IMMUNOMODULATORS

Compiled by:

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Outline

- Introduction to immunology
- Immunosuppressant and immunostimulant
- Immunomodulators in HIV & Cancer

Immunity: Two Intrinsic Defense Systems

1. Innate (nonspecific) system responds quickly and consists of:

- First line of defense – intact skin and mucosae prevent entry of microorganisms
- Second line of defense – antimicrobial proteins, phagocytes, and other cells
  - Inhibit spread of invaders throughout the body
  - Inflammation is its hallmark and most important mechanism

Immunity: Two Intrinsic Defense Systems

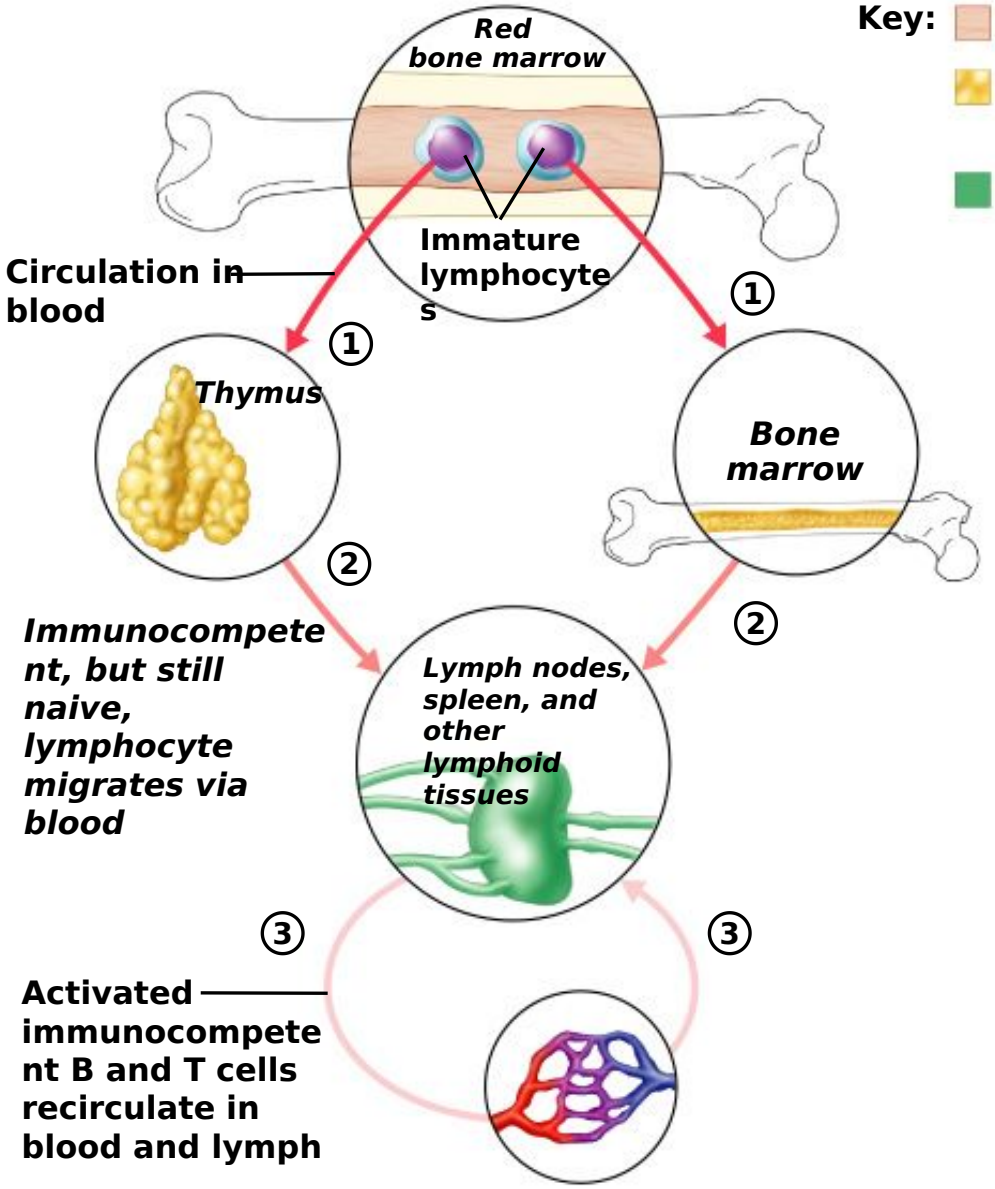
2. Adaptive (specific) defense system

- Third line of defense – mounts attack against particular foreign substances
  - Takes longer to react than the innate system
  - Works in conjunction with the innate system

Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
  - Skin acidity (pH of 3 to 5) inhibits bacterial growth
  - Sebum contains chemicals toxic to bacteria
  - Stomach mucosae secrete concentrated HCl and protein-digesting enzymes
  - Saliva and lacrimal fluid contain lysozyme
  - Mucus traps microorganisms that enter the digestive and respiratory systems

Immunocompetent B or T cells



Key:

- = Site of lymphocyte origin
- = Site of development of immunocompetence as B or T cells; primary lymphoid organs
- = Site of antigen challenge and final differentiation to activated B and T cells

1 Lymphocytes destined to become T cells migrate to the thymus and develop immunocompetence there. B cells develop immunocompetence in red bone marrow.

2 After leaving the thymus or bone marrow as naive immunocompetent cells, lymphocytes "seed" the lymph nodes, spleen, and other lymphoid tissues where the antigen challenge occurs.

3 Mature (antigen-activated) immunocompetent lymphocytes circulate continuously in the bloodstream and lymph and throughout the lymphoid organs of the body.

Figure 21.8

Clonal Selection-B cells

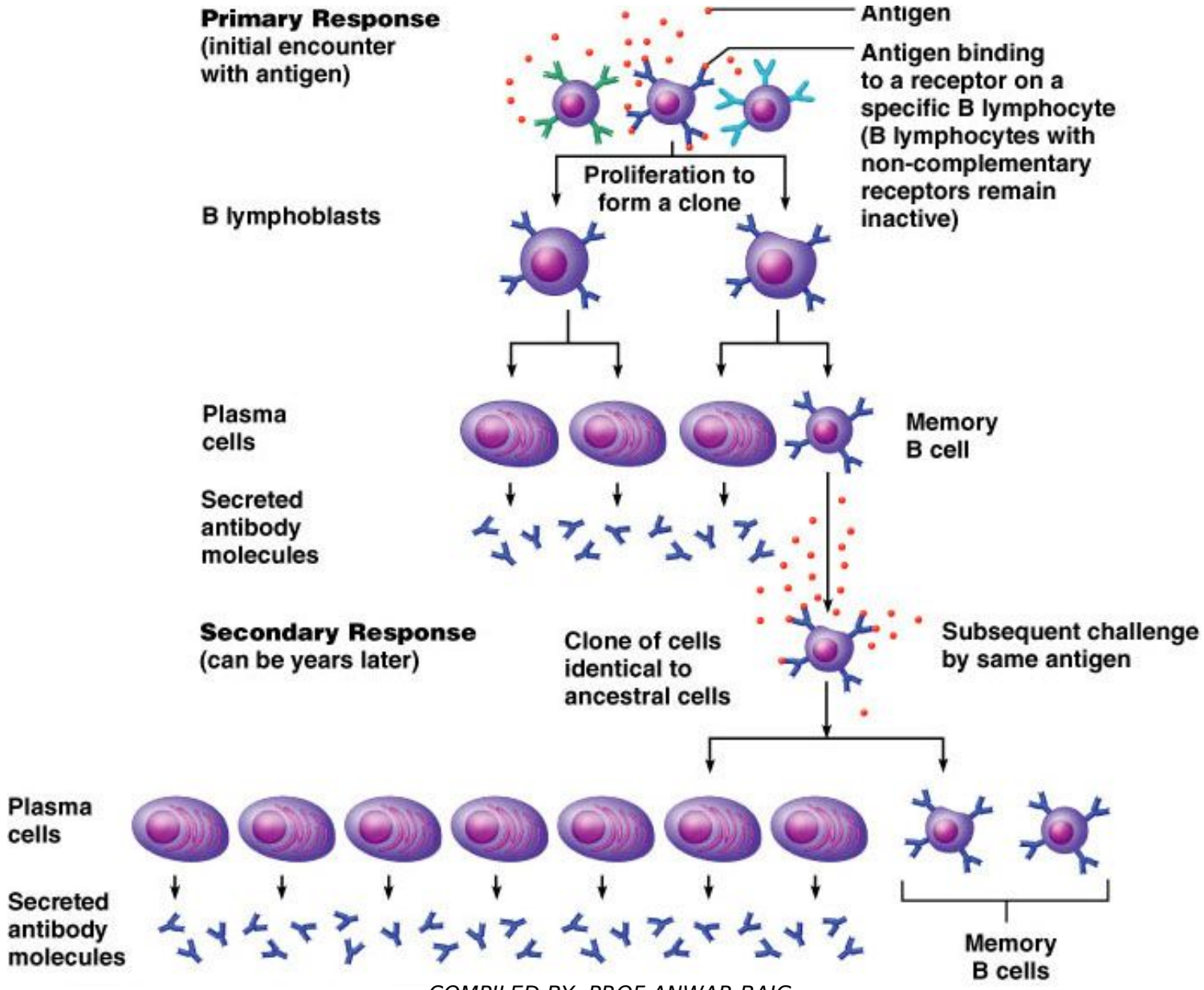


Figure 21.9

Antibodies

- Also called immunoglobulins
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with that antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE

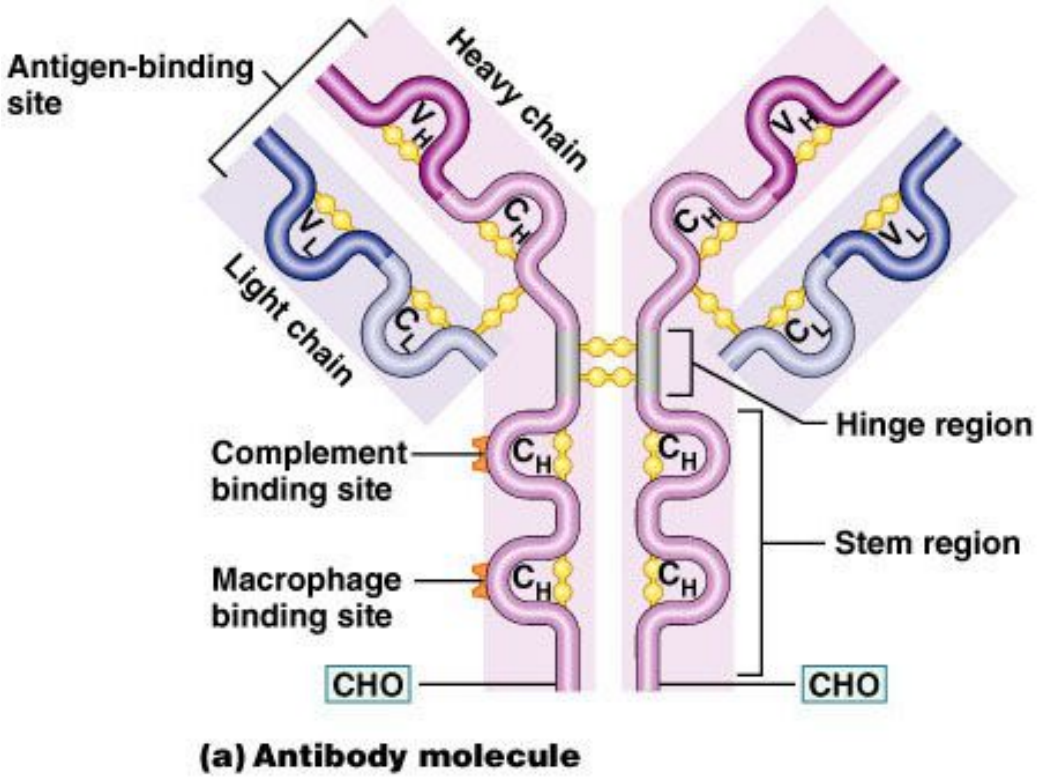
Classes of Antibodies

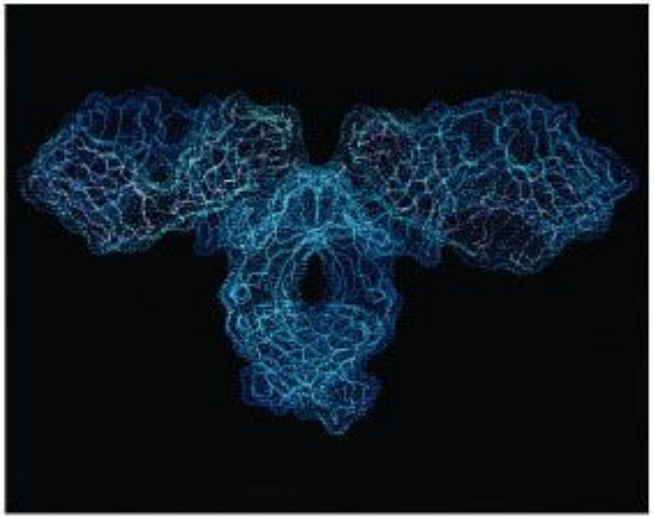
- IgD – monomer attached to the surface of B cells, important in B cell activation
- IgM – pentamer released by plasma cells during the primary immune response
- IgG – monomer that is the most abundant and diverse antibody in primary and secondary response; crosses the placenta and confers passive immunity
- IgA – dimer that helps prevent attachment of pathogens to epithelial cell surfaces
- IgE – monomer that binds to mast cells and basophils, causing histamine release when activated

