T-cell mediated immune response

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Cross presentation

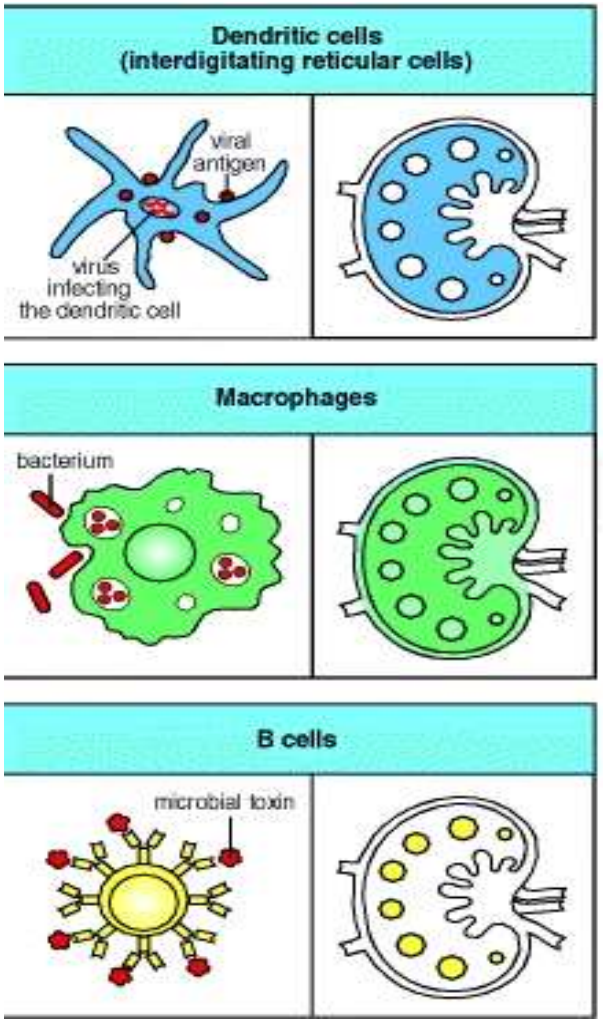
- The class I MHC pathway of antigen presentation
  to CD8+ T cells requires that protein antigens be present
  in the cytosol of infected presenting cells

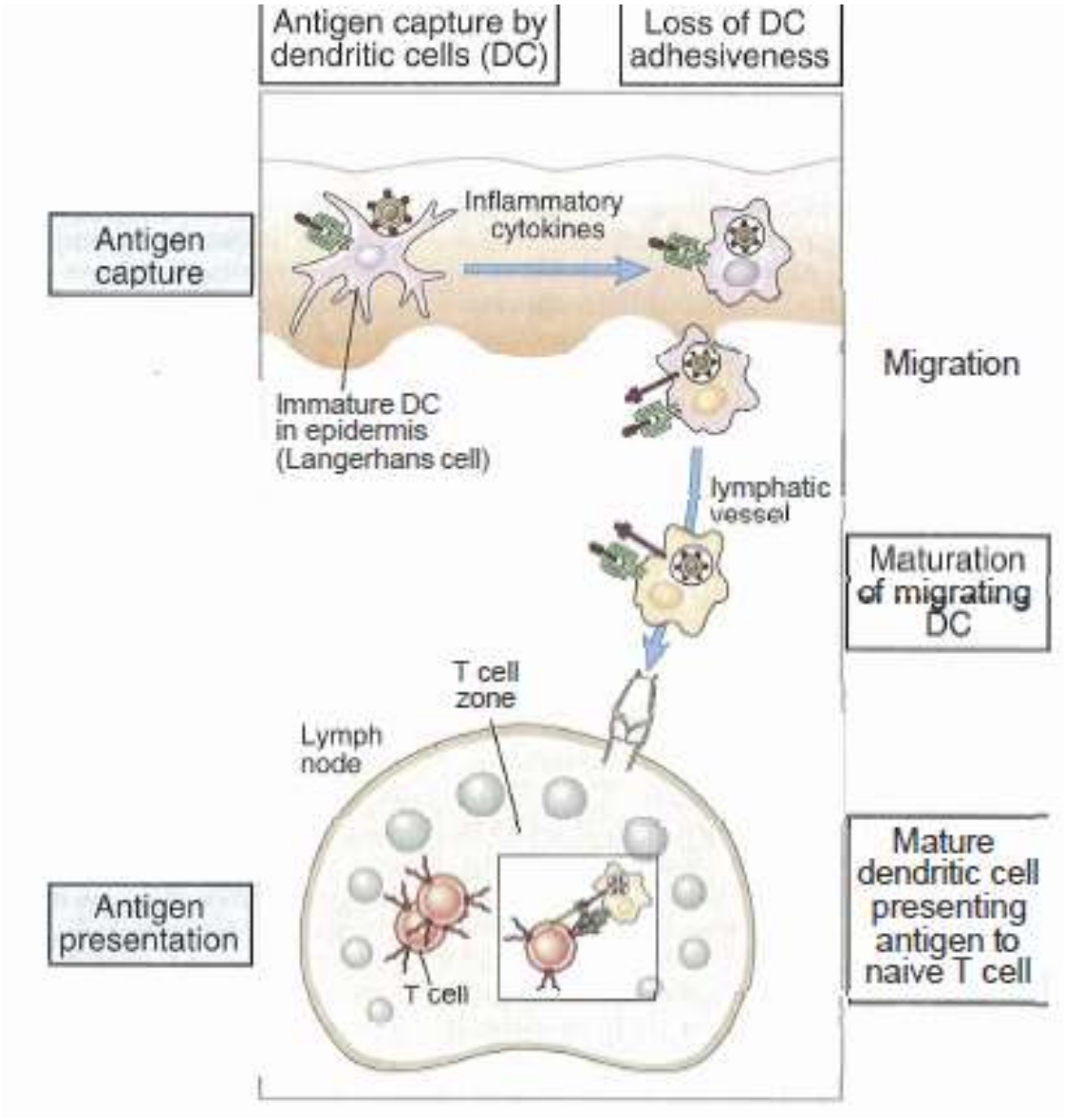
- Virus that infects a specific cell type taken into APC by phagocytosis but these APCs are not infected by the virus and do not endogenously synthesize viral antigen. the immune system deals with this problem by the process of cross presentation.

