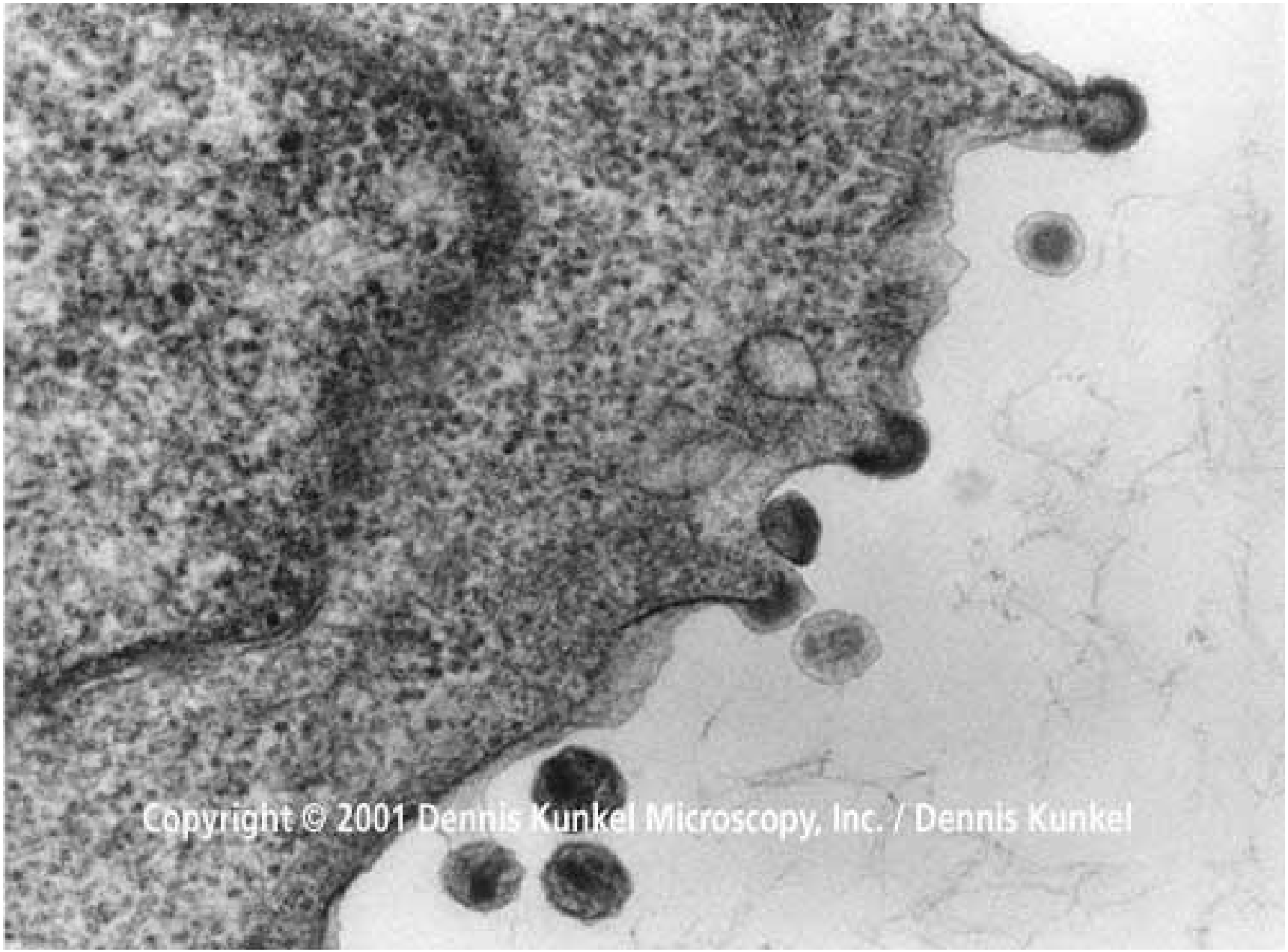
Normally they are rapidly removed from the bloodstream. If they continue to circulate, can be trapped and damage the tissues of the kidneys, as seen here, or in the lungs, skin, joints, or blood vessels.



AIDS

AIDS is an immunodeficiency disorder caused by a virus that destroys helper T cells and that is harbored in macrophages as well as helper (T4) T cells. The AIDS virus splices its DNA into the DNA of the cell it infects; the cell is thereafter directed to churn out new viruses.