Basic Antibody Structure

- Consists of four looping polypeptide chains linked together with disulfide bonds
  - Two identical heavy (H) chains and two identical light (L) chains
- The four chains bound together form an antibody monomer
- Each chain has a variable (V) region at one end and a constant (C) region at the other
- Variable regions of the heavy and light chains combine to form the antigen-binding site

Basic Antibody Structure





(b)

Key:

= Disulfide bond

CHO = Carbohydrate side chain

Figure 21.12a, b

Antibody Targets

- Antibodies themselves do not destroy antigen; they inactivate and tag it for destruction
- All antibodies form an antigen-antibody (immune) complex
- Defensive mechanisms used by antibodies are neutralization, agglutination, precipitation, and complement fixation

Mechanisms of Antibody Action

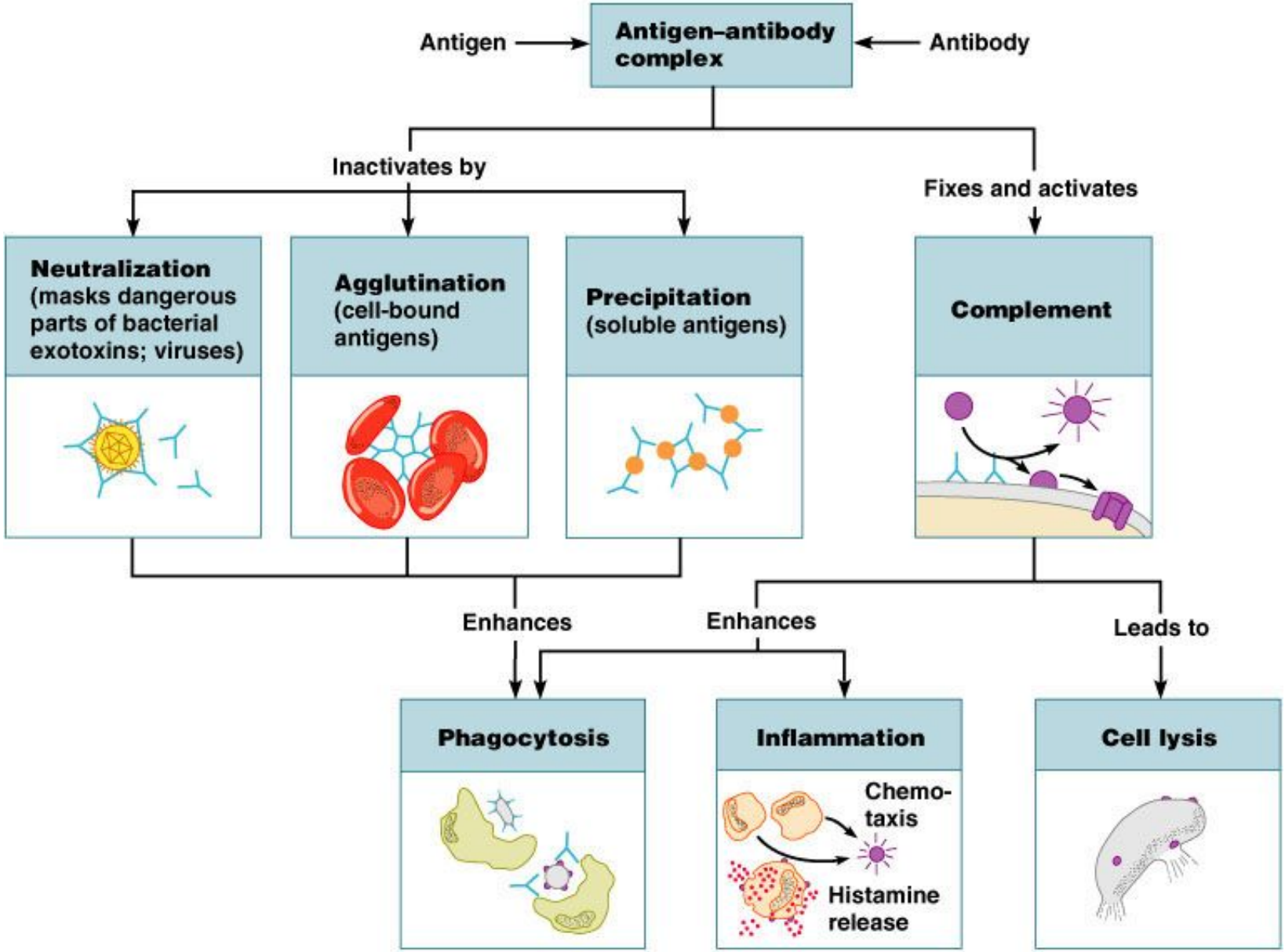


Figure 21.13

Major Types of T Cells

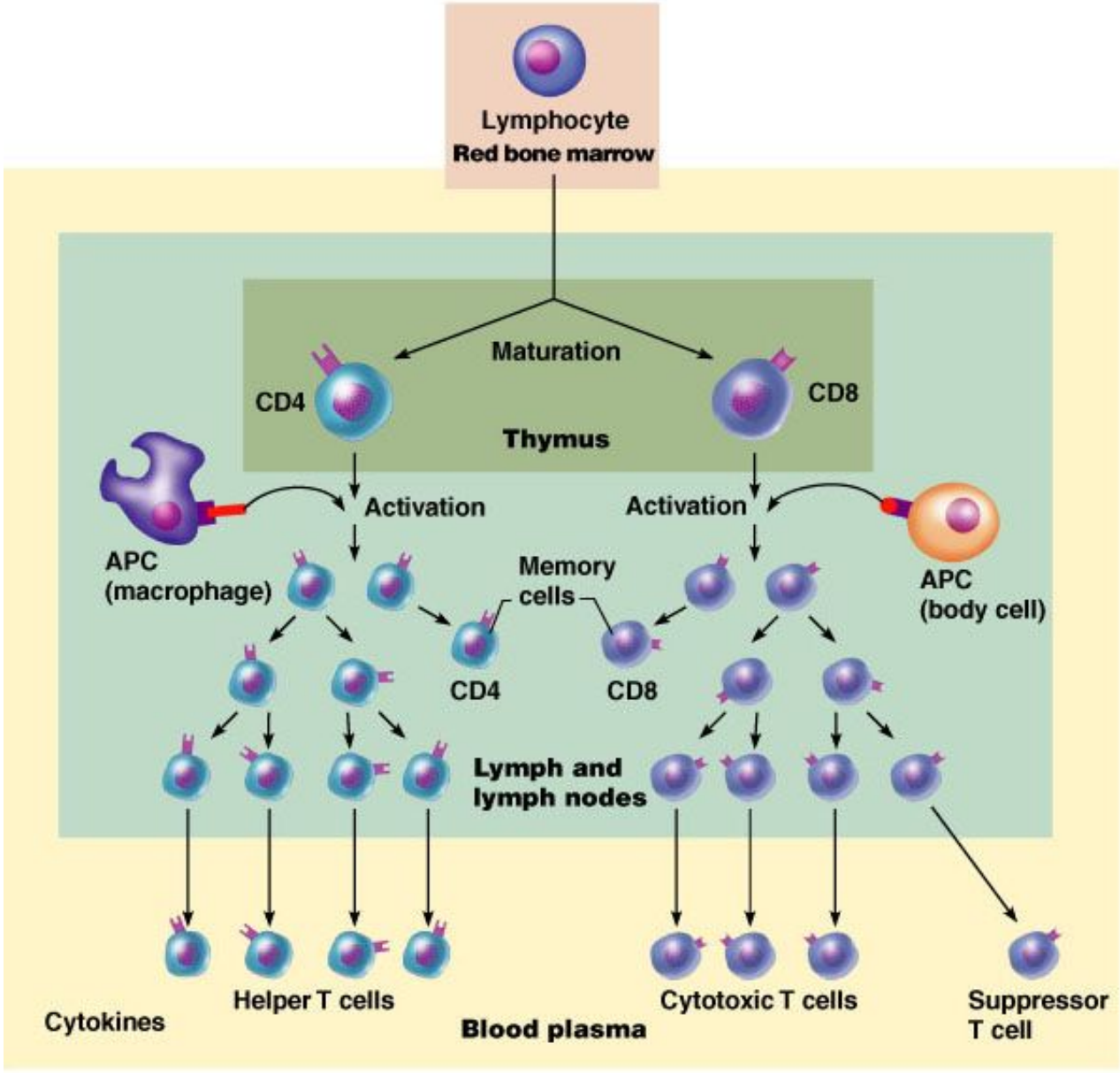


Figure 21.14

Importance of Humoral Response

- Soluble antibodies
  - Interact in extracellular environments such as body secretions, tissue fluid, blood, and lymph

Importance of Cellular Response

- T cells recognize and respond only to processed fragments of antigen displayed on the surface of body cells
- T cells are best suited for cell-to-cell interactions, and target:
  - Cells infected with viruses, bacteria, or intracellular parasites
  - Abnormal or cancerous cells
  - Cells of infused or transplanted foreign tissue

Antigen Recognition and MHC Restriction

- Immunocompetent T cells are activated when the V regions of their surface receptors bind to a recognized antigen
- T cells must simultaneously recognize:
  - Nonself (the antigen)
  - Self (a MHC protein of a body cell)

MHC Proteins

- Both types of MHC proteins are important to T cell activation
- Class I MHC proteins
  - Always recognized by CD8 T cells
  - Display peptides from endogenous antigens

Class I MHC Proteins

- Endogenous antigens are:
  - Degraded by proteases and enter the endoplasmic reticulum
  - Transported via TAP (**t**ransporter associated with **a**ntigen **p**rocessing)
  - Loaded onto class I MHC molecules
  - Displayed on the cell surface in association with a class I MHC molecule

Class I MHC Proteins

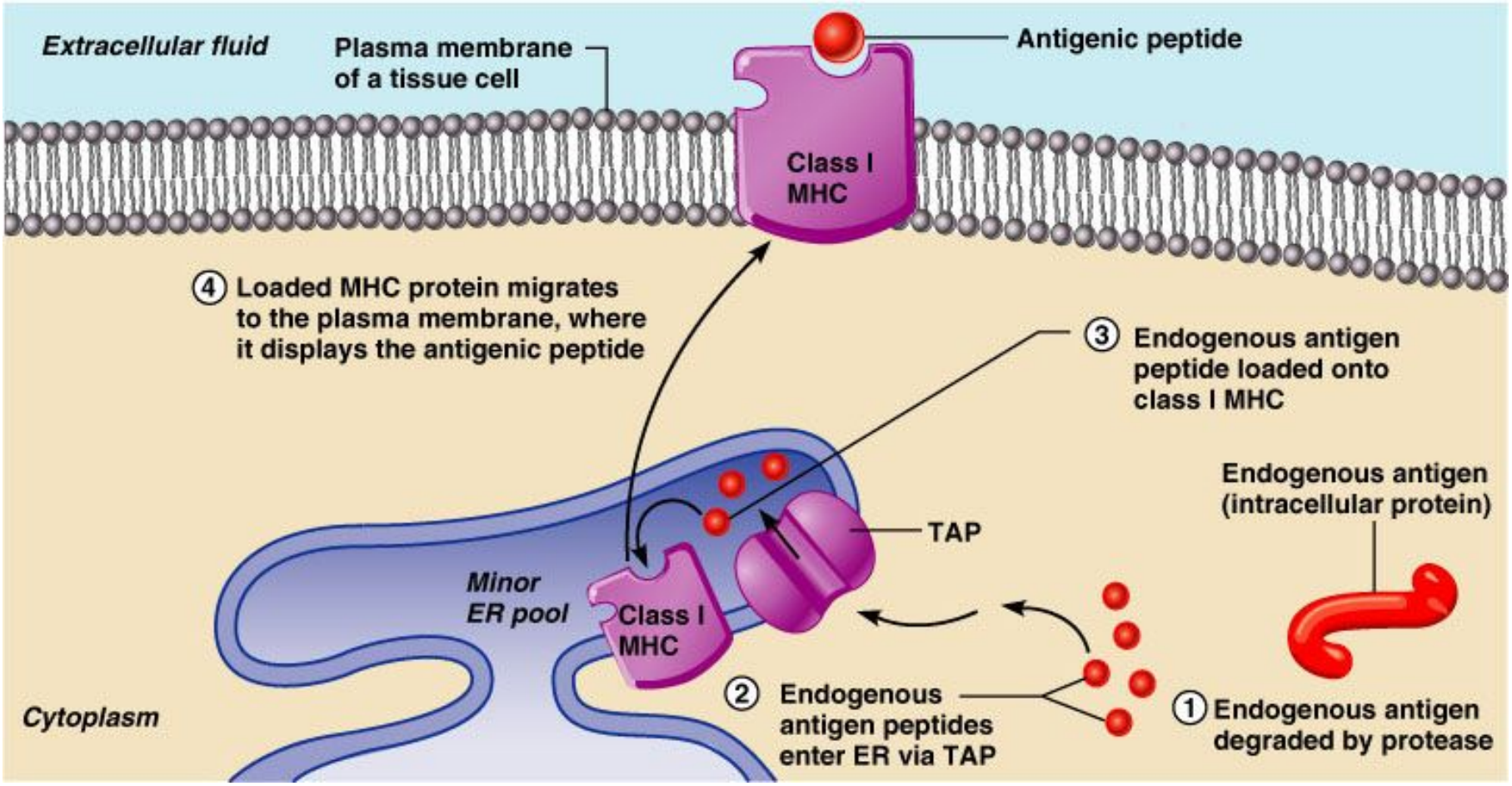


Figure 21.15a

Class II MHC Proteins

- Class II MHC proteins are found only on mature B cells, some T cells, and antigen-presenting cells
- A phagosome containing pathogens (with exogenous antigens) merges with a lysosome
- Invariant protein prevents class II MHC proteins from binding to peptides in the endoplasmic reticulum