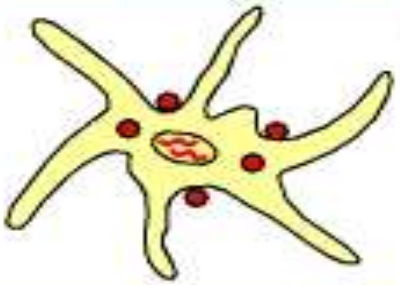
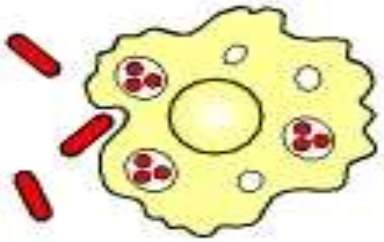
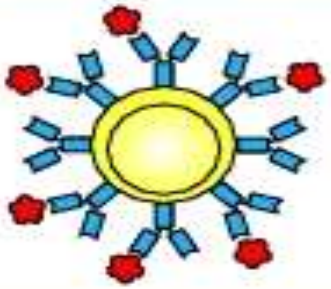
- In this process; dendritic cells ingest infected cells, tumor cells, or proteins expressed by these cells, express them on MHC2 **and besides that they transfer the protein antigens into the cytosol, and process the antigens to enter the class I MHC antigen presentation pathway for recognition by CD8+ T cells** besides Th1

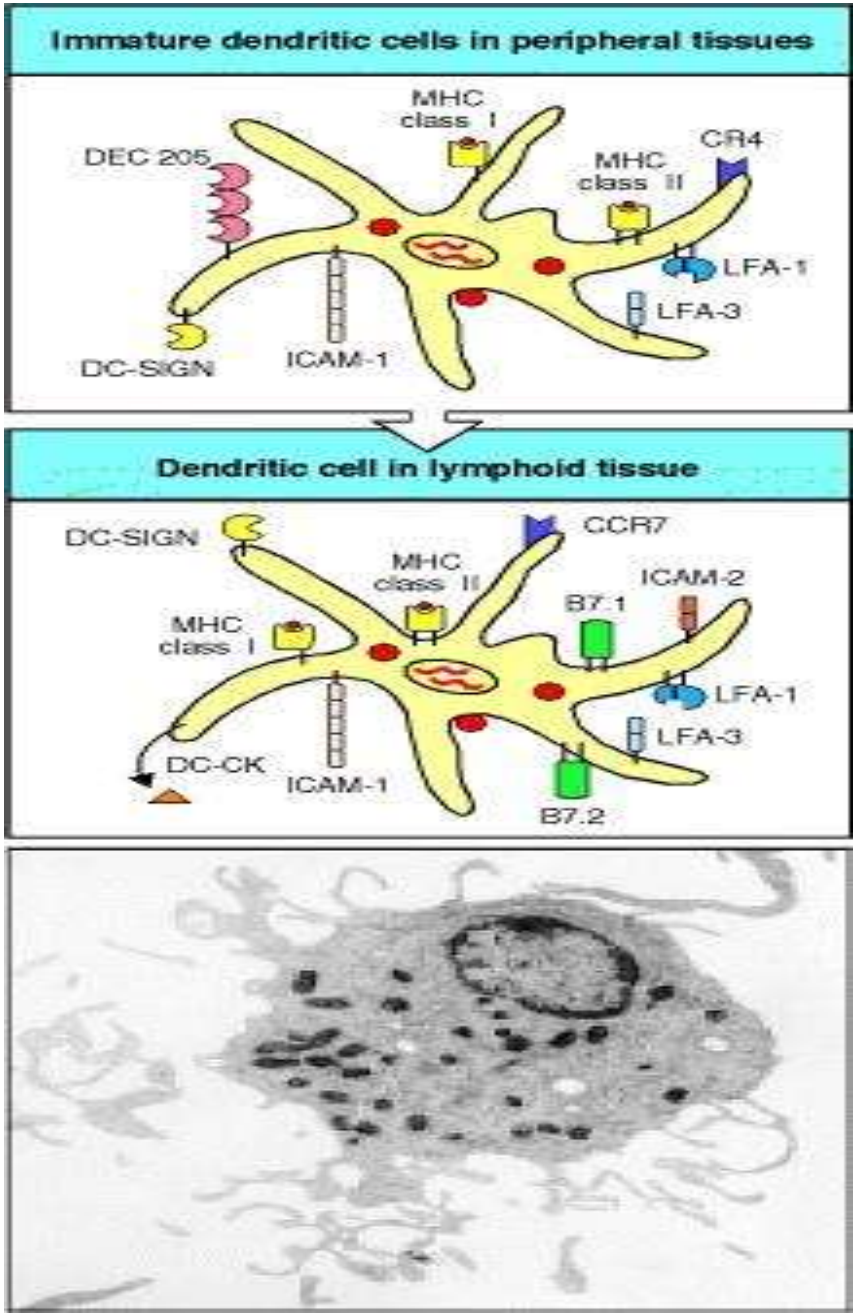
APCs

- **Antigen-presenting cells are distributed in tissues, blood and in the lymph node**
- Dendritic cells, Macrophages and B cells
- Mature dendritic cells are by far the most important activators of naive T cells and activated by wide range of antigens (viral. Bacterial and allergens)
- B cell bind soluble intact antigen and present it to TH by MHC2

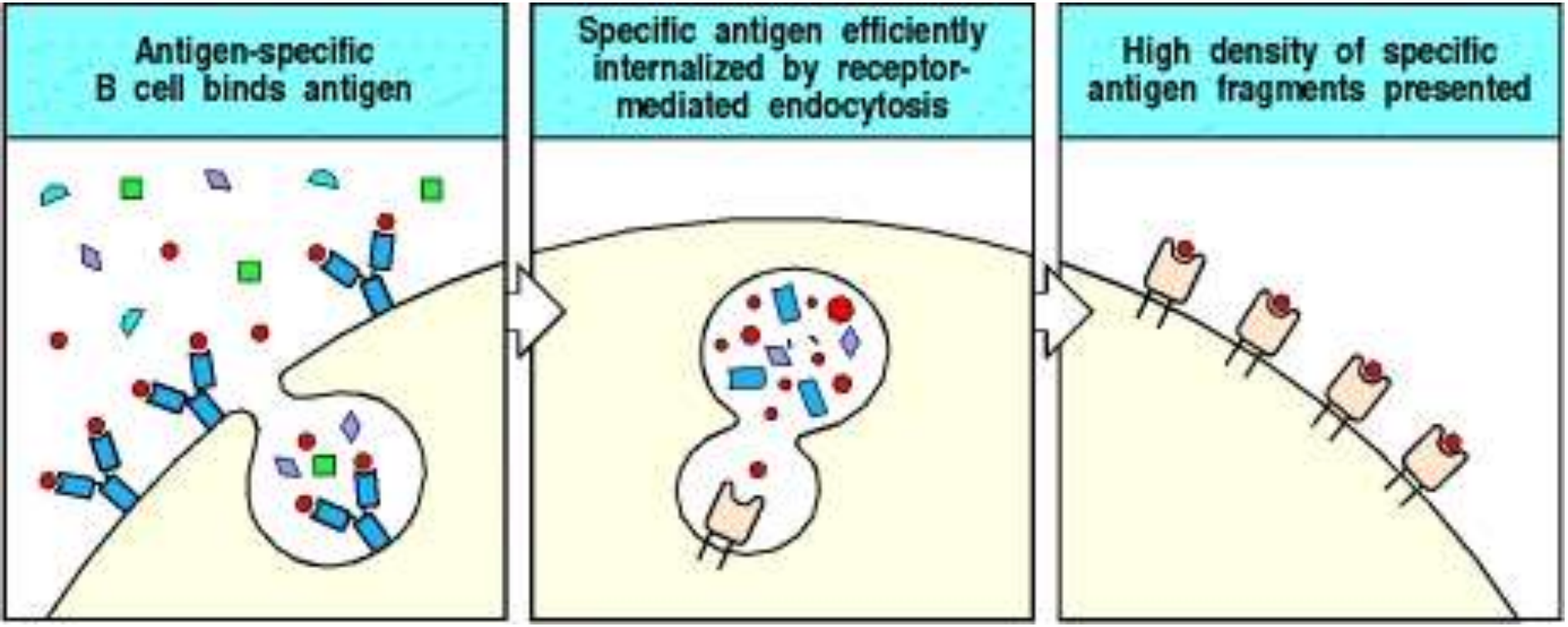



Antigen capture by dendritic cells (DC)
Loss of DC adhesiveness
Antigen capture
Inflammatory cytokines
Immature DC in epidermis (Langerhans cell)
Migration
lymphatic vessel
Maturation of migrating DC
T cell zone
Lymph node
Antigen presentation
T cell
Mature dendritic cell presenting antigen to naive T cell

