IMMUNE RESPONSE

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Immune Response

- Specific reactivity induced in a host following an antigenic stimulus is known as immune response
- Humoral immune response
- Cell mediated immune response

Humoral immune response

- Antibody mediated
- Provides defence against most extra cellular bacterial pathogen * helps in defence against viruses those infect through respiratory or intestinal tracts.
- Participates in pathogenesis of immediate hypersensitivity & certain autoimmune disease.

Humoral Immunity

- Results in production of proteins called “immunoglobulins” or “antibodies”.
- Body exposed to “foreign” material termed “antigen” which may be harmful to body: virus, bacteria, etc.
- Antigen has bypassed other protective mechanisms, ie, first and second line of defense.

Dynamics of Antibody Production

- Primary immune response
  - Latent period
  - Gradual rise in antibody production taking days to weeks
  - Plateau reached
  - Antibody level declines

Primary Response:

- After *initial* exposure to antigen, no antibodies are found in serum for several days.
- A gradual increase in titer, first of IgM and then of IgG is observed.
- Most B cells become plasma cells, but some B cells become long living *memory cells*.
- Gradual decline of antibodies follows.

Dynamics of Antibody Production

- Antibody production
  - Initial antibody produced in IgM
  - Lasts 10-12 days
  - Followed by production of IgG
  - Lasts 4-5 days
  - Without continued antigenic challenge antibody levels drop off, although IgG may continue to be produced.

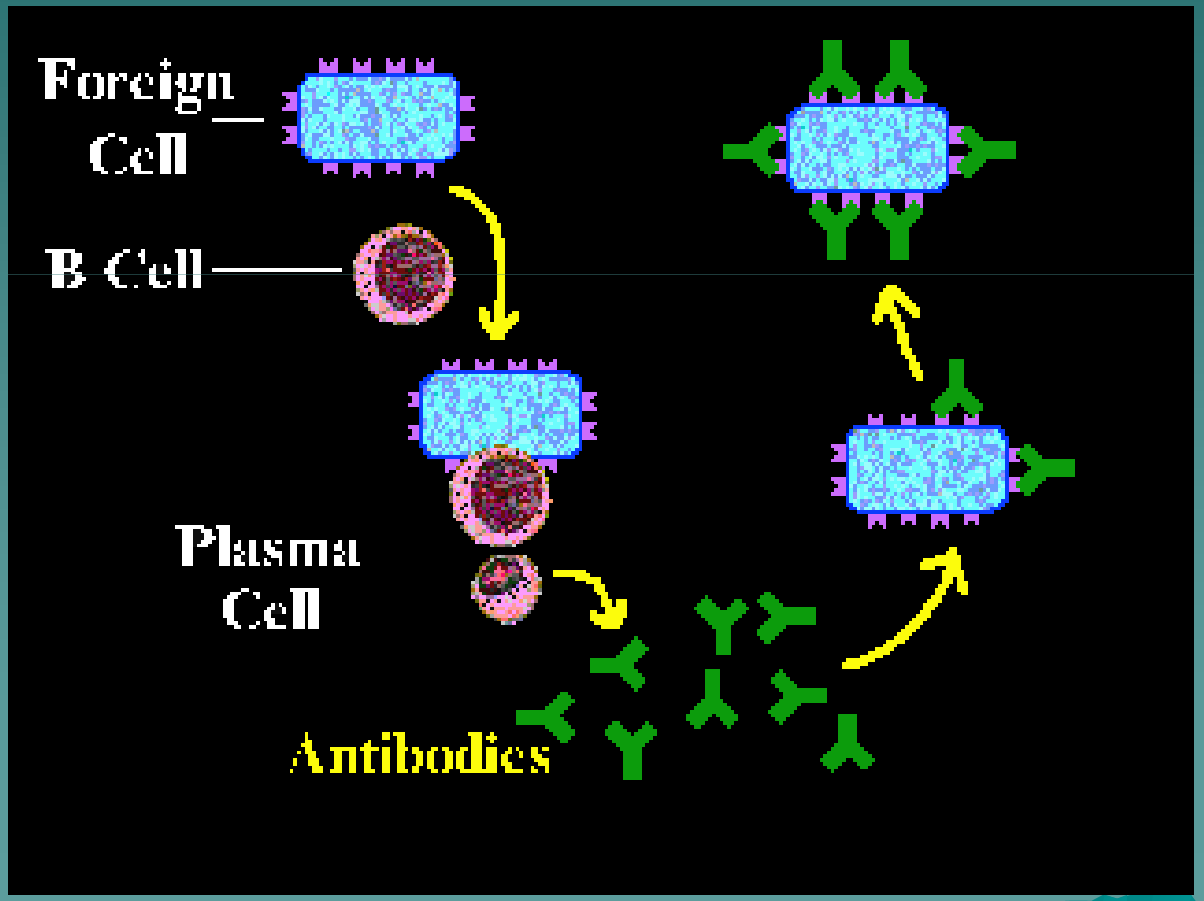
Secondary Response:

- Subsequent exposure to the same antigen displays a faster and more intense antibody response.
- Increased antibody response is due to the existence of memory cells, which rapidly produce plasma cells upon antigen stimulation.