Class II MHC Proteins

- Class II MHC proteins migrate into the phagosomes where the antigen is degraded and the invariant chain is removed for peptide loading
- Loaded Class II MHC molecules then migrate to the cell membrane and display antigenic peptide for recognition by CD4 cells

Class II MHC Proteins

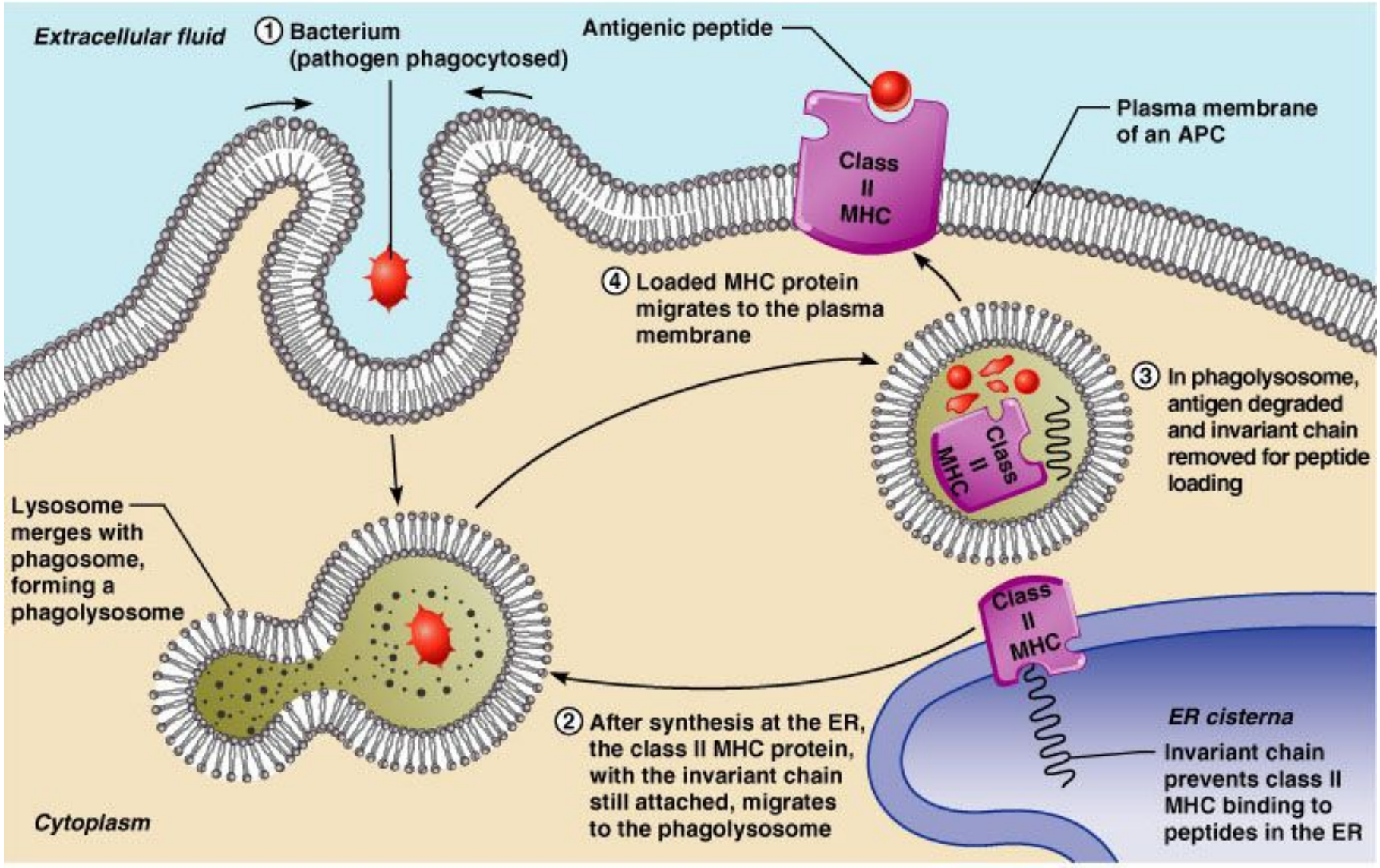


Figure 21.15b

T Cell Activation: Step One – Antigen Binding

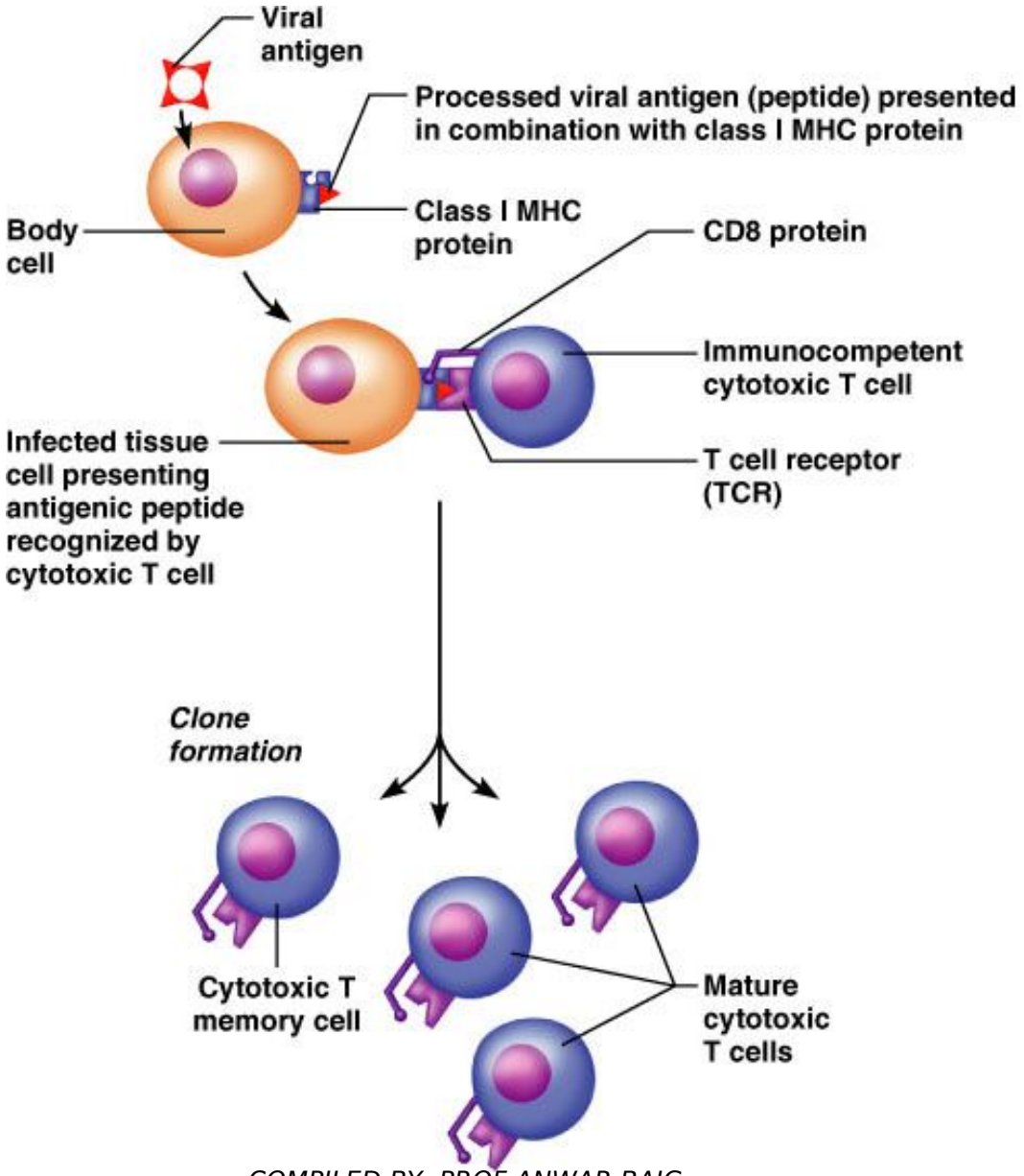


Figure 21.16

Helper T Cells (T_H)

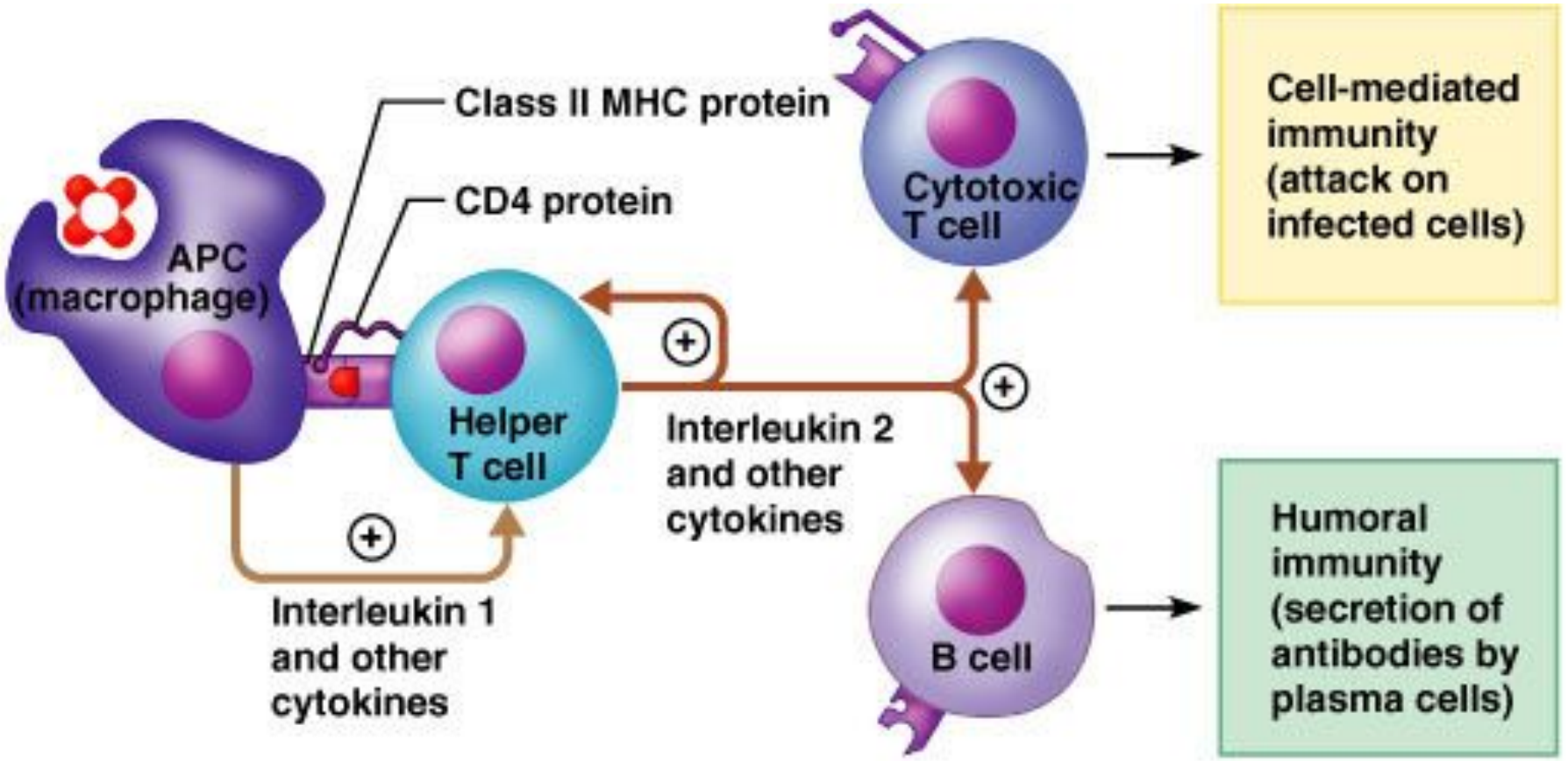


Figure 21.17a

Cytotoxic T Cell (T_c)