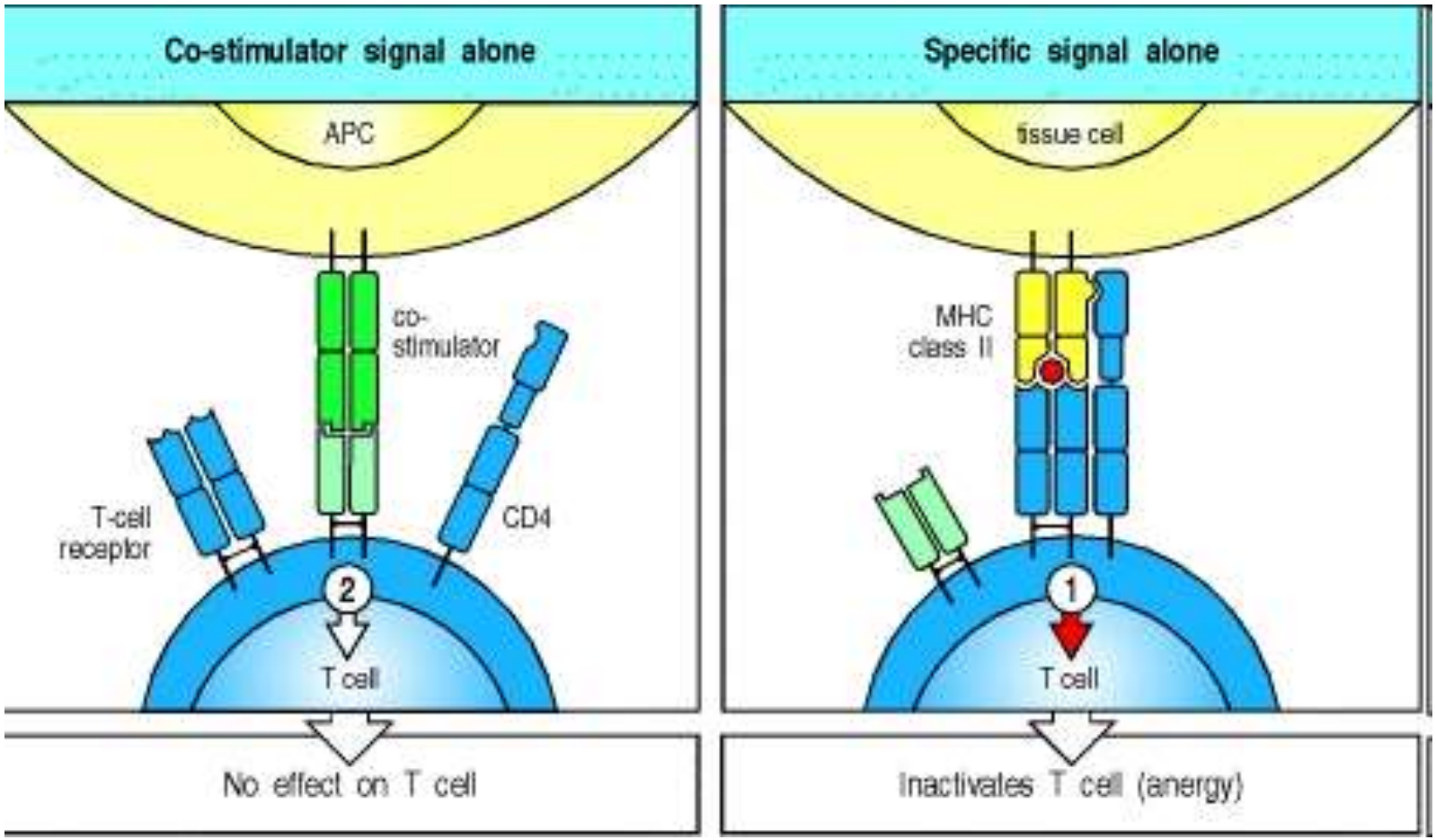
	Dendritic cells	Macrophages	B cells
			
Antigen uptake	+++ Macropinocytosis and phagocytosis by tissue dendritic cells Viral infection	Phagocytosis +++	Antigen-specific receptor (Ig) ++++
MHC expression	Low on tissue dendritic cells High on dendritic cells in lymphoid tissues	Inducible by bacteria and cytokines – to +++	Constitutive Increases on activation +++ to ++++
Co-stimulator delivery	Constitutive by mature, nonphagocytic lymphoid dendritic cells ++++	Inducible – to +++	Inducible – to +++
Antigen presented	Peptides Viral antigens Allergens	Particulate antigens Intracellular and extracellular pathogens	Soluble antigens Toxins Viruses
Location	Lymphoid tissue Connective tissue Epithelia	Lymphoid tissue Connective tissue Body cavities	Lymphoid tissue Peripheral blood



- Immature dentritic cells, exist at tissues and sites of infection, they express low levels of MHC1 & 2 and phagocytic receptor PRR, but low adhesion molecules.
- Internalization occur as a result of binding the Ag with PRR or by macropinocytosis.
- After engulfing the pathogen they become mature DC; migrate to peripheral L.N.
  - lose their phagocytic activity
  - and express more adhesion molecules, MHC and co-stimulatory molecules,
  - secret chemotactic factors to attract naïve T cells to the LN.