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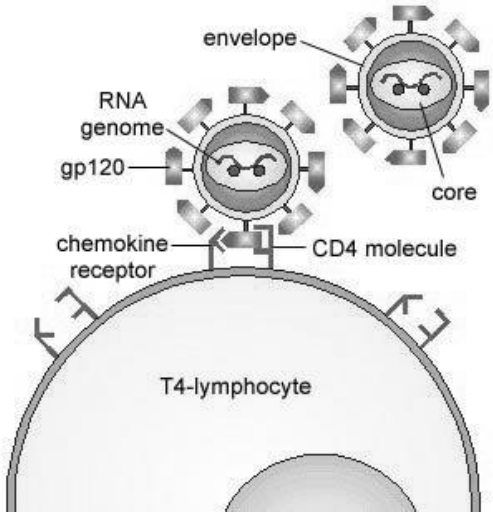
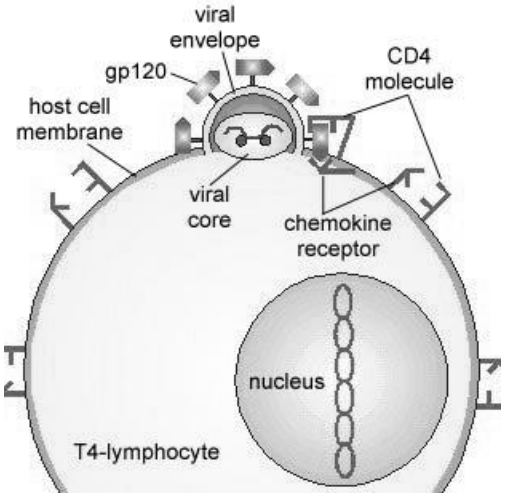
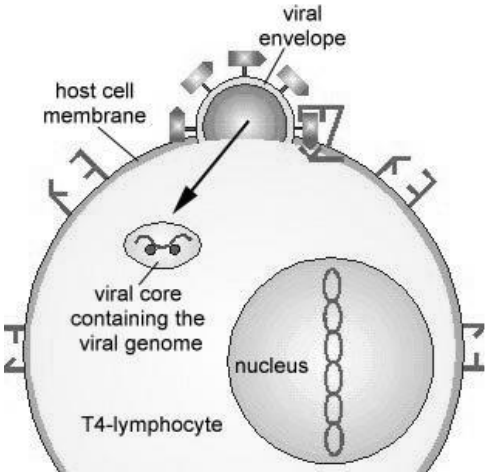
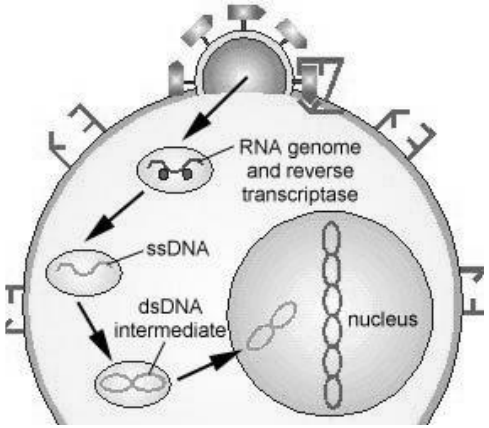
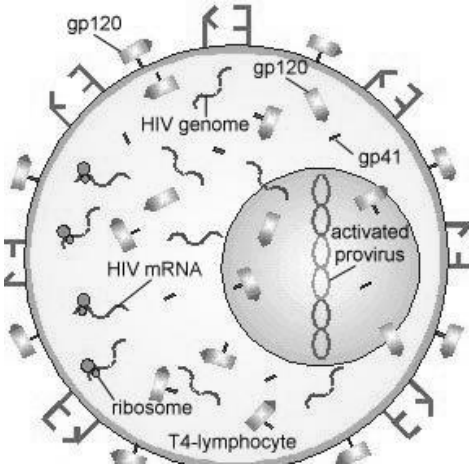
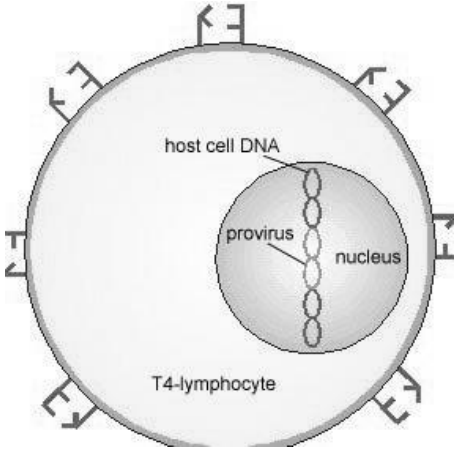