- T_C cells, or killer T cells, are the only T cells that can directly attack and kill other cells
- They circulate throughout the body in search of body cells that display the antigen to which they have been sensitized
- Their targets include:
  - Virus-infected cells
  - Cells with intracellular bacteria or parasites
  - Cancer cells
  - Foreign cells from blood transfusions or transplants

Mechanisms of T_c Action

- In some cases, T_C cells:
  - Bind to the target cell and release perforin into its membrane
    - In the presence of Ca^{2+} perforin causes cell lysis by creating transmembrane pores
- Other T_C cells induce cell death by:
  - Secreting lymphotoxin, which fragments the target cell's DNA
  - Secreting gamma interferon, which stimulates phagocytosis by macrophages

Mechanisms of T_c Action

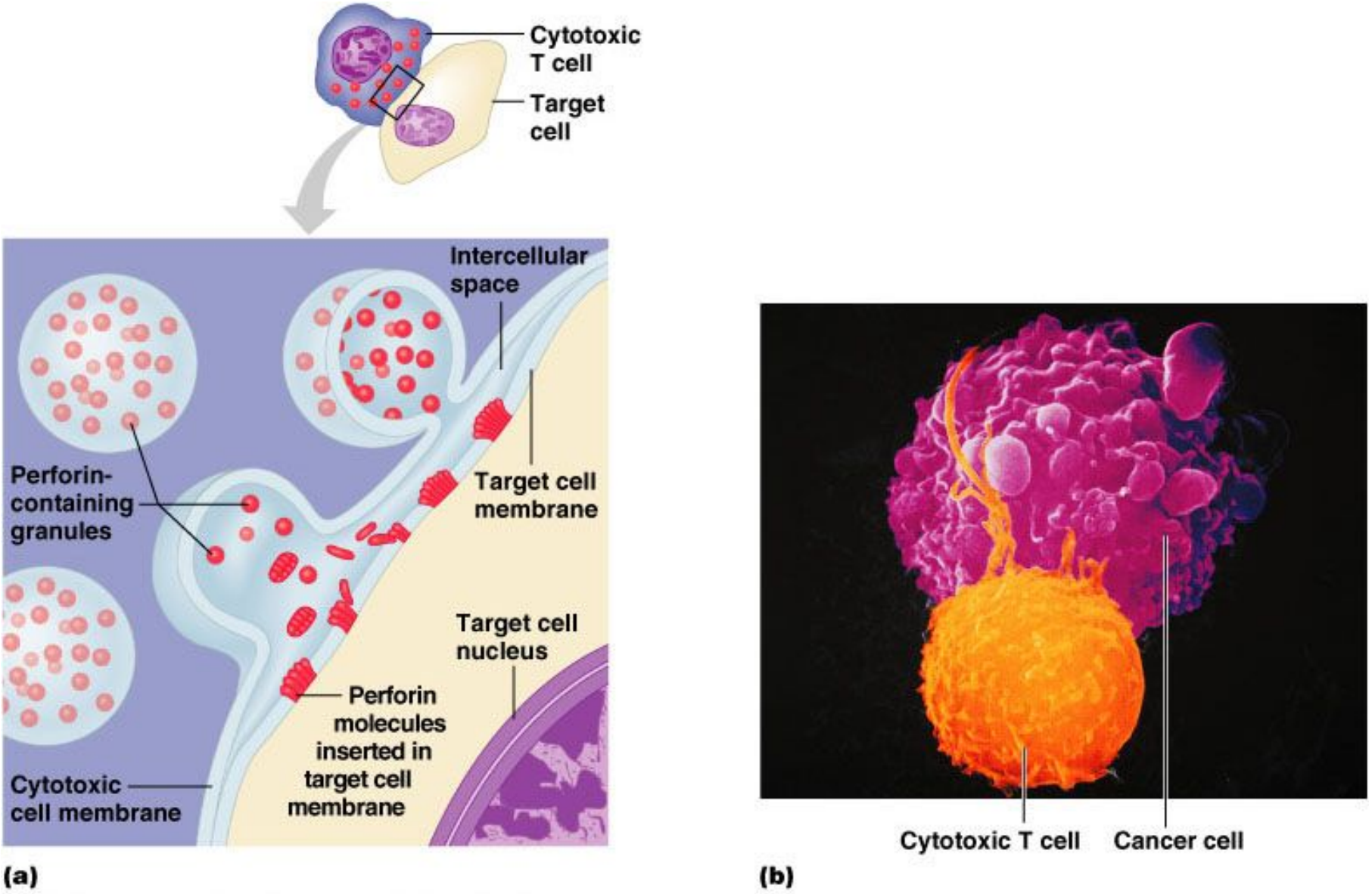


Figure 21.18a, b

Other T Cells

- Suppressor T cells (T_S) – regulatory cells that release cytokines, which suppress the activity of both T cells and B cells
- Gamma delta T cells (T_{gd}) – 10% of all T cells found in the intestines that are triggered by binding to MICA receptors

Summary of the Primary Immune Respons

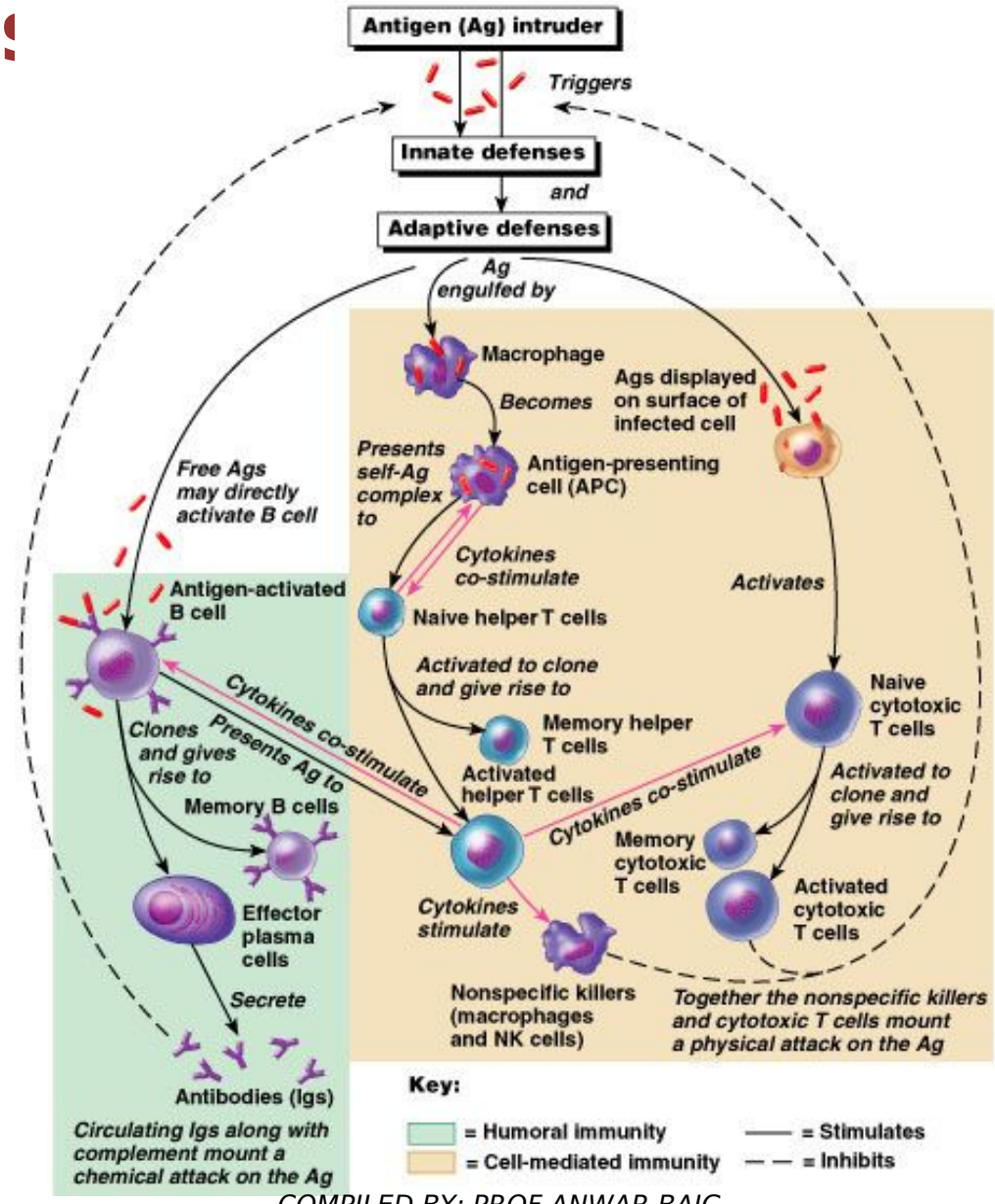


Figure 21.19

Organ Transplants

- The four major types of grafts are:
  - Autografts – graft transplanted from one site on the body to another in the same person
  - Isografts – grafts between identical twins
  - Allografts – transplants between individuals that are not identical twins, but belong to same species
  - Xenografts – grafts taken from another animal species

Prevention of Rejection

- Prevention of tissue rejection is accomplished by using immunosuppressive drugs
- However, these drugs depress patient's immune system so it cannot fight off foreign agents

Severe Combined Immunodeficiency (SCID)

- SCID – severe combined immunodeficiency (SCID) syndromes; genetic defects that produce:
  - A marked deficit in B and T cells
  - Abnormalities in interleukin receptors
  - Defective adenosine deaminase (ADA) enzyme
    - Metabolites lethal to T cells accumulate
- SCID is fatal if untreated; treatment is with bone marrow transplants

Acquired Immunodeficiencies

- Hodgkin's disease – cancer of the lymph nodes leads to immunodeficiency by depressing lymph node cells
- Acquired immune deficiency syndrome (AIDS) – cripples the immune system by interfering with the activity of helper T (CD4) cells
  - Characterized by severe weight loss, night sweats, and swollen lymph nodes
  - Opportunistic infections occur, including pneumocystis pneumonia and Kaposi's sarcoma

AIDS

- Caused by human immunodeficiency virus (HIV) transmitted via body fluids – blood, semen, and vaginal secretions
- HIV enters the body via:
  - Blood transfusions
  - Contaminated needles
  - Intimate sexual contact, including oral sex
- HIV:
  - Destroys T_H cells
  - Depresses cell-mediated immunity

AIDS

- HIV multiplies in lymph nodes throughout the asymptomatic period
- Symptoms appear in a few months to 10 years
- Attachment
  - HIV’s coat protein (gp120) attaches to the CD4 receptor
  - A nearby protein (gp41) fuses the virus to the target cell

AIDS

- HIV enters the cell and uses reverse transcriptase to produce DNA from viral RNA
- This DNA (provirus) directs the host cell to make viral RNA (and proteins), enabling the virus to reproduce and infect other cells

AIDS

- HIV reverse transcriptase is not accurate and produces frequent transcription errors
  - This high mutation rate causes resistance to drugs
- Treatments include:
  - Reverse transcriptase inhibitors (AZT)
  - Protease inhibitors (saquinavir and ritonavir)
  - New drugs currently being developed that block HIV's entry to helper T cells

Autoimmune Diseases

- Loss of the immune system's ability to distinguish self from nonself
- The body produces autoantibodies and sensitized T_C cells that destroy its own tissues
- Examples include:
  - multiple sclerosis
  - myasthenia gravis
  - Graves' disease
  - Type I (juvenile) diabetes mellitus
  - systemic lupus erythematosus (SLE)
  - Glomerulonephritis
  - rheumatoid arthritis

Mechanisms of Autoimmune Diseases

- Ineffective lymphocyte programming – self-reactive T and B cells that should have been eliminated in the thymus and bone marrow escape into the circulation
- New self-antigens appear, generated by:
  - Gene mutations that cause new proteins to appear
  - Changes in self-antigens by hapten attachment or as a result of infectious damage

Mechanisms of Autoimmune Diseases

- If the determinants on foreign antigens resemble self-antigens:
  - Antibodies made against foreign antigens cross-react with self-antigens

Hypersensitivity

- Immune responses that cause tissue damage
- Different types of hypersensitivity reactions are distinguished by:
  - Their time course
  - Whether antibodies or T cells are the principle immune elements involved
- Antibody-mediated allergies are immediate and subacute hypersensitivities
- The most important cell-mediated allergic condition is delayed hypersensitivity

Immediate Hypersensitivity

- Acute (type I) hypersensitivities begin in seconds after contact with allergen
- Anaphylaxis – initial allergen contact is asymptomatic but sensitizes the person
  - Subsequent exposures to allergen cause:
    - Release of histamine and inflammatory chemicals
    - Systemic or local responses

Immediate Hypersensitivity

- The mechanism involves IL-4 secreted by T cells
- IL-4 stimulates B cells to produce IgE
- IgE binds to mast cells and basophils causing them to degranulate, resulting in a flood of histamine release and inducing the inflammatory response