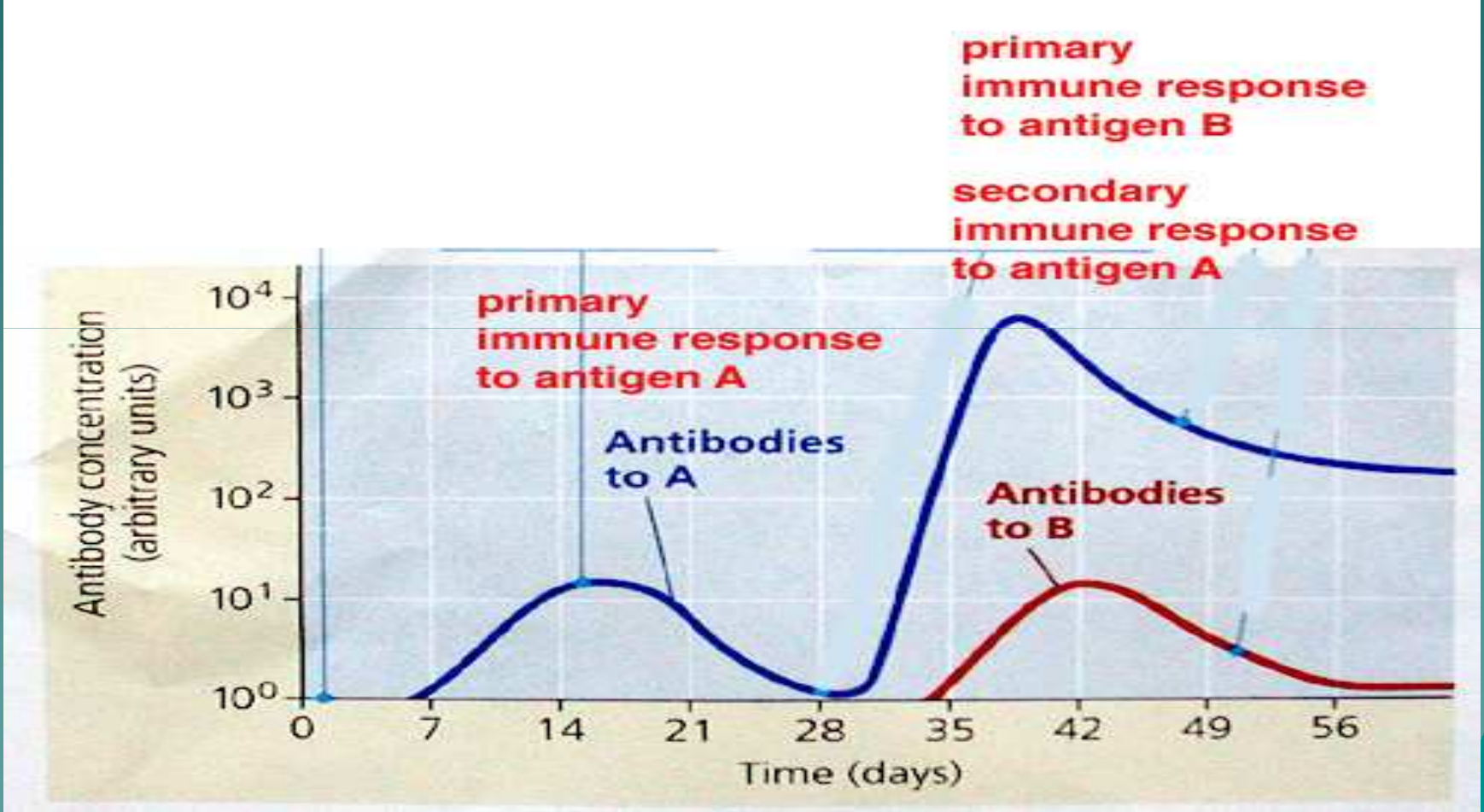
Secondary Response

- Second exposure to SAME antigen.
- Memory cells are a beautiful thing.
- Recognition of antigen is immediate.
- Results in immediate production of protective antibody, mainly IgG but may see some IgM

Humoral Immune Response



Dynamics of Antibody Production



Cellular Events

- Antigen is “processed” by T lymphocytes and macrophages.
- Possess special receptors on surface.
- Termed “antigen presenter cell” APC.
- Antigen presented to B cell