envelope
RNA genome
gp120
core
chemokine receptor
CD4 molecule
T4-lymphocyte

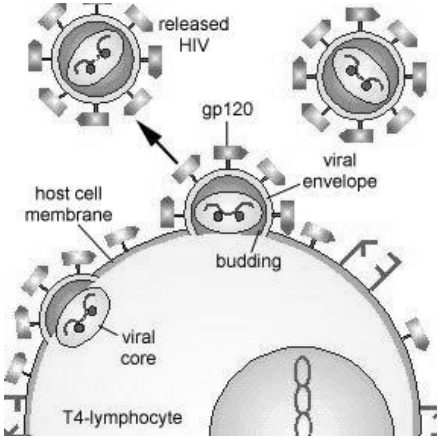

viral envelope
gp120
CD4 molecule
host cell membrane
viral core
chemokine receptor
nucleus
T4-lymphocyte

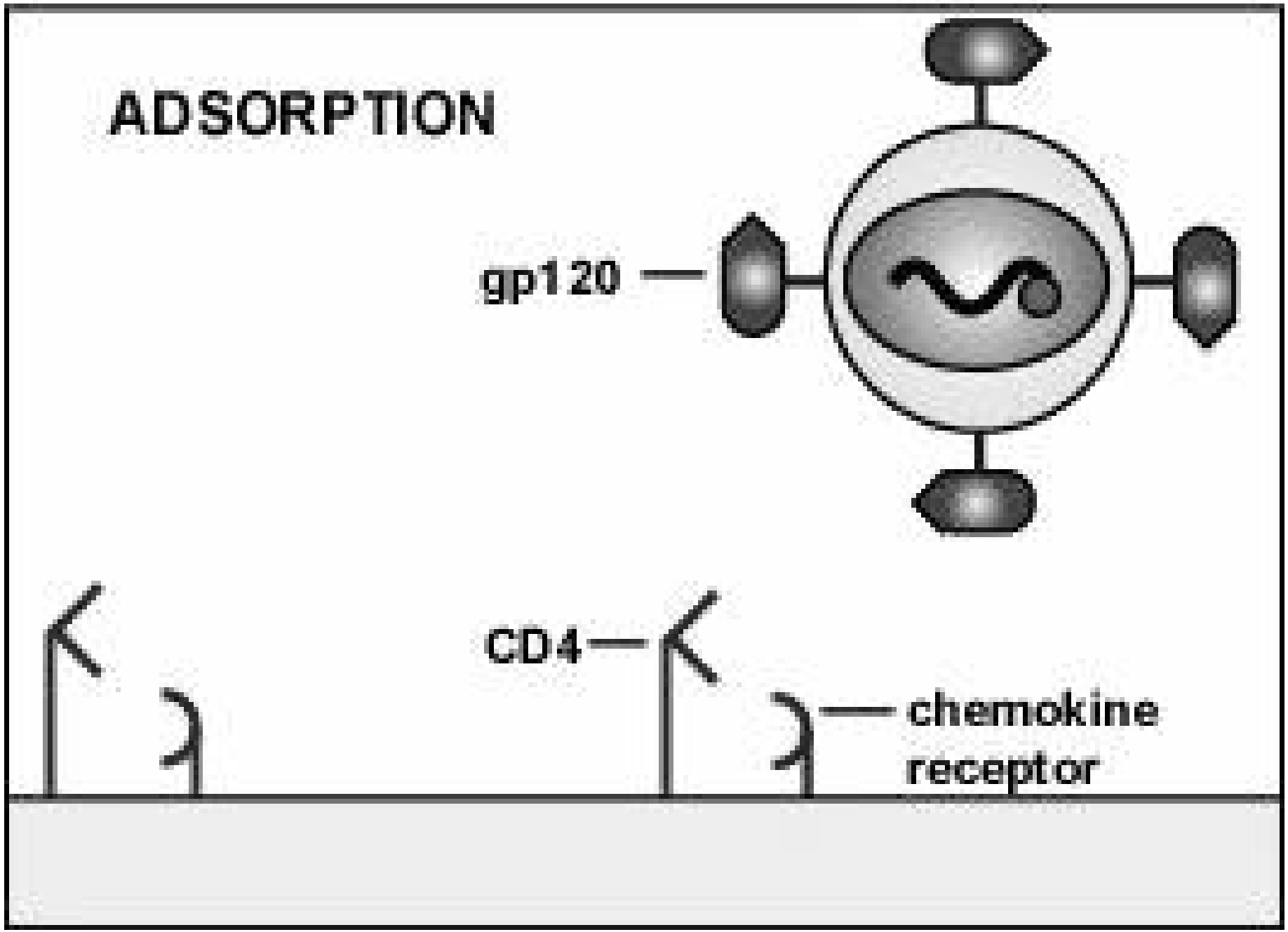

viral envelope
host cell membrane
viral core containing the viral genome
nucleus
T4-lymphocyte


RNA genome and reverse transcriptase
ssDNA
dsDNA intermediate
nucleus


gp120
gp120
HIV genome
gp41
activated provirus
HIV mRNA
ribosome
T4-lymphocyte


host cell DNA
provirus
nucleus
T4-lymphocyte


released HIV
gp120
viral envelope
host cell membrane
budding
viral core
T4-lymphocyte