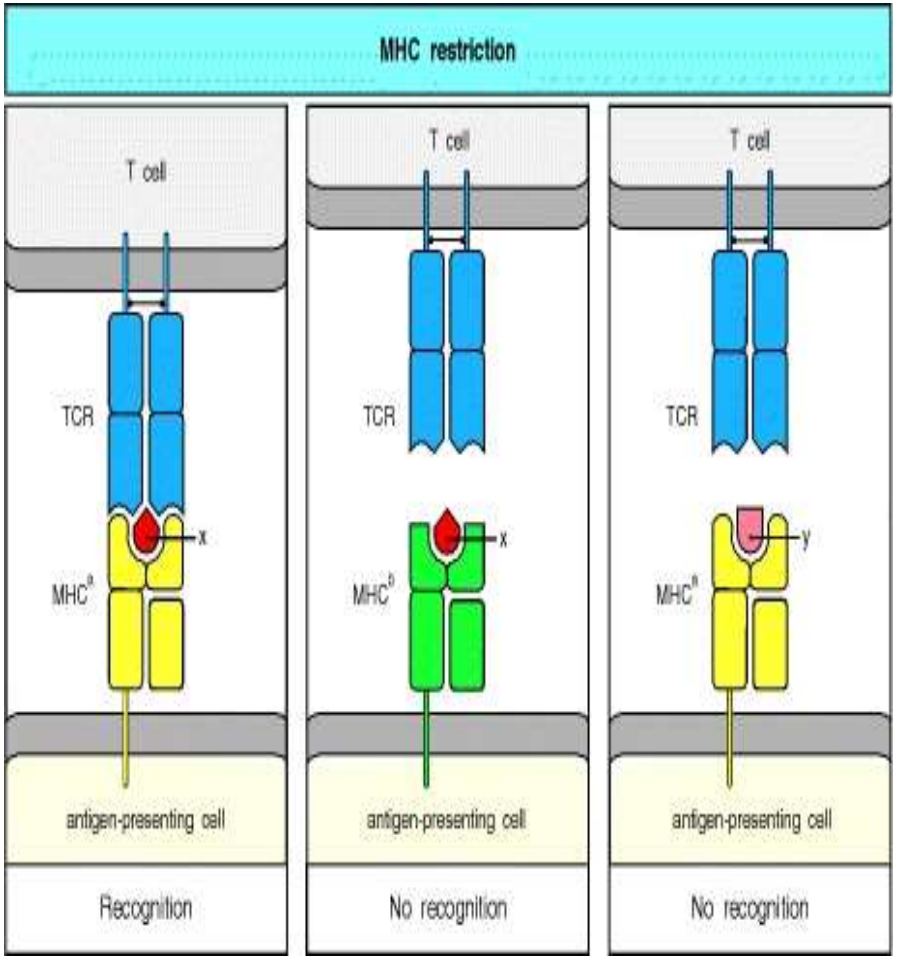


- Surface immunoglobulin (IGM or IGD) allows B cells to bind and internalize specific soluble intact antigen very efficiently. The internalized antigen is processed in intracellular vesicles where it binds to MHC class II molecules. These vesicles are then transported to the cell surface where the MHC class II:antigen complex can be recognized by Th2 cells. Because of high specificity, it is perfect when Ag concentration is low.


Co-stimulator signal alone
APC
co-
stimulator
T-cell
receptor
CD4
2
T cell
No effect on T cell
Specific signal alone
tissue cell
MHC
class II
1
T cell
Inactivates T cell (anergy)

Inappropriate Ag or MHC

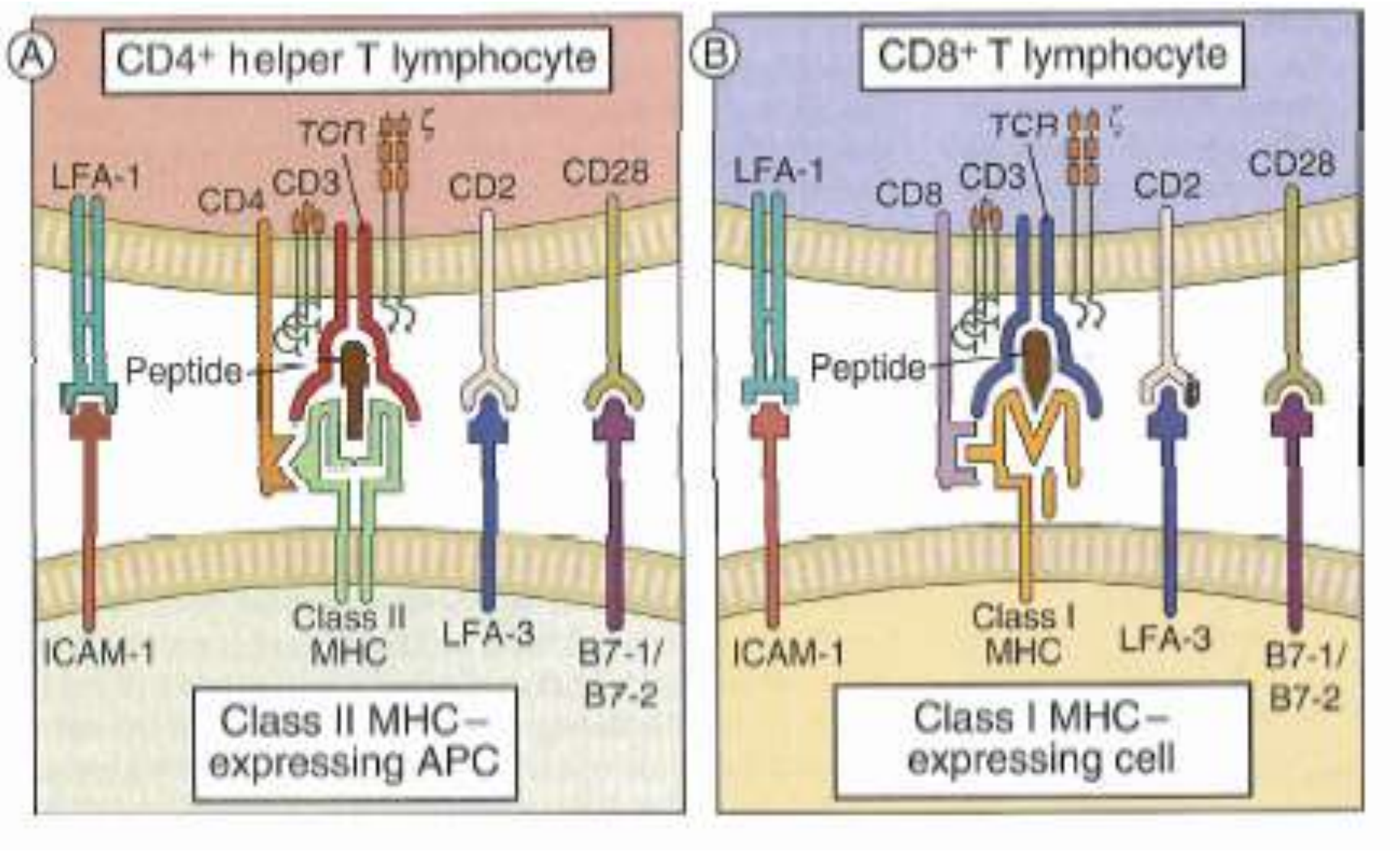
- CD4 bind MHC2 and CD8 bind MHC1
- TCR bind both the Ag and part of MHC
- Self Ag result in immature DC and macrophages (no co-stimulatory molecules)….T cell anergy.



The immunologic synapse.

- When the TCR complex recognizes MHC-associated peptides on an APC, several T cell surface proteins and intracellular signaling molecules are rapidly mobilized to the site of T cell–APC contact
- This region of physical contact between the T cell and the APC is called an immunologic synapse or a supramolecular activation cluster (SMAC).
- The T cell molecules that are rapidly mobilized to the center of the synapse include the TCR complex (the TCR, CD3, and ζ chains), CD4 or CD8 coreceptors, receptors for costimulators (such as CD28), enzymes, and adaptor proteins that associate with the cytoplasmic tails of the transmembrane receptors.

The immunologic synapse.