Fate of antigen in tissue

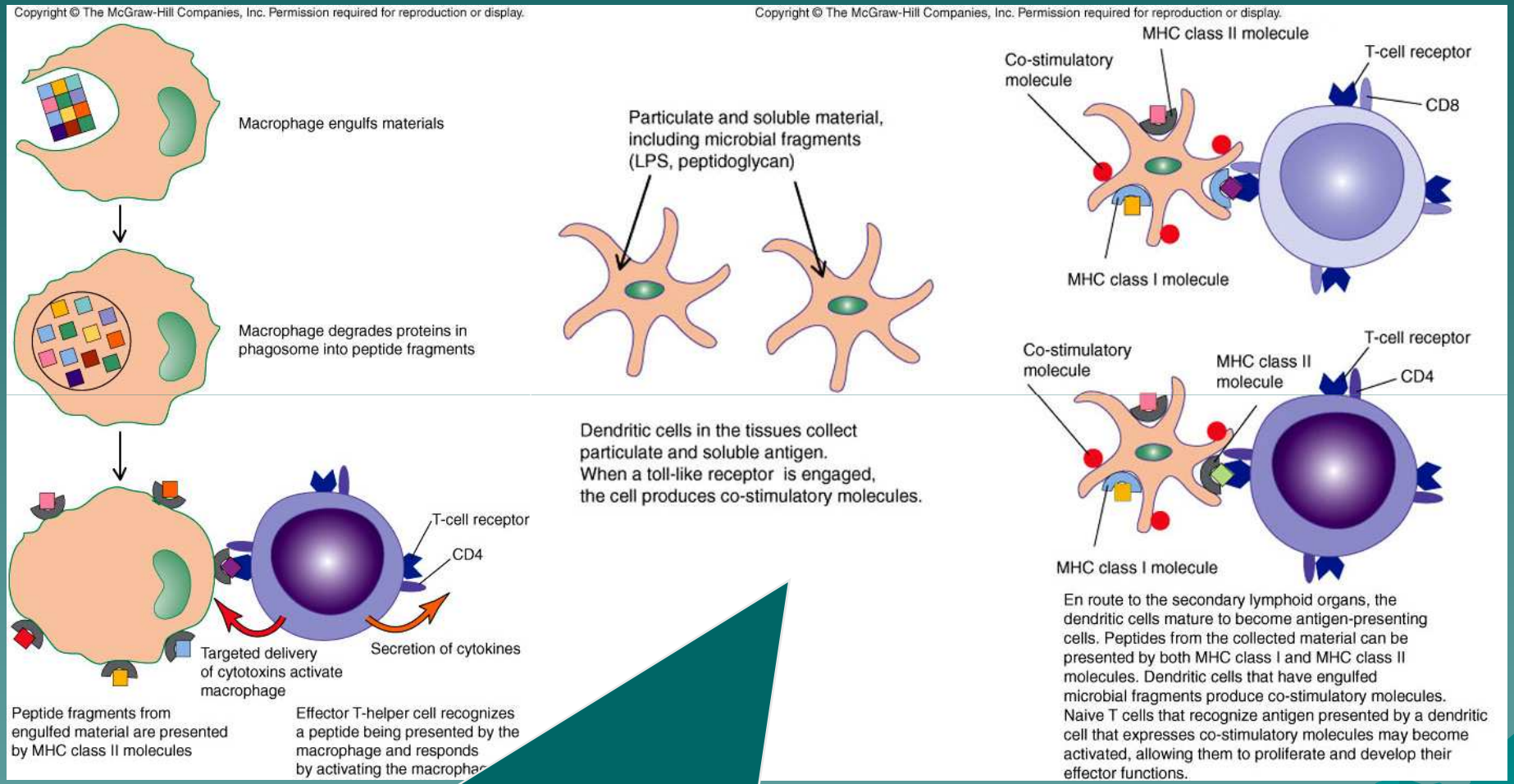
- Antigens introduced intravenously are rapidly localized in the spleen, liver, bone-marrow, kidney & lungs. about 70% - 80% antigens are broken down by reticuloendothelial cells & excreted in urine.
- Subcutaneous antigen localized in the draining lymph nodes & small amount being found in the spleen

- Particulate antigen removed from circulation in two ways
- Nonimmune phase
- Immune phase
- Speed of elimination of antigen is related to the speed at which it is metabolized.

Production of Antibodies

- Immune response to an antigen is brought by three types of cells : APC(macrophages & Dendritic cells), T & B cells
- The first step is the capture& processing of antigen by APC & their presentation, in association with appropriate MHC molecule to T cells.
- CD4 helper cells antigen complexed with MHC2 & For CD8 It is MHC1