Acute Allergic Response

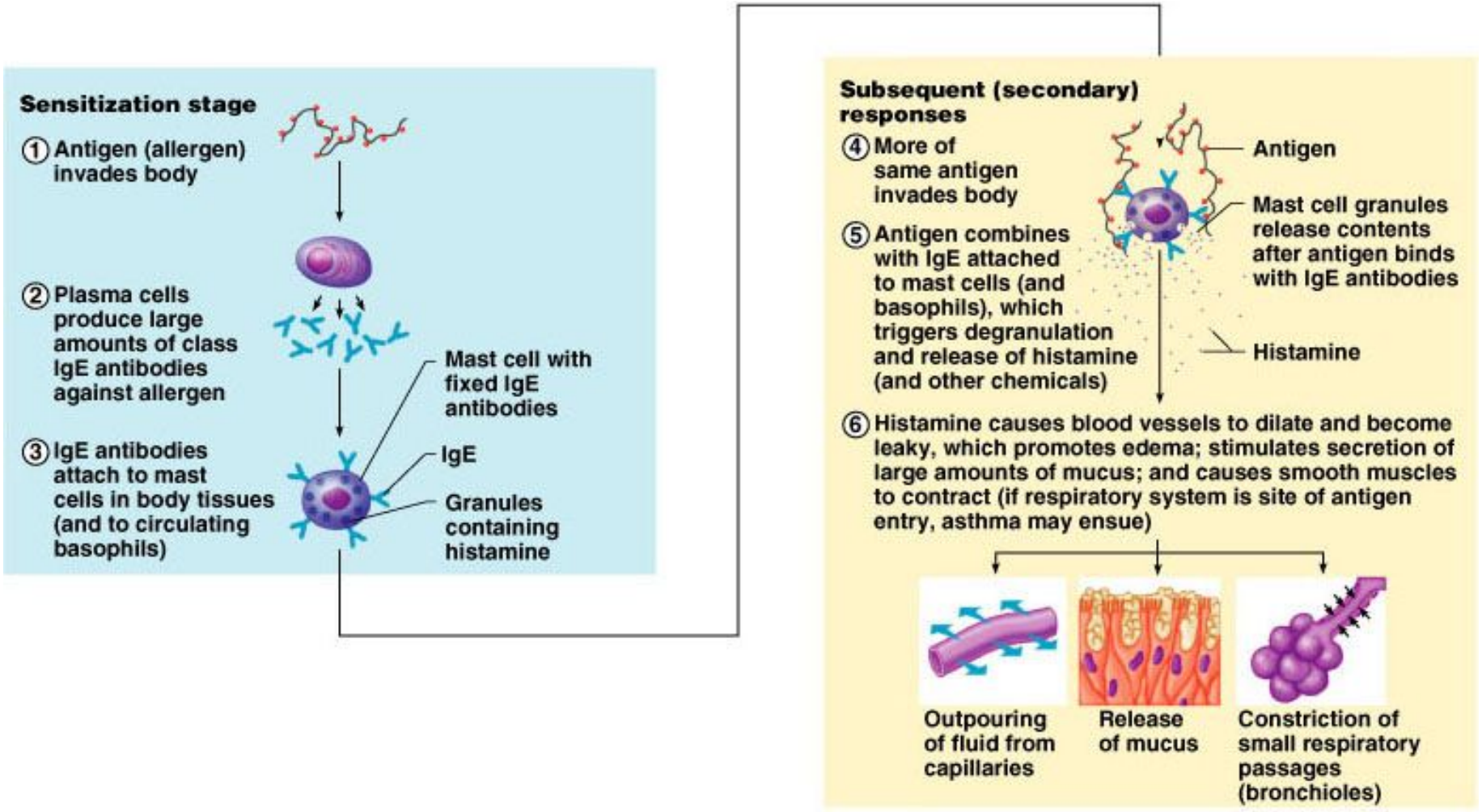


Figure 21.20

Anaphylaxis

- Reactions include runny nose, itching reddened skin, and watery eyes
- If allergen is inhaled, asthmatic symptoms appear – constriction of bronchioles and restricted airflow
- If allergen is ingested, cramping, vomiting, or diarrhea occur
- Antihistamines counteract these effects

Anaphylactic Shock

- Response to allergen that directly enters the blood (e.g., insect bite, injection)
- Basophils and mast cells are enlisted throughout the body
- Systemic histamine releases may result in:
  - Constriction of bronchioles
  - Sudden vasodilation and fluid loss from the bloodstream
  - Hypotensive shock and death
- Treatment – epinephrine is the drug of choice

Subacute Hypersensitivities

- Caused by IgM and IgG, and transferred via blood plasma or serum
  - Onset is slow (1–3 hours) after antigen exposure
  - Duration is long lasting (10–15 hours)
- Cytotoxic (type II) reactions
  - Antibodies bind to antigens on specific body cells, stimulating phagocytosis and complement-mediated lysis of the cellular antigens
  - Example: mismatched blood transfusion reaction

Subacute Hypersensitivities

- Immune complex (type III) hypersensitivity
  - Antigens are widely distributed through the body or blood
  - Insoluble antigen-antibody complexes form
  - Complexes cannot be cleared from a particular area of the body
  - Intense inflammation, local cell lysis, and death may result
  - Example: systemic lupus erythematosus (SLE)

Delayed Hypersensitivities (Type IV)

- Onset is slow (1–3 days)
- Mediated by mechanisms involving delayed hypersensitivity T cells and cytotoxic T cells
- Cytokines from activated T_C are the mediators of the inflammatory response
- Antihistamines are ineffective and corticosteroid drugs are used to provide relief

Delayed Hypersensitivities (Type IV)

- Example: allergic contact dermatitis (e.g., poison ivy)
- Involved in protective reactions against viruses, bacteria, fungi, protozoa, cancer, and rejection of foreign grafts or transplants

Summary of the Primary Immune Response

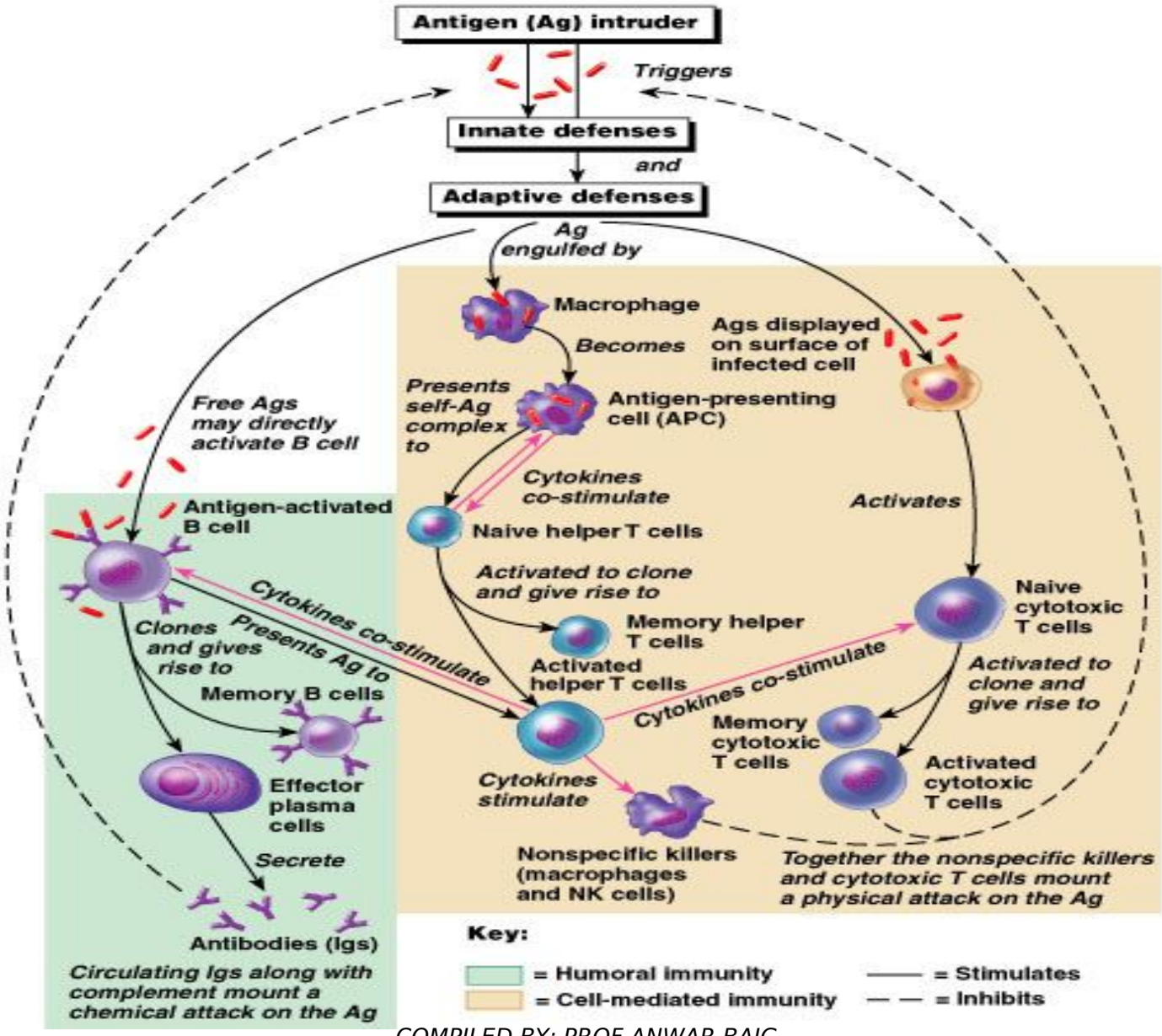


Figure 21.19

Immunosuppresants

- Immunosuppressants are the drugs which inhibits the immunity (cell mediated or humoral)
- It is necessary to suppress immune reaction in organ transplantation and autoimmune disorder.

Classification:

1. T cell inhibitor or Calcineurin inhibitor:

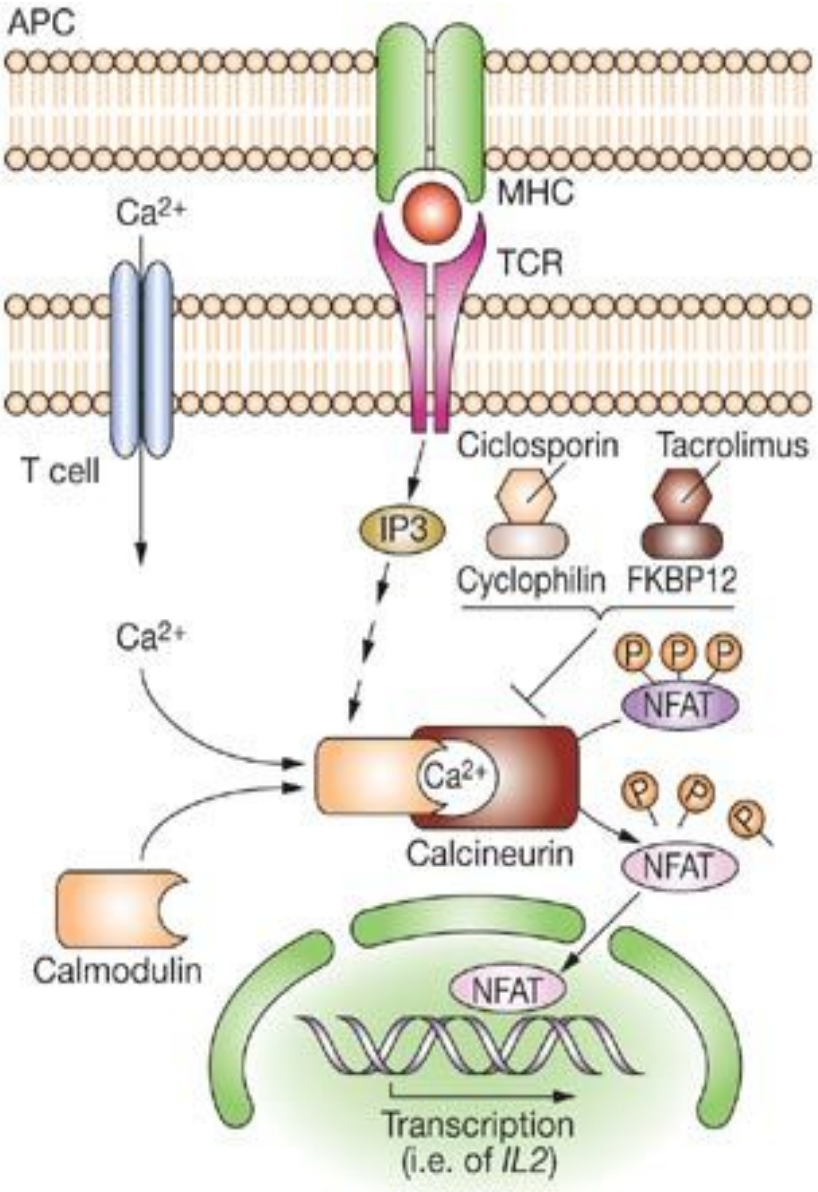
eg.Cyclosporine,tacrolimus,sirlimus,mycophenolate mofetil