Memory T cells

- Both CD4+ and CD8+ memory T cells (CD45RO+) can be subdivided into 2 subsets based on their homing properties and functions.
- Central memory T cells express the chemokine receptor CCR7 and L-selectin and home mainly to lymph nodes.
- Effector memory T cells, on the other hand, do not express CCR7 or L-selectin and home to peripheral sites, especially mucosal tissues.
- During a secondary infection, memory T cells in peripheral tissues can be directly activated by pro-inflammatory cytokines to induce effector functions outside of the draining lymphoid tissue

Regulation of T lymphocyte responses

- To prevent tissue damage as a result of over stimulation
- To prevent auto-immunity
- Methods

-After clearing the Ag CTLA-4 expressed instead of CD28 on T cells which bind B7 on APC and inhibit T cell activity

-persistent activation of T cells lead to activation induced cell death (AICD) by surface interactions of fas-fasL on natural killer cells with the target T cell

-elimination of Ag result in passive cell death

-CD4 reg in the presence of IL-10 and TGF beta

-PD-1 on T cells; programmed cell death 1, PD-1 recognizes two ligands, called PD-L1 and PD-L2; PD-L1 is expressed on APCs and many other tissue cells, and PD-L2 is expressed mainly on APCs. Engagement of PD-1 by either ligand leads to inactivation of the T cells or rarely conversion to T reg.

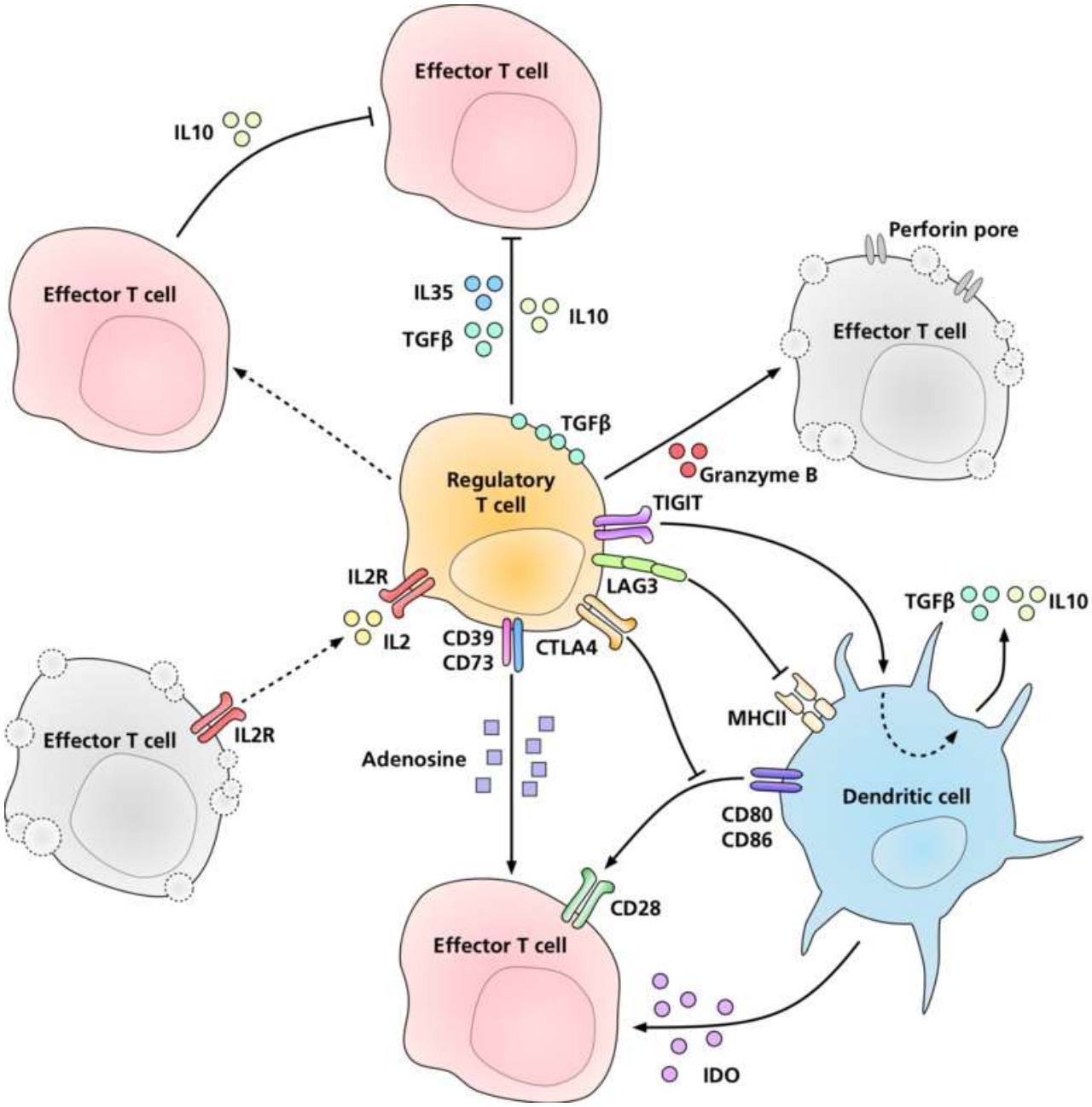
.

New T cell phenotypes

- Regulatory T cells
  - Subset of CD4 T cells
  - Naturally occurring (FoxP3, CD25 and CD4 positive)
  - Induced (IL-10 and TGF-β)

T reg

- ***Regulatory T cells are generated mainly by self antigen recognition in the thymus (central) and by recognition of self and foreign antigens in peripheral lymphoid organs (peripheral)***
- ***Differentiated from CD4***
- ***The generation of some regulatory T cells requires the cytokine TGF-β. And IL-2***
- ***Functions***
- Production of the immunosuppressive cytokines IL-10 and TGF-β.
- Consumption of IL-2. Because of the high level of expression of the IL-2 receptor, these cells may absorb IL-2 and deprive other cell populations of this growth factor, resulting in reduced proliferation and differentiation of other IL-2–dependent cells.
- Reduced ability of APCs to stimulate T cells. One proposed mechanism of this action is dependent on binding of CTLA-4 on regulatory cells to B7 molecules on APCs,
- Secret granzyme B act on activated T cells


Effector T cell
IL10
Effector T cell
IL35
TGFβ
IL10
Perforin pore
Effector T cell
TGFβ
Granzyme B
Regulatory
T cell
TIGIT
IL2R
LAG3
TGFβ
IL10
IL2
CD39
CD73
CTLA4
Effector T cell
IL2R
Adenosine
MHCII
Dendritic cell
CD80
CD86
CD28
Effector T cell
IDO

T reg cytokines

- TGF-β inhibits T cells and macrophages
- Interleukin-10.
  - IL-10 is an inhibitor of a activated macrophages and dendritic cells and TH1 and CD8 cells
  - By inhibition the production of IL-12 by activated dendritic cells and macrophages (inhibit TH1 and CD8)
  - IL-10 inhibits the expression of costimulators and class II MHC