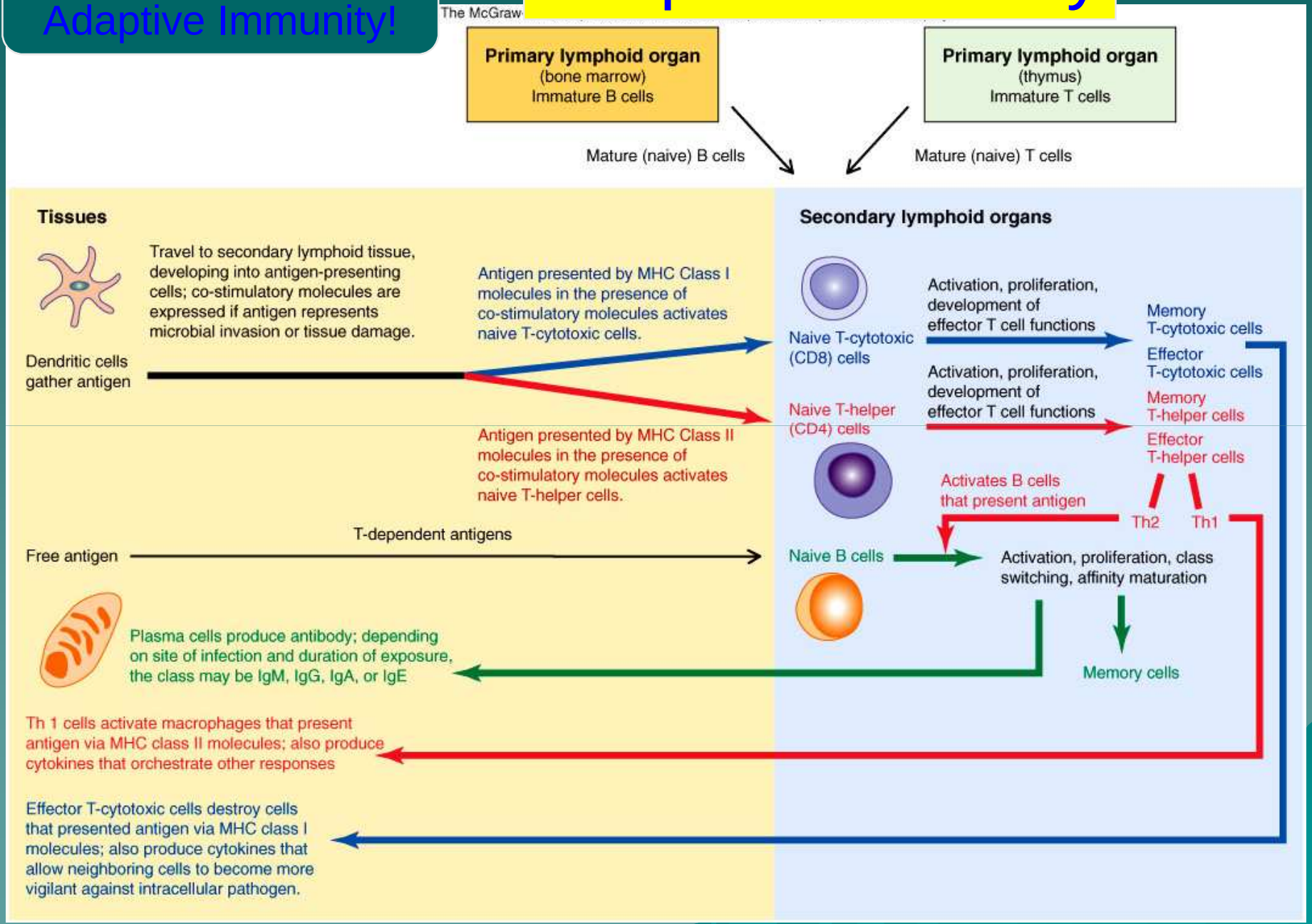
Stimulating T-Helper Cells



Macrophages and Dendritic cells present antigens to, and thereby stimulate, T-helper cells.

Good summary of Adaptive Immunity!