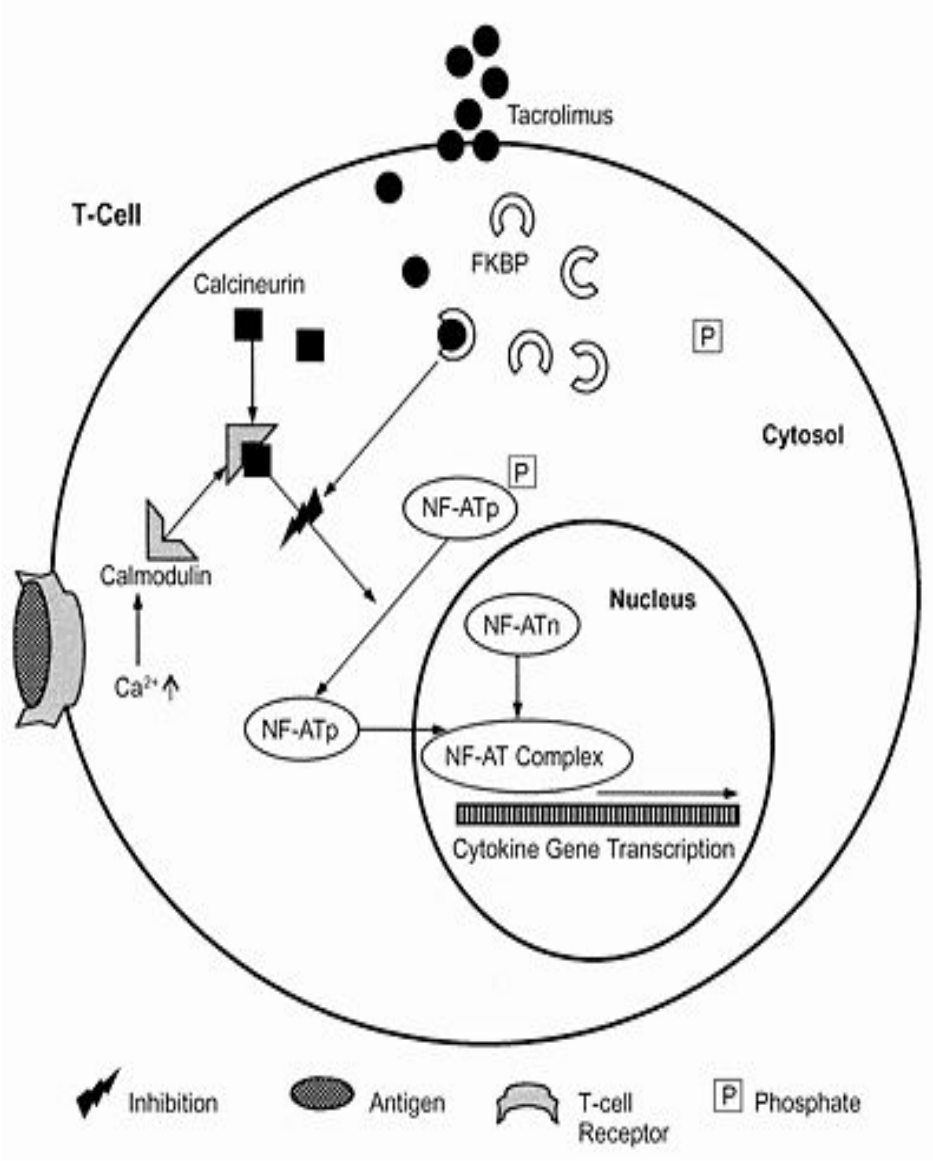
2. Cytotoxic drug:
   eg.Azathioprine,methotrexate,cyclophosphamide, chlorambucil.

3. Glucocorticoids

4. Antibody reagents: eg Muromonab CD3, antithymocyte globulin

MOA of cyclosporine and Tacrolimus:





Cyclosporin

- Fat-soluble peptide antibiotic (obtained from fugus Beauveria nivea),now been synthesized.
- it is cyclic decapeptide.

Pharmacokinetics

- Slowly and incompletely absorbed after oral administration.
- Almost totally metabolized and excreted in the bile.

Adverse reactions:

- major manifestation is nephrotoxicity,hypertension and hyperlipidemia.
- others are gum hypertrophy,leucopenia,thrombocytopenia etc

MOA of Cyclosporin:Calcineurin Inhibitor

- calcineurin (enzyme),dephosphorylates the nuclear factor of activated T-cells (NFATc)(transcription factor), translocates to the nucleus of the T-cell and increases the expression of IL-2 and related cytokines.
- Thus it is responsible for activating the transcription of interleukin 2 and growth and differentiation of T cells.
- Cyclosporin binds to the cytosolic protein cyclophilin (immunophilin) of lymphocytes, especially T cells. This complex of cyclosporin and cyclophilin inhibits calcineurin.
- Thus growth and differentiation of T cells is inhibited
- also arrest growth in Go & G1 phase.
- It does not have cytostatic activity.

Helper T Cells (T_H) and cyclosporin

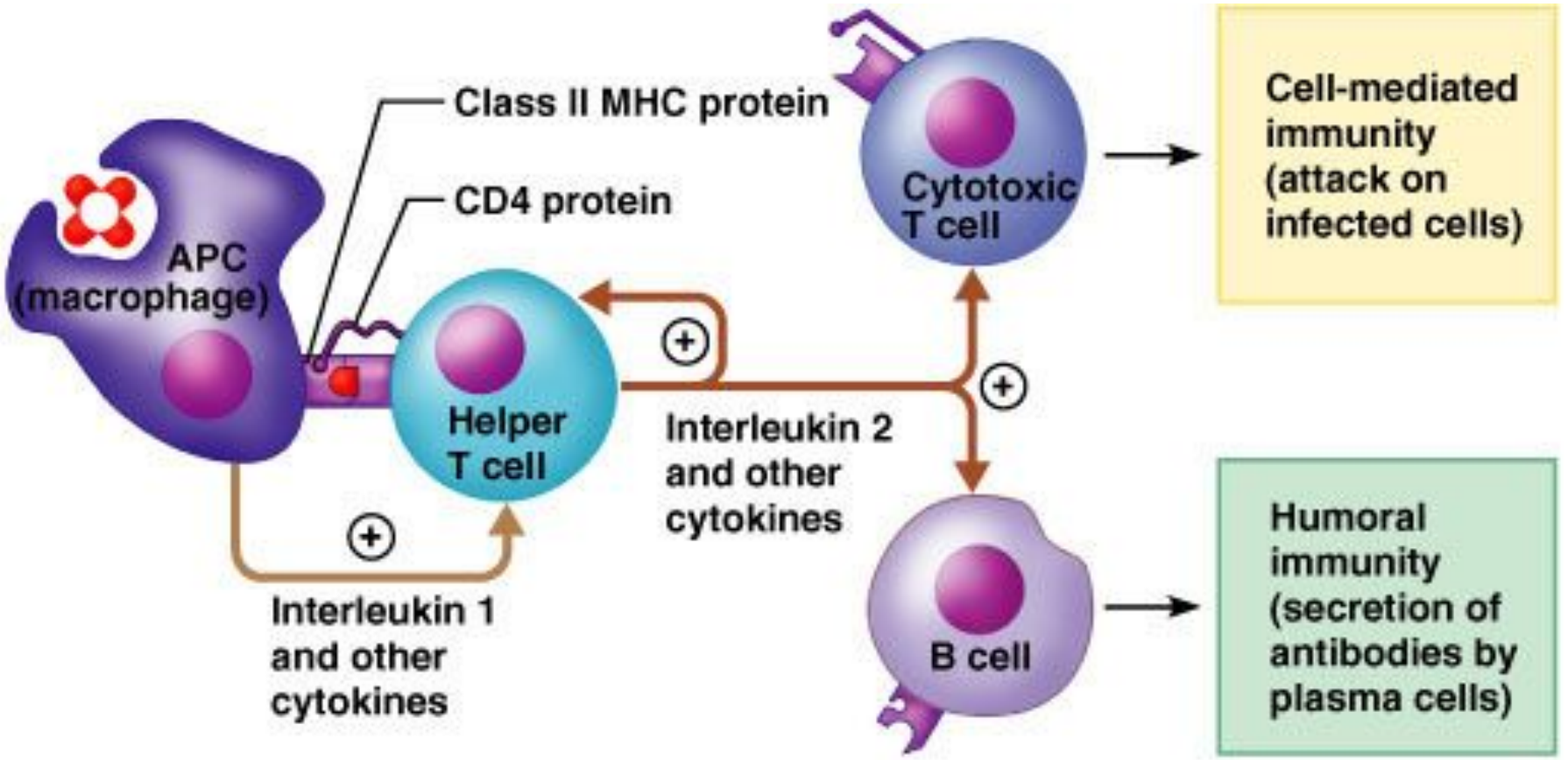


Figure 21.17a

- In addition, suppress the responses of primed helper T cells, hence usefull in autoimmune disease as well.
- Cyclosporin selectively supresses cell mediated immunity,prevent graft rejection and yet leaves the recipeint with enough immune activity to combat bacterial infection.
- Unlike cytotoxic immunosuppresant it is free of toxic effect on bone marrow and RE system.

Uses:

- Ciclosporin is approved by the FDA is used in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants.
- It is also approved in the US for the treatment of rheumatoid arthritis and psoriasis, as an ophthalmic emulsion for the treatment of dry eyes.
- Ciclosporin has also been used to help treat patients with acute severe ulcerative colitis and autoimmune urticaria that do not respond to treatment with steroids.

Drug Interaction:

- All nephrotoxic drugs like aminoglycosides, vancomycin, amphotericin B and NSAID enhance its toxicity.
- Enzyme inducer like rifampicin,phenytoin,phenobarbitone lower its blood level,,transplant rejection can occur.
- CYP3A4 inhibitors inhibits its metabolism and causes toxicity like erythromycine,ketocanozole etc.

Tacrolimus

- Macrolide antibiotic produced by *streptomyces tsukubaensis*.
- It is not chemically related to cyclosporine, but their machanisms of action are similar, both bind to calcineurin
- 100 times more potent than cyclosporine.
- It binds to different cytoplasmic immunophilin (FKBP) other steps are same ie inhibition of helper T Cells via calcineurin.
- Administered orally or by I.V route.
- For liver, kidney, heart, pancreas, and bone marrow transplant applications. usefull in supressing acute rejection.
- Toxic effects: hypertension,hirutism,gum hyperplasia are less marked than cycloserine but more likely to cause nephrotoxicity, neurotoxicity, hyperglycemia (requiring insulin therapy), gastrointestinal dysfunction.
- Valuable in liver transplant becs its absorption is not dependent on bile.

Anti prolierative drug or cytotoxic drugs

Azathioprine: Purine anatimetabolite having more marked immunosupperesant than antitumour action. (used in cancer chemotherapy).

Selective uptake by immune cells and conversion to 6-MP,inhibits *de novo* protein synthesis and damage DNA.

§Cell mediated immunity is depressed.

§Mainly prevent clonal expansion of T and B lymphocytes.

§Selectively affects differentiation and function of T cells and inhibit cytolytic lymphocytes.

Uses: Used alone or in combination with cyclosporine to prevent renal and other graft rejection. But less effective than cyclosporine.

§Used alone in patients having cyclosporine toxicity.

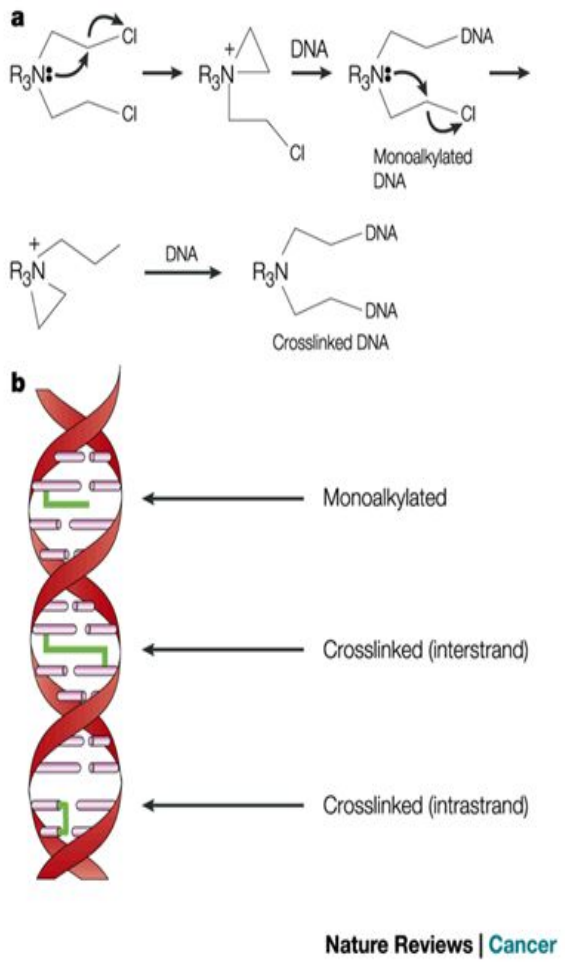
Cyclophosphamides:

- More marked Affect B cells (humoral immunity) than T cells (Cell mediated immunity).
- Prodrug, converts to active metabolites ie aldophosphamide, phosphoramide mustard in liver.
- adds alkyl group at guanine base on number 7 nitrogen atom of imidazole ring of DNA.
- thus interfere with replication of DNA by forming intrastrand and interstrand DNA cross link.