Privileged sites

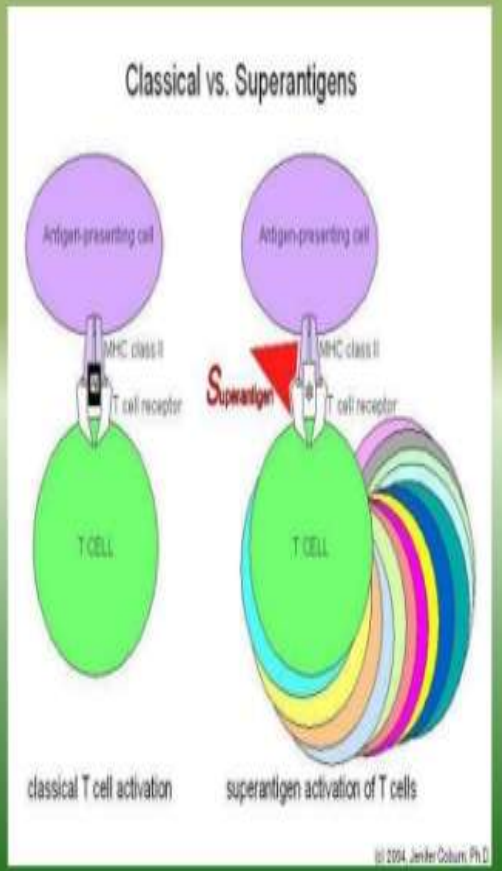
- Immune response do not normally occur in these sites
- Anterior chamber of eye and testes
- Because high inhibitory proteins
  - IL-10 TGF beta
  - Migration inhibition factor
  - Expression of Fas L on their cells

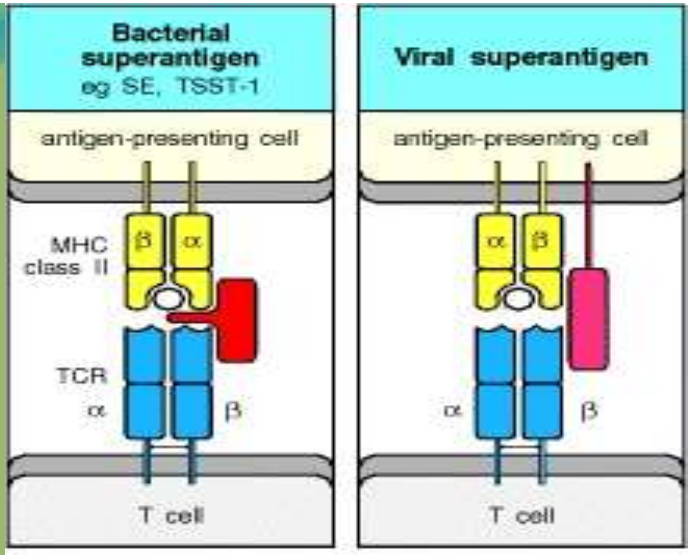
In appropriate T cell activation; T cell stimulation by Super antigens

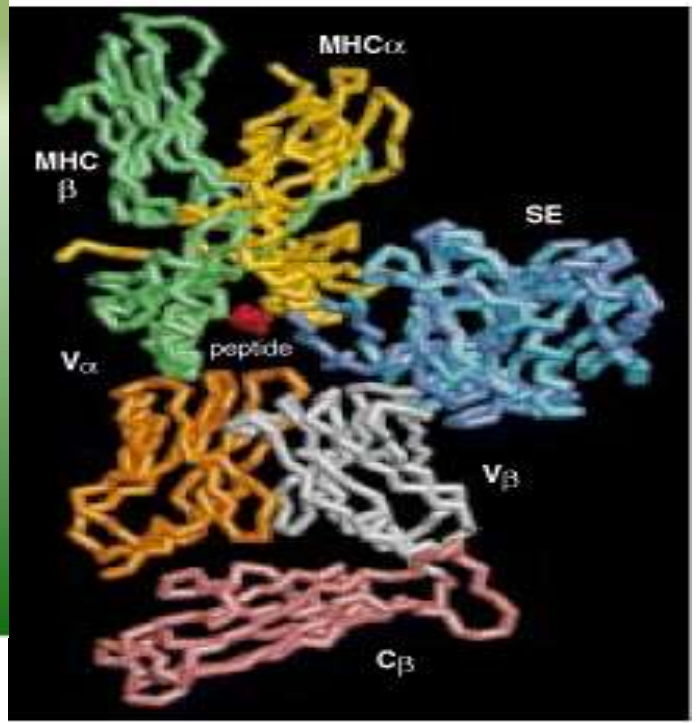
- Super antigens; are a class of antigens which cause non-specific activation of T-cells resulting in and massive cytokine release from macrophages
- Causes; exoproteins, which include toxic shock syndrome toxin-1 (TSST-1), the staphylococcal enterotoxins, the exfoliative toxins (ETA and ETB), and leukocidin. and exotoxins A from streptococcal Streptococcus pyogenes leading to toxic shock-like syndrome, Others include EBV and HIV.
- Pathology; Bind in-appropriately to the outer part of Vß domain of the TCR and to outer part of MHC 2 and cause activation of massive no. of T cells and huge amount of produced cytokines, as the frequency of T cells that have Ag specific Vß domain is higher than to have both Ag specific Vα and Vß TCR (10% : 0.01%)
- Immunological effects; increase in IL1, TNF alpha and IL2 as a result of increased macrophage activation by T cells….fever, massive vascular leakage and toxic shock syndrome (TSS).

MECHANISM OF ACTION

- Binding to MHC class ll
- Binding to T cell receptor
- T cell signalling







- Immunoglobulin superfamily includes the antigen receptors of T and B cells, CD3, the co-receptors CD4, CD8, most Fc receptors, CD28 and B7 adhesion molecules, cytokine receptors and the MHC molecules.

Cytokines

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Definition

- **Cytokines** are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
- They are produced by virtually all cells involved in innate and adaptive immunity,
- The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity.
- Cytokines are pleiotropic, redundant, and multifunctional.
- **Pleiotropic** means that a particular cytokine can act on a number of different types of cells rather than a single cell type.
- **Redundant** refers to the ability of a number of different cytokines to carry out the same function.
- **Multifunctional** means the same cytokine is able to regulate a number of different functions.
- **They can act locally or in a distance**

Cytokine families

- the cytokine superfamily includes
  - interleukins,
  - chemokines,
  - colony-stimulating factors (CSF),
  - interferons,
  - Monokines and lymphokines.

Nomenclature...

- Interleukins – that act as mediators between leukocytes. The vast majority of these are produced by T-helper cells.
- Lymphokines – produced by lymphocytes.
- Monokines – produced exclusively by monocytes.
- Interferons – involved in antiviral responses.
- Colony Stimulating Factors – support the growth of cells blood cell .
- Chemokines – mediate chemoattraction (chemotaxis) between cells.