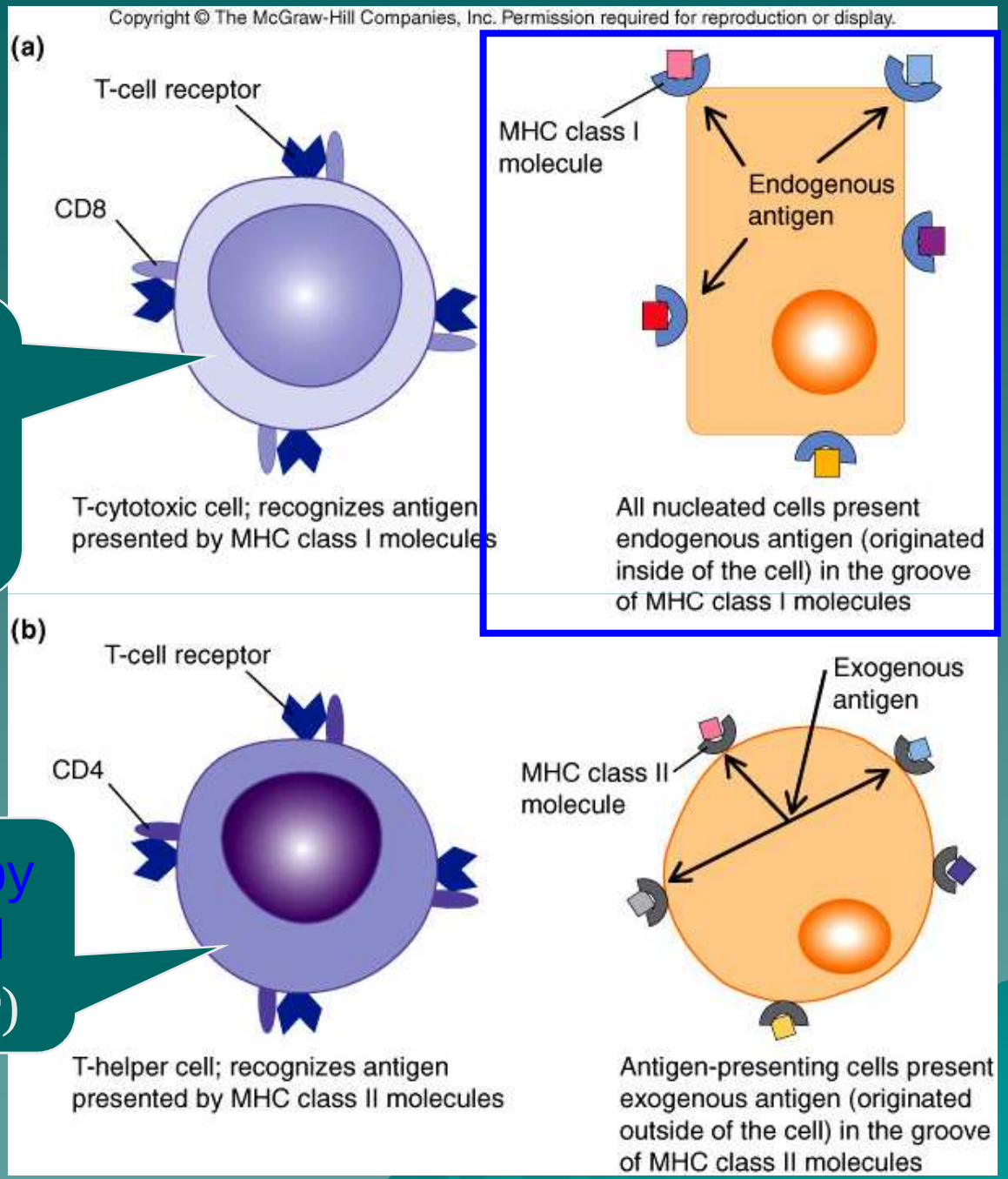
Adaptive Immunity

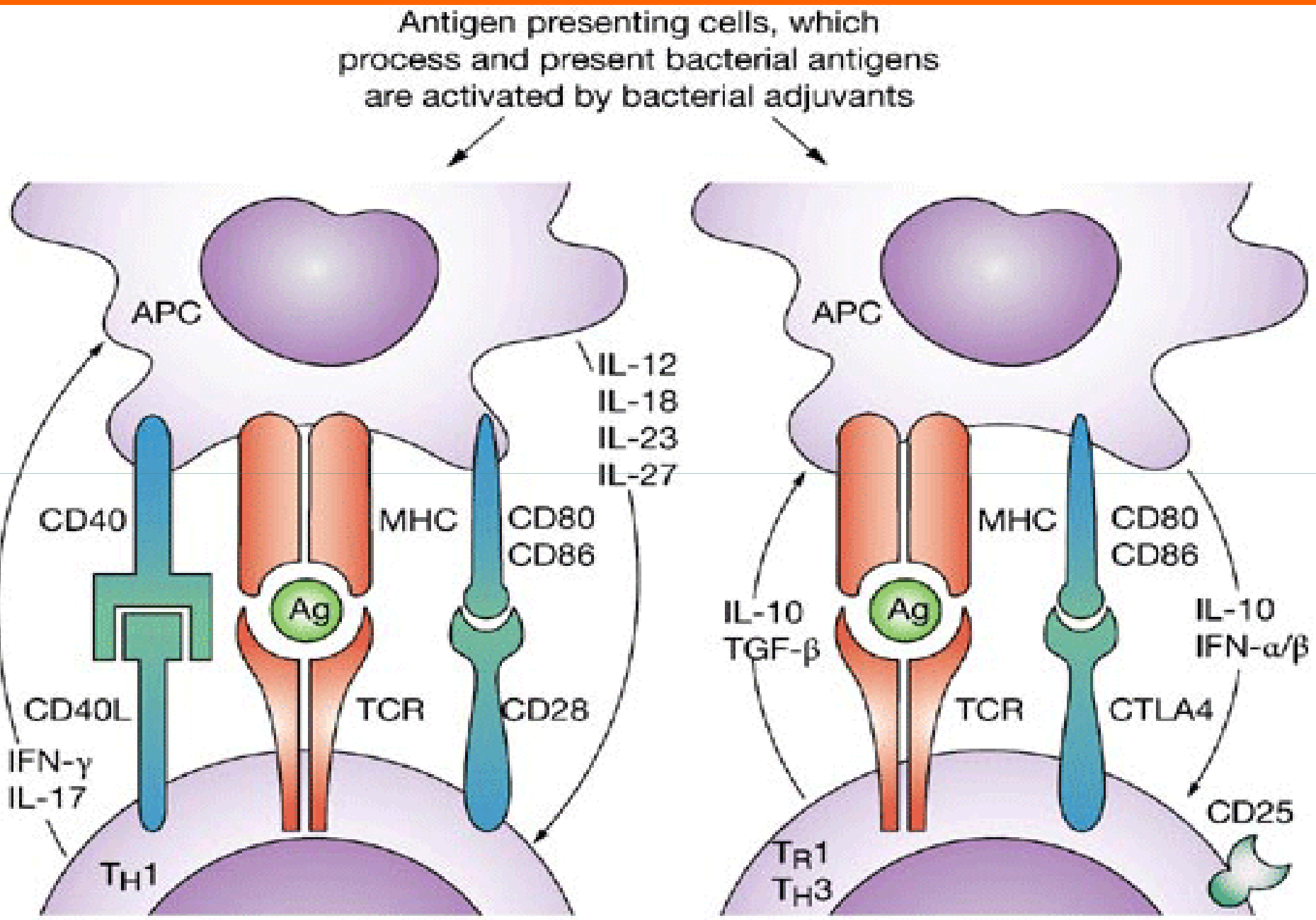


Antigen Recognition by T Cells

Recognition by Cytotoxic T cell (CD8 receptor)

Recognition by Helper T cell (CD4 receptor)





- The actived T helper cells forms interleuikn 2 & other cytokines required for B cell stimulation.