Uses:

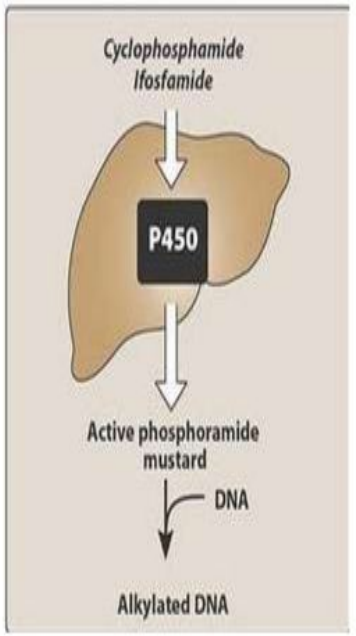
- Mainly used in red bone marrow trasnplantation.
- Used as reserve drug for other transplantion.

MOA of cyclophosphamides:

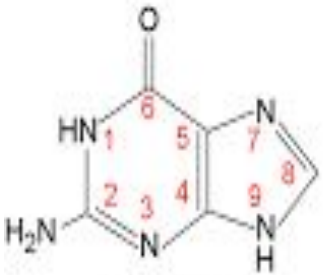


Cyclophosphamide

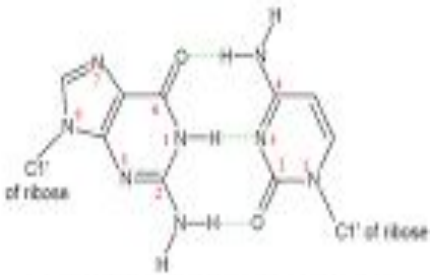
- Most commonly used alkylating agent a prodrug



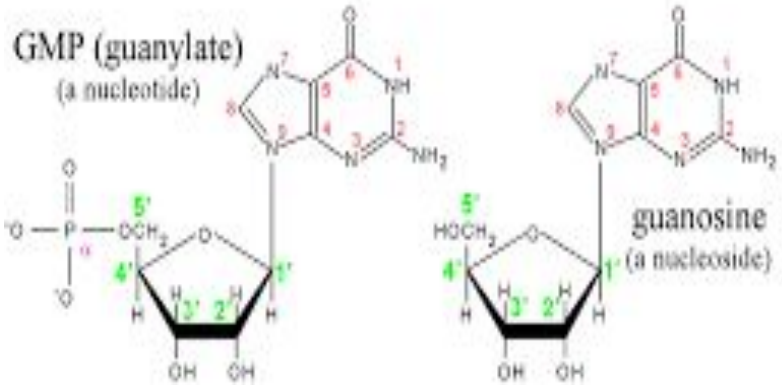
MOA of cyclophoshamide:

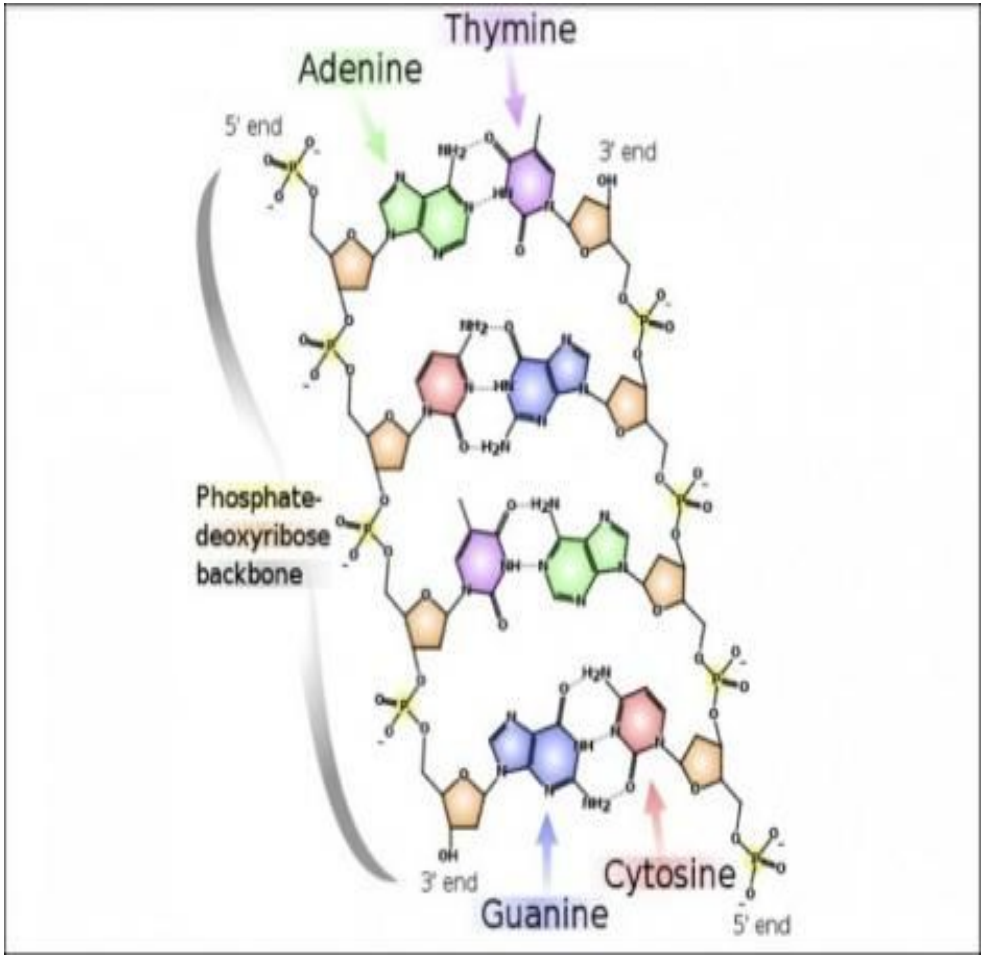


guanine



guanine-cytosine base pair





Clinical uses:

- Cyclophosphamide is used to treat cancers and autoimmune diseases. It is used to quickly control the disease.
- Because of its toxicity, it is discontinued as soon as possible, and replaced by less toxic drugs if necessary.
- Regular and frequent laboratory evaluations are required to monitor kidney function, avoid drug-induced bladder complications, and screen for bone marrow toxicity.
- Like other alkylating agents, cyclophosphamide is teratogenic and contraindicated in pregnant women (Pregnancy Category D) except for life-threatening circumstances in the mother..
- Used in medical research to produce an animal model for Type 1 diabetes in a large dose as well as Type 2 diabetes with multiple low doses.

Methotrexate:

- It is folate antagonist.
- Depress cytokine production and cellular immunity.
- Used as first line therapy in many autoimmune diseases like rapidly progressive RA,Mysthania gravis,psoriasis,pemphigus,uveitis,chronic active hepatitis.

Chlorambucil (Nitrogen musturd alkylating agent):

- Weak immunosuppressant.
- Some times used in organ transplantation and autoimmune diseases.

Mycophenolate mofetil (MMF):

- Prodrug of mycophenolic acid
- selectively inhibits inosine monophosphate dehydrogenase an enzyme essential for de novo synthesis of guanosine nucleotide in T and B cells (these cells unlike other do not have purine salvage pathway).
- Lymphocyte proliferation and antibody production are inhibited.
- Uses: used as Add on therapy to cyclosporine+glucocorticoids in renal transplantation.
- Superior to azathioprine.
- Help to reduce the dose of cyclosporine and its toxicity.
- Adverse effect: vomiting, diarrhoea, leucopenia gi.bleeding

Glucocorticoids:

- Inhibit IL-2 release from macrophages
- Inhibit IL-2 formation– T cell proliferation is not stimulated and suppress natural killer cells.
- Interrupt communication between cells involved in immune process and thus interfere with production and action of lymphokines.
- Inhibit MHC expression.
- Use: A companion of cyclosporine

  Used in all cases of autoimmune diseases.

Long term complications are greatest limitation.

Immunosuppressant antibodies: Muromonab CD3

- It is a murine monoclonal antibody against the CD3 glycoprotien located near to the T Cell receptor on helper T cells.
- Binding obstruct the binding of MHC II antigen complex to the T-cell receptor (antigen recognition is interfered).
- Participation of T cell is prevented,T cell rapidly disappears from circulation.
- Less likely to produce allergic reactions.
- It is used in induction therapy with corticoids and azathioprine with delayed use of cyclosporine in sequential regimen for organ transplantion.
- This serves to postpone potential nephro-hepatotoxicity of cyclosporine.
- Initial dose of muromonab are associated with cytokine release which manifest flu like symptoms, high dose corticosteriod pretreatment reduces the reactions.

Antithymocyte globulin (ATG)

- It is polyclonal antibodies purified from horse or rabbit immunized with human thymic lymphocytes which binds to T lymphocytes and depletes them.
- Used to suppress acute graft rejection,steroid resistant cases .
- Responses are less consistent than muromonab CD3.
- Potential of producing serum sickness or anaphylaxis but less expensive than muromonab CD3.

Anti Rh(D) immunoglobulin:

- It is solution having antibodies for Rh(D) antigen of RBC.
- When Rh negative mother delivers Rh positive baby, Rh positive antigen enters mother blood stream this sensitize mother to produce antibodies for Rh +ve antigen.
- In subsequent pregnancies, the maternal antibodies for Rh +ve cells reaches the foetus and may result in hemolytic disease of new born.
- Injection of anti Rh(D) antibodies to the mother at the time of child birth or abortion (within 24-72 hrs) will bind with the antigens on the RBC of the baby which have entered the maternal circulation. This prevents formation of antibody in Rh negative mother against the Rh positive RBCs.
- Thus subsequent pregnancies would not be affected.

Adrenocortical Hormones

- Lympholytic properties
- Interfere with the cell cycle of activated lymphoid cells.
- Their immunologic effects are due to their ability to modify cellular functions rather than to direct cytotoxicity.
- Immunosuppressive and anti- inflammatory properties.
- Indications include organ transplantation and autoimmune disorders.

Immunostimulants

- Increase the immune responsiveness of patients who have either selective or generalized immunodeficiency.
- Such agents act by increasing the humoral response, phagocytic activity of macrophages or modifying the cell mediated immune response.
- Use for immunodeficiency disorders, chronic infectious diseases, and cancer.

Immunostimulants

- Bacillus Calmette-Guerin-Vaccine (BCG)
- Cytokines
- Levamisole
- Glatiramer acetate
- Amantadine & tilorane
- Thymosin
- Immunoglobulines
- Transfer factor (TF)

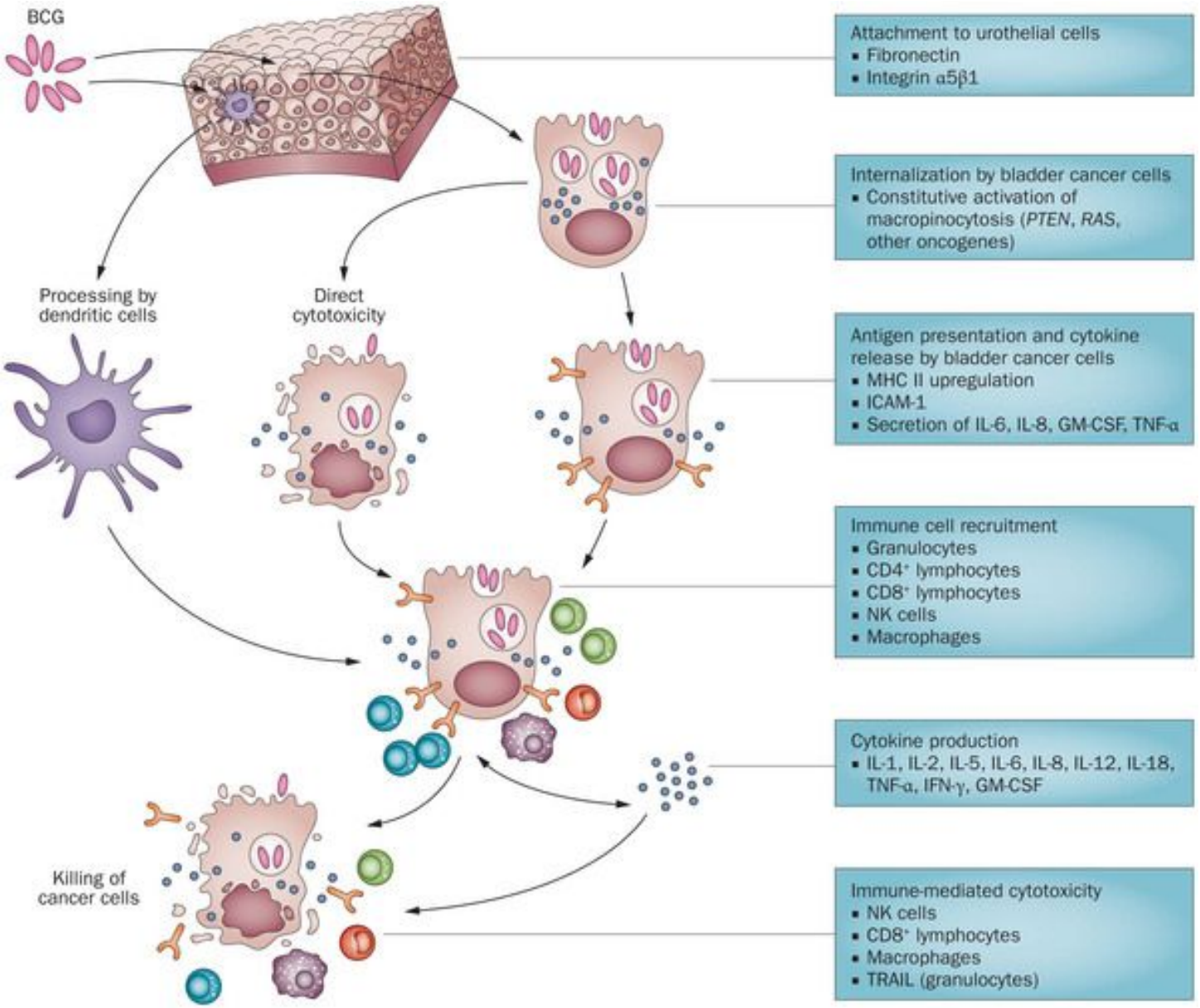
1. BCG:

- Bacillus Calmette-Guerin-Vaccine (BCG) is a attenuated, viable strain of *Mycobacterium bovis* that has been used for immunization against tuberculosis.
- BCG is indicated for prevention of tuberculosis.
- It is a nonspecific immunostimulator.