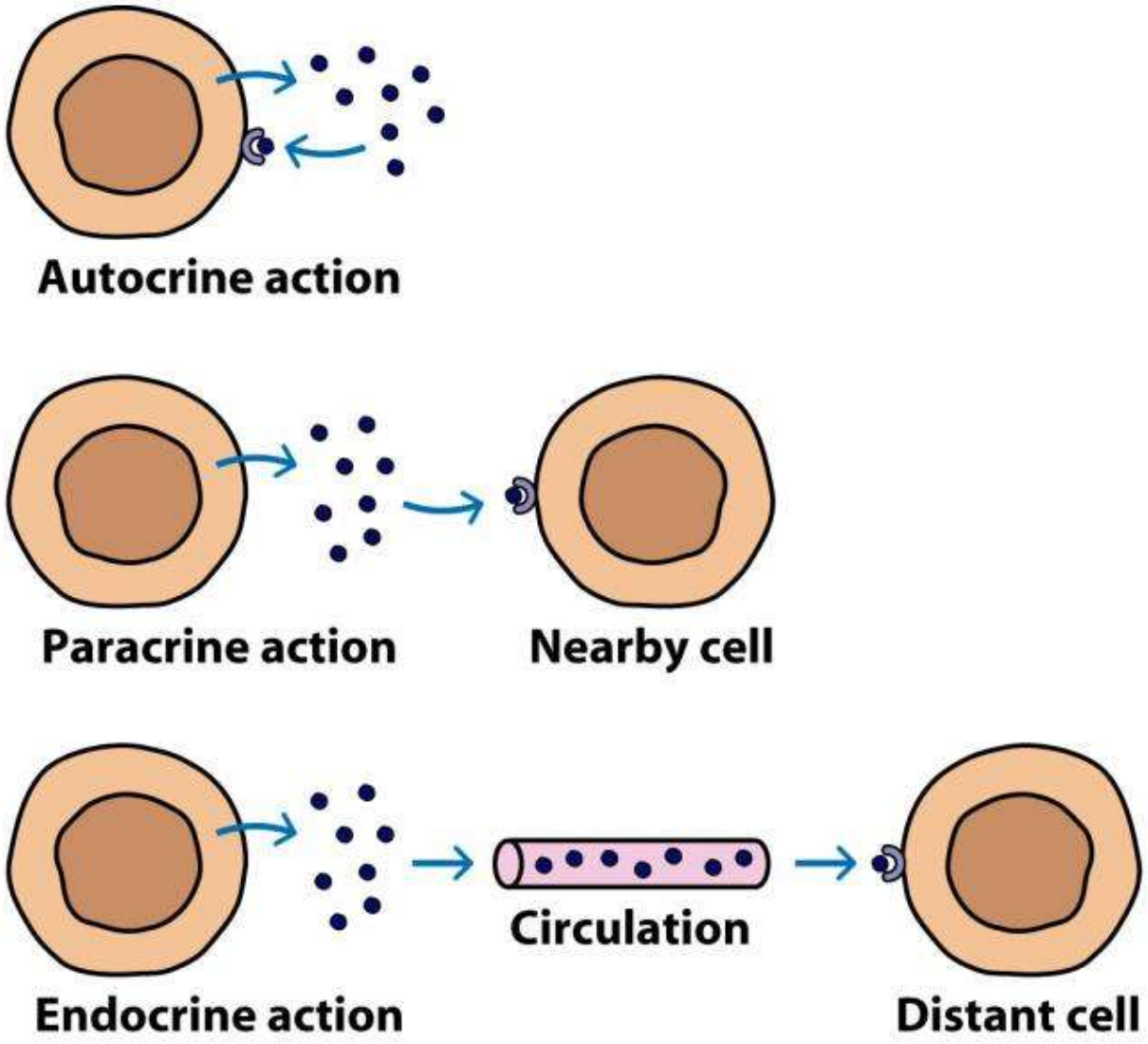


Figure 12-1b
Kuby IMMUNOLOGY, Sixth Edition

Functional features

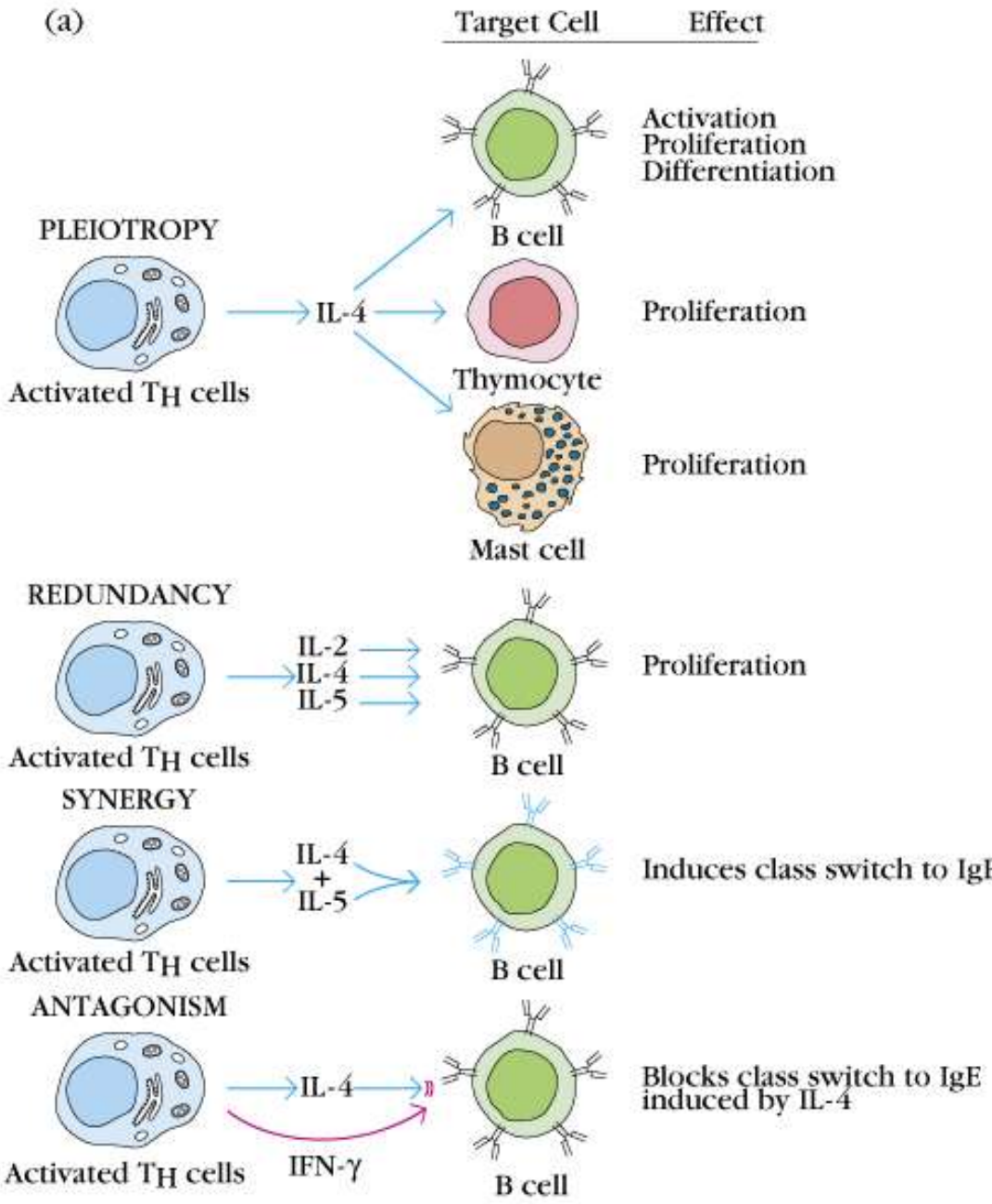
- Highly interactive

pleiotropic

redundant

synergistic

antagonistic



Cytokines

- There are **three functional categories of cytokines**:

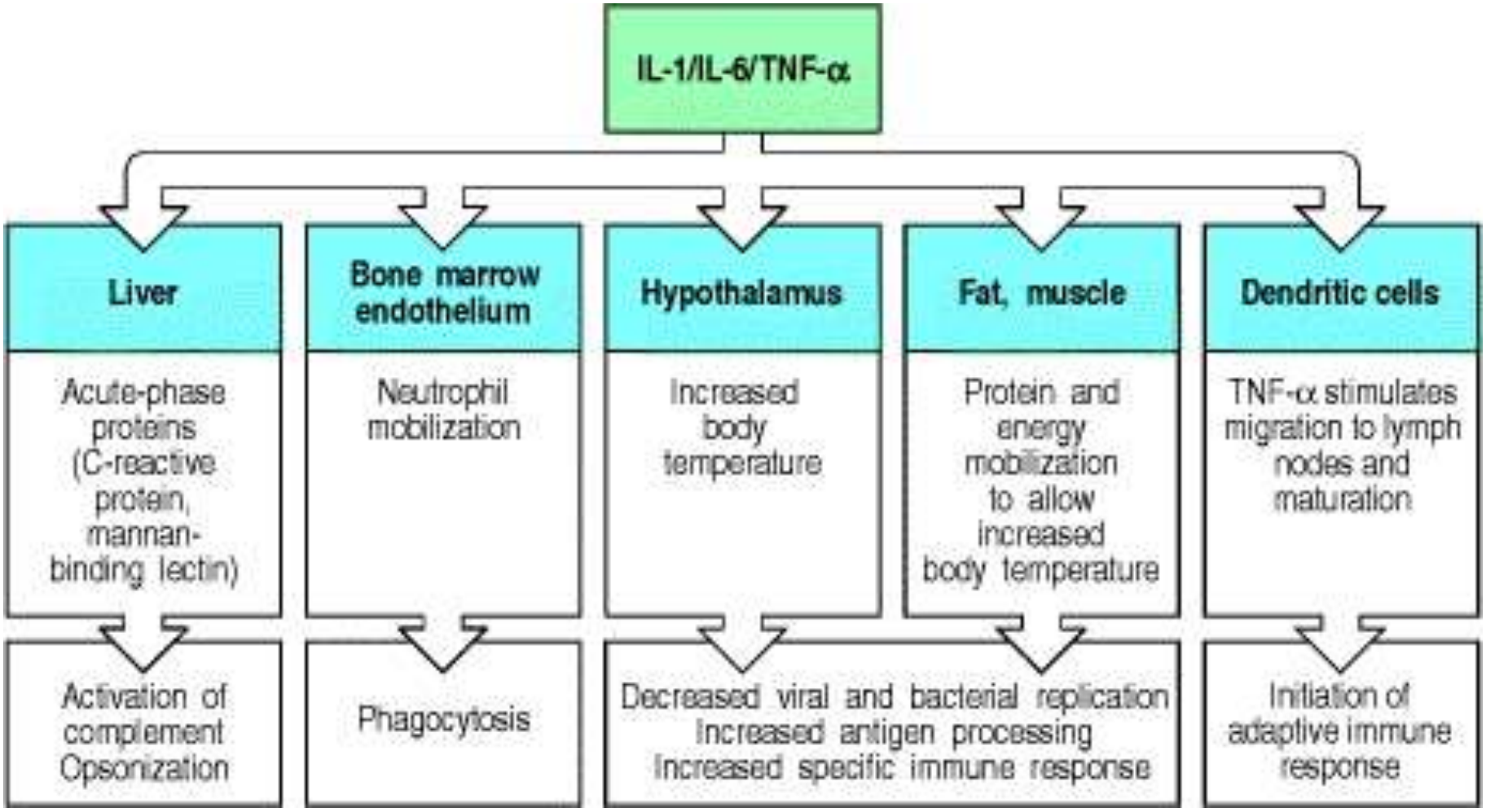
1. cytokines that produced by innate immune responses,
2. cytokines that produced by adaptive Immune responses, and
3. cytokines that stimulate hematopoiesis.

Features	Innate immunity	Adaptive immunity
Examples	*TNF-α*, IL-1, IL-12, IFN-γ *	IL-2, IL-4, IL-5, IFN-γ *
Major cell source	Macrophages, NK cells	T lymphocytes
Principal physiologic functions	Mediators of innate immunity and inflammation (local and systemic)	Adaptive immunity: regulation of lymphocyte growth and differentiation; activation of effector cells (macrophages, eosinophils, mast cells)
Stimuli	LPS (endotoxin), bacterial peptidoglycans, viral RNA, T cell–derived cytokines (IFN-γ)	Protein antigens
Amounts produced	May be high; detectable in serum	Generally low; usually undetectable in serum
Local or systemic effects	Both	Usually local only
Roles in disease	Systemic diseases (e.g., septic shock)	Local tissue injury (e.g., granulomatous inflammation)
Inhibitors of synthesis	Corticosteroids	Cyclosporine, FK-506

cytokines that produced by innate immune responses

- **cytokines that regulate innate immune responses are** produced primarily by mononuclear phagocytes, dendritic cells and NK (some of them called pro-inflammatory cytokines)

1. **Interleukin 1 (IL-1) and Tumor necrosis factor (TNF alpha) (PRO-INFLAMMATORY CYTOKINES); IL-1 function similarly to TNF in that it mediates acute inflammatory responses**. It also works synergistically with TNF to enhance inflammation.
    1. They stimulate the synthesis of adhesion factors on endothelial cells and leukocytes that help in cell migration
    2. They are both produced primarily by local activated monocytes, macrophages and by neutrophils.
    3. they produced in high quantity affecting on hypothalamus to increase prostaglandin syn. causing fever (endogenous pyrogens) (this is inhibited by aspirin)
    4. and stimulate the production of acute phase proteins from *liver*


IL-1/IL-6/TNF-α
Liver
Bone marrow endothelium
Hypothalamus
Fat, muscle
Dendritic cells
Acute-phase proteins (C-reactive protein, mannan-binding lectin)
Neutrophil mobilization
Increased body temperature
Protein and energy mobilization to allow increased body temperature
TNF-α stimulates migration to lymph nodes and maturation
Activation of complement Opsonization
Phagocytosis
Decreased viral and bacterial replication
Increased antigen processing
Increased specific immune response
Initiation of adaptive immune response

2. IL-12 is a primary mediator of immune responses to intracellular microbes (listeria, mycobacteria and viruses) produced by DC and macrophags

1. **It is an activator CD8 T cells differentiation,**
2. **TH1 cell differentiation**
3. **CD8, TH1 and NK activation**
4. It also stimulates interferon-gamma production from these cells

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