- Activated B cells clonally proliferate & differentiate into plasma cell memory cells.
- Antibody production by B lymphocyte I regulated by T cells.

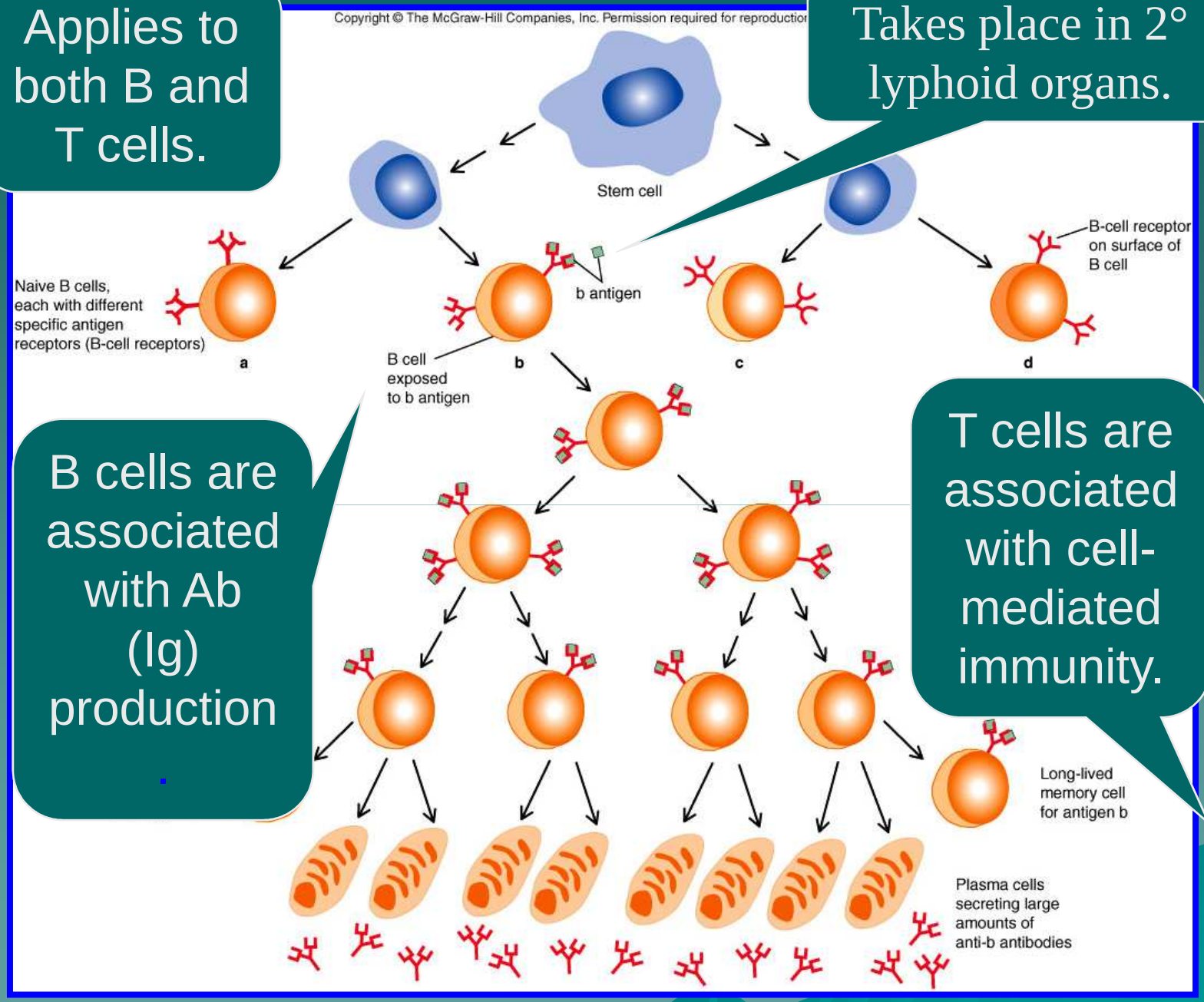
Theories of Antibody formation

- Instructive theory :
- Direct template theory, Indirect template theory
- Selective theory;
- Slide chain, Natural selection,Clonal selection- widely accepted theory