Mechanism of action:

- Mechanism of antimelignancy is not well understood.
- It stimulates RES and increase resistance against bacterial and viral infection.
- It activate the NK cells, macrophages, production of hemopoietic stem cells.

Mechanism of action of BCG:



Uses:

Also been employed as a nonspecific adjuvant or immunostimulant in cancer therapy.

§BCG has been effectively used in the management of bladder cancer (MOA is unclear) as adjuvant therapy before surgery

§BCG exerts its urological effects by inducing a strong immune response and by causing cell cycle arrest at the G1/S transition phase.

§Used in leukemias, melanoma and lung cancer.

§Also useful in leprosy prophylaxis.

2. Levamisol:

- It is an anthelmintic having immunotropic property.

Mechanism of action:

- It enhances T cell mediated immunity.
- Enhances phagocytic activity of the macrophages.

Uses:

- It restores cutaneous delayed type of hyper sensitivity reaction in anergic (a state of immunologic deficiency) patients with cancer.

Adverse effect:

- GI distrubances, headache,dizziness,insomnia,thrombocytopenia and agranulocytosis.

3. Cytokines

- Interferon (INF): INF-α,β,γ
  - Antiviral, anticancer, immunomodulating effects.
  - Antiviral effects : INF-α,β > INF-γ
  - immunomodulating effects: INF-γ
  - Adverse Effects: flu-like symptoms, fatigue, malaise
- Interleukin-2 (IL-2)
  - T cell proliferation, T_H, NK, LAK cell activation
  - lymphokine-activated killer cell (LAK cell) is a white blood cell that has been stimulated to kill tumor cells activated by IL-2.

  Mechanism:
  - LAK cells are capable of lysing fresh, non-cultured cancer cells, both primary and metastatic. LAK cells lysing tumor cells that resistant to NK cell.
  - LAK cells are also capable of acting against cells that do not display the major histocompatibility complex.
  - LAK cells are specific to tumor cells and do not display activity against normal cells.

Uses of cytokin:

- Treatment of malignant melanoma, renal cell carcinoma, Hodgkin disease , under trial for AIDS patients.
- Adverse Effects: fever, anorexia, et al.

Table 56–2. The cytokines.

Cytokine	Properties
Interferon-α (IFN-α)	Antiviral, oncostatic, activates NK cells
Interferon-β (IFN-β)	Antiviral, oncostatic, activates NK cells
Interferon-γ (IFN-γ)	Antiviral, oncostatic, secreted by and activates or upregulates TH1 cells, NK cells, CTLs, macrophages
Interleukin-1 (IL-1)	T cell activation, B cell proliferation and differentiation, HCF[1]
Interleukin-2 (IL-2)	T cell proliferation, TH1, NK, and LAK cell activation
Interleukin-3 (IL-3)	Hematopoietic precursor proliferation and differentiation
Interleukin-4 (IL-4)	TH2 and CTL activation, B cell proliferation
Interleukin-5 (IL-5)	Eosinophil proliferation, B cell proliferation and differentiation
Interleukin-6 (IL-6)	HCF, TH2, CTL, and B cell proliferation
Interleukin-7 (IL-7)	CTL, NK, LAK, and B cell proliferation, thymic precursor stimulation
Interleukin-8 (IL-8)	Neutrophil chemotaxis, proinflammatory
Interleukin-9 (IL-9)	T cell proliferation
Interleukin-10 (IL-10)	TH2 suppression, CTL activation, B cell proliferation
Interleukin-11 (IL-11)	Megakaryocyte proliferation, B cell differentiation
Interleukin-12 (IL-12)	TH1 and CTL proliferation and activation
Interleukin-13 (IL-13)	Macrophage function modulation, B cell proliferation
Interleukin-14 (IL-14)	B cell proliferation and differentiation
Interleukin-15 (IL-15)	TH1, CTL, and NK/LAK activation
Interleukin-16 (IL-16)	T lymphocyte chemotaxis, suppresses HIV replication
Interleukin-17 (IL-17)	Stromal cell cytokine production
Tumor necrosis factor-α (TNF-α)	Oncostatic, macrophage activation, proinflammatory
Tumor necrosis factor-β (TNF-β)	Oncostatic, proinflammatory, chemotactic
Granulocyte colony-stimulating factor (G-CSF)	Granulocyte production
Granulocyte-macrophage colony-stimulating factor (GM-CSF)	Granulocyte, monocyte, eosinophil production
Macrophage colony-stimulating factor (M-CSF)	Monocyte production, macrophage activation
Erythropoietin (epoetin, EPO)	Red cell production
Thymopoietin (TPO)	Platelet production

[1]Hematopoietic cofactor (HCF): Plays some role, but not the central role, in growth and differentiation of bone marrow cells.

Interferon Family

- Interferons are a family of related proteins each with slightly different physiological effects
- Lymphocytes secrete gamma interferon, but most other WBCs secrete alpha interferon
- Fibroblasts secrete beta interferon
- FDA-approved alpha IFN is used:
  - As an antiviral drug against hepatitis C virus
  - To treat genital warts caused by the herpes virus

Interferons (MOA):

- Enhance the innate defenses by: Attacking microorganisms directly & Hindering microorganisms' ability to reproduce
- Interferons also activate macrophages and mobilize NKs
- Naturally occurring protein.

Uses:

- Beneficial effect in certain human lymphoreticular and other cancers.
- Multiple cancer and hepatitis B.

Interferon (IFN): secretion and mechanism of action:

- Genes that synthesize IFN are activated when a host cell is invaded by a virus
- Interferon molecules leave the infected cell and enter neighboring cells
  - Interferon stimulates the neighboring cells to activate genes for PKR (an antiviral protein)
    - PKR nonspecifically blocks viral reproduction in the neighboring cell

Interferon (IFN)

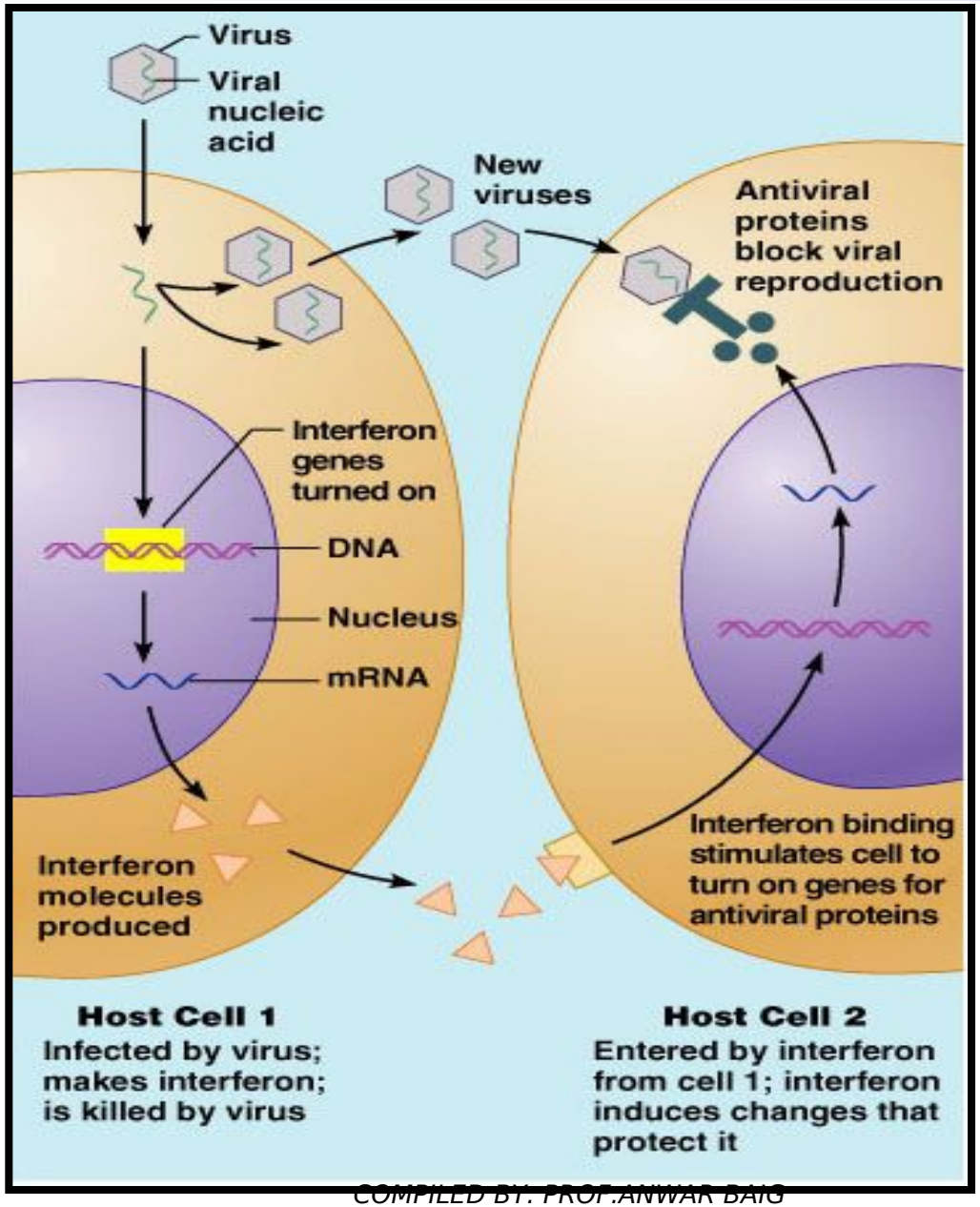


Figure 21.4

4. Glatiramer acetate:

- It is synthetic co-polymer, with some immunological property, similarity with myelin basic components.
- It is claimed to reduce rate of relapse in relapsing multiple sclerosis, act like immunomodulator.
- Mechanism is not fully understood.

5. Thymosin:

- Lower molecular weight hormone obtained from bovine thymus extracts.
- It is under trial for various immunodeficiencies in patients with T lymphocyte mediated immune diseases (Systemic lupus erythermatosus, RA) and cancer.

6.Immunoglobulin:

- Appropriate use of immunoglobuline in the tratment of immunodeficiency states due to impaired or absent antibody synthesis.
- It is used to treat primary humoral immunodeficiency, congenital agammaglobulinaemias, idiopathic thrombocytopenic purpura, hepatitis and measles.

7. Transfer factor (TF):

- It is a small RNA molecule derived from normal human lymphoid cells.
- causes antigen-specific cell mediated immunity,primarily delayed hypersensitivity.
- TF are specific for given antigen.
- They often converts negative delayed hypersensitivity skin test to positive.
- It is under trial for mucocutaneous candidiasis and leprosy.

Immunomodulators for HIV:

- Interferon:
- Amantadine & tilorane: Stimulate humoral immune system
- Subcutaneous IL-2 (under trial): increases CD4 count along with ART.
- Growth hormones: increases T cell count. (under trial)
- IL-12 vaccine: increase in proliferation of lymphocytes (under trial)

Immunomodulators for Cancer:

Immunostimulant agents:

E.g: Thymosine, Interferons or interferon inducer, Interleukin- 2,Immunoglobulin,levamisole,transfer factor, BCG vaccine.

Methods under trial:

1.Stimulation of nonspecific cellular immunity: BCG is injected-regression and elimination of metastatic cells.

2. Killed tumour cell or extract of tumour cells: tumour cell extracts are injected at intervals to induce immune response.

Other Immunomodulators

- Entanercept
- Transfer Factor (TF)
- Thymosin
- Levamisole (LSM)
- Isoprinosine