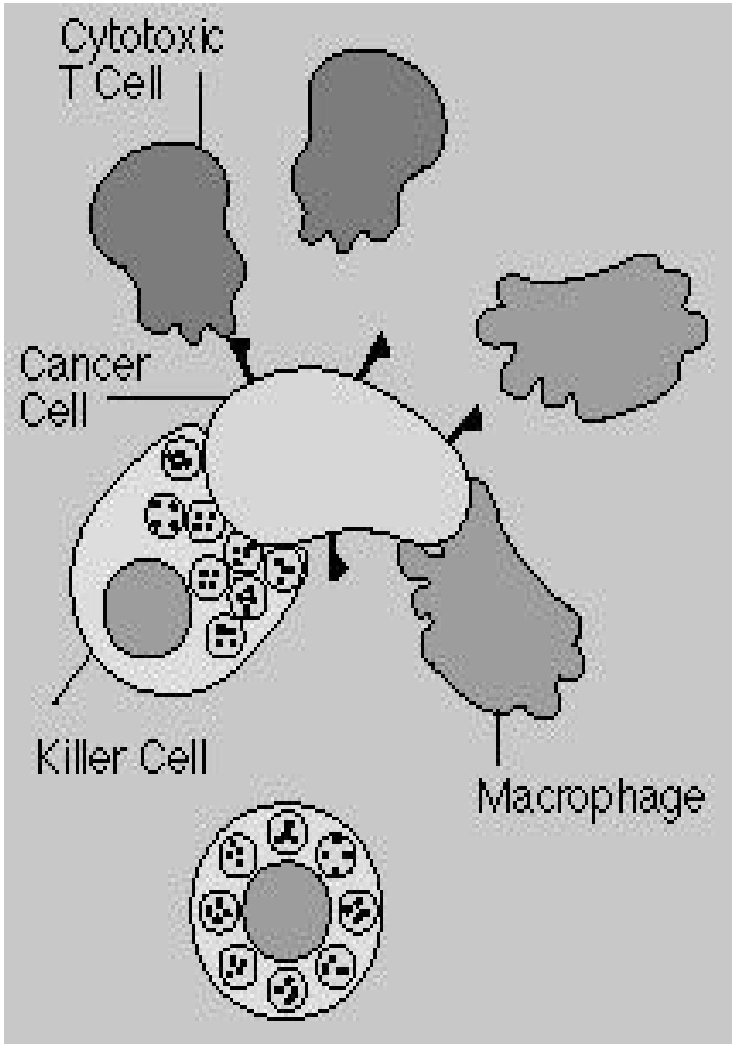

ADSORPTION
gp120
CD4
chemokine
receptor

Immunity and Cancer

When normal cells turn into cancer cells, some of the antigens on their surface change.

These new or altered antigens flag immune defenders, (cytotoxic T cells, NK cells, and macrophages) that eliminate cancerous cells.

Tumors develop when the surveillance system breaks down or is overwhelmed.



The Immune & Nervous Systems

Hormones and other chemicals, (neuropeptides: messengers among nerve cells), "speak" to cells of the immune system—and some immune cells even manufacture such chemicals (neuropeptides)

Networks of nerve fibers connect directly to the lymphoid organs.