Clonal Selection Theory

Applies to both B and T cells.

Takes place in 2° lyphoid organs.



B cells are associated with Ab (Ig) production

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T cells are associated with cell-mediated immunity.

Monoclonal Antibodies

- A single antibody forming cells or clones produces antibodies directed against a single antigen or antigenic determinant such antibodies are called monoclonal.
- Very useful for diagnostic & research technique.

Factors affecting Antibody Production

- Age :
- Genetic Factor:
- Nutritional Status
- Routes of Administration
- Dose of Antigen
- Multiple Antigen
- Adjuvant: Depot, Bacterial, Chemical
- Immunosuppressive Agents: x irradiation, Radiometric drugs, corticosteroids, anti metabolites, Antilymphocytic serum, cycloserine

- Super antigens:
- Mitogens:

Cell Mediated immune response

- Specific acquired immune responses mediated by sensitized T cells.
- Cell mediated immunity plays an important role in the following function:

(1) Delayed hypersensitivity

(2) Immunity in infectious diseases caused by intracellular organisms

(3) Transplantation immunity & graft-versus host reaction

(4) Immunological surveillance & immunity against cancer

(5) Pathogenesis of certain autoimmune disease

T Lymphocytes: Cell Mediated

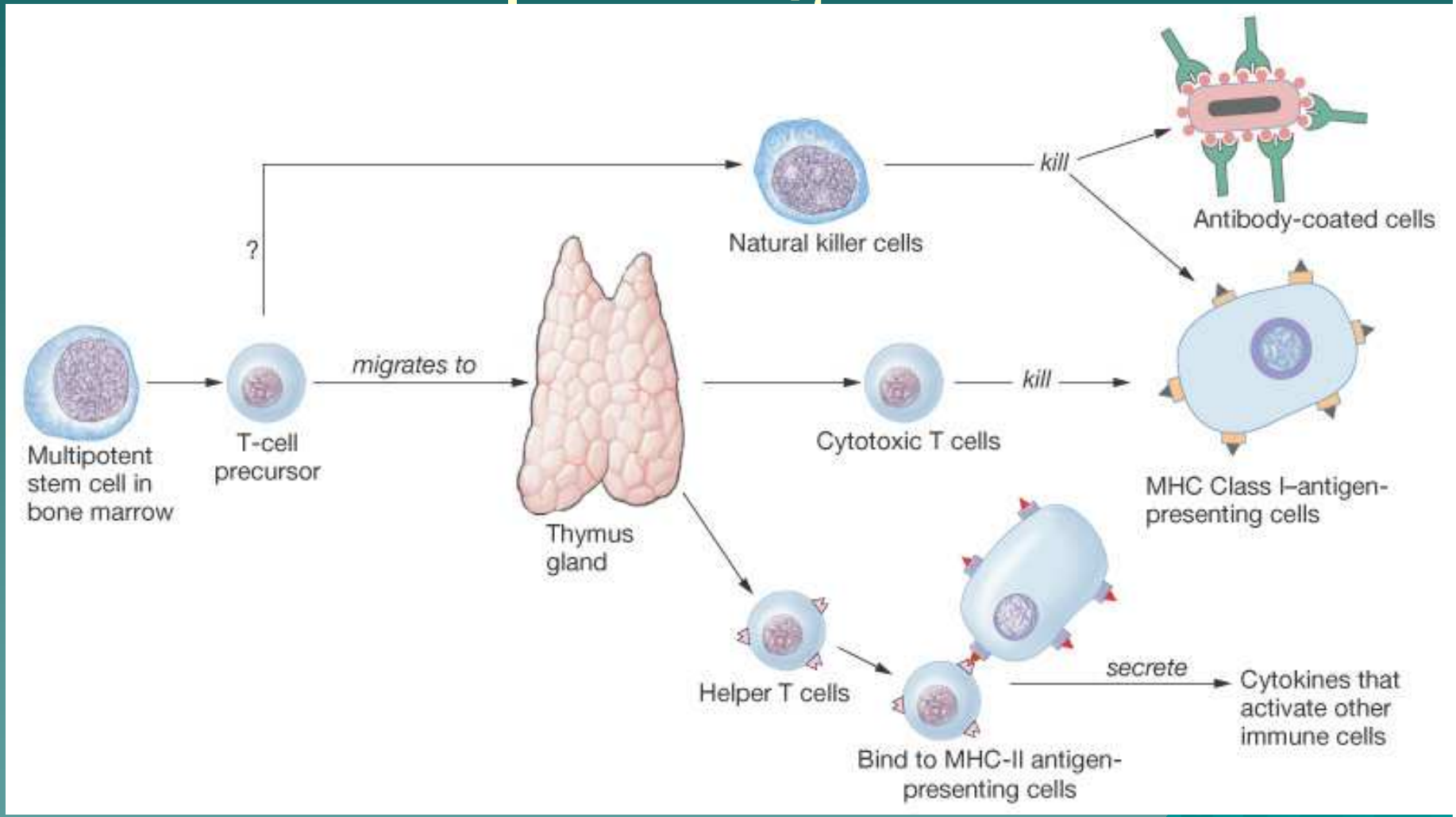

Figure 24-16: T lymphocytes and NK cells

Induction of CMI

- T cell recognize antigens only when presented with MHC molecule.
- Helper T cells react with antigens presented on the surface of macrophage complexed with MHC class 2 molecule.
- Biological mediators kills intracellular parasites.
- CD 8 cells recognize antigen with MHC class1

Cytokines

- These are biologically active substances secreted by monocytes, lymphocytes & other cells.
- Lymphokines
- Monokines
- Interleukins: chemical substance act as growth & differentiating factors, exerts a regulatory influences on other cells

- Interleukin 1: principally secreted by Macrophage & monocyte, stable polypeptide
- Effects : Stimulation of T cells for production of IL2 & other lymphokines,

  B cell proliferation & Antibody synstheis,Neutrophil chemo taxis

- *Interleukin 2:*
- *Major activator of T & B cells & stimulated Tc cells & NK cells*
- *Converts certain null cells into LAK cells, formerly known as T cell growth factor*
- *Interleukin 3: growth factor for Bone marrow stem cells, Multicolony stimulating factor*
- *Interleukin 4: B cell differentiating factor*

- Interleukin 5: causes proliferation of B cells
- Interleukin 6:Produced by T & B cells,macrophages.induces Immunoglobulin synthesis
- Colony stimulating factor:
- Tumour necrosis factor : Alpha-produced by activated macrophage & Beta-formed by T helper cells

- Interferons:

Aplha, Beta, Gamma

Lymphokines:

(1)Migration inhibiting factor

(2) Macrophage activating factor

(3) Macrophage chemotactic factor

(4)Macrophage stimualtin factor

Detection of CMI

- Skin test for delayed hypersensitivity
- Lymphocyte Transformation test
- Migration Inhibiting factor test
- Rosette Formation
- Detection of Tcells by Immunoflureseence Technique

Transfer factor

- Lawrence(1954) reported transfer of CMI in human beings by the injection of extracts from leukocytes. This extracts is known as transfer factor
- The transferred immunity is specific in that CMI can be transferred only to those antigens to which the donor is sensitive

- TF is a low molecular substance,resistant to trypsin but gets inactivated at 56°c in 30minutes.
- Remains stable for several years at -20°c & Lyophilized form at 4°c.
- Not it is antigenic, chemically it is polypeptide-polynucleotide.
- Transferred CMI is systemic not local.
- Mechanism of action is not known probably it stimulates the release of lymphokines from sensitized T lymphocytes.

- Uses of Transfer factor:

(1) T cell deficiency patients

(2) Treatment of disseminated infection

associated with CMI(lepromatous leprosy & tuberculosis)

(3)Treatment of malignant melanoma & other types of cancer

Immunological Tolerance

- **Specific unresponsive state induced by exposure to antigenic epitopes**
- **Tolerance to self is initially induced during embryonic life, and is maintained by antigen**
- **Tolerance occurs in both T and B cells**
- **Multiple mechanisms of tolerance exist**

- Natural tolerance: limited to self antigen
- Acquired tolerance : arises when a potential antigen induces a state of unresponsiveness to itself.
- Depends on the species & immunocompetence of the host, physical nature, dose & route of administration of antigen.

- Newborns & embryos are susceptible for tolerance
- Soluble antigen & hapten are more toleragenic than particulate antigen
- Induction of tolerance is dose dependant, high dose of antigen induces B cell tolerance & repeated minute doses induce T cell tolerance
- Tolerance can be overcome spontaneously or by an injection of cross reacting immunogens.

Mechanisms of Immunological Tolerance - Overview

- Central Tolerance through Clonal Deletion
  - Clones of cells that have receptors for self-antigens are deleted during development
- Peripheral Tolerance
  - Clonal Anergy-failure of APC to deliver a second signal during antigen presentation (example: B7-CD28 interaction)
  - Suppression of responses may occur by production of regulatory T cells that inhibit immune response to self-antigen (example: TGF-β, IL10 and Th1 vs. Th2 cytokines)
  - Ignorance to some self antigens may also exist

Tolerance: Establishment and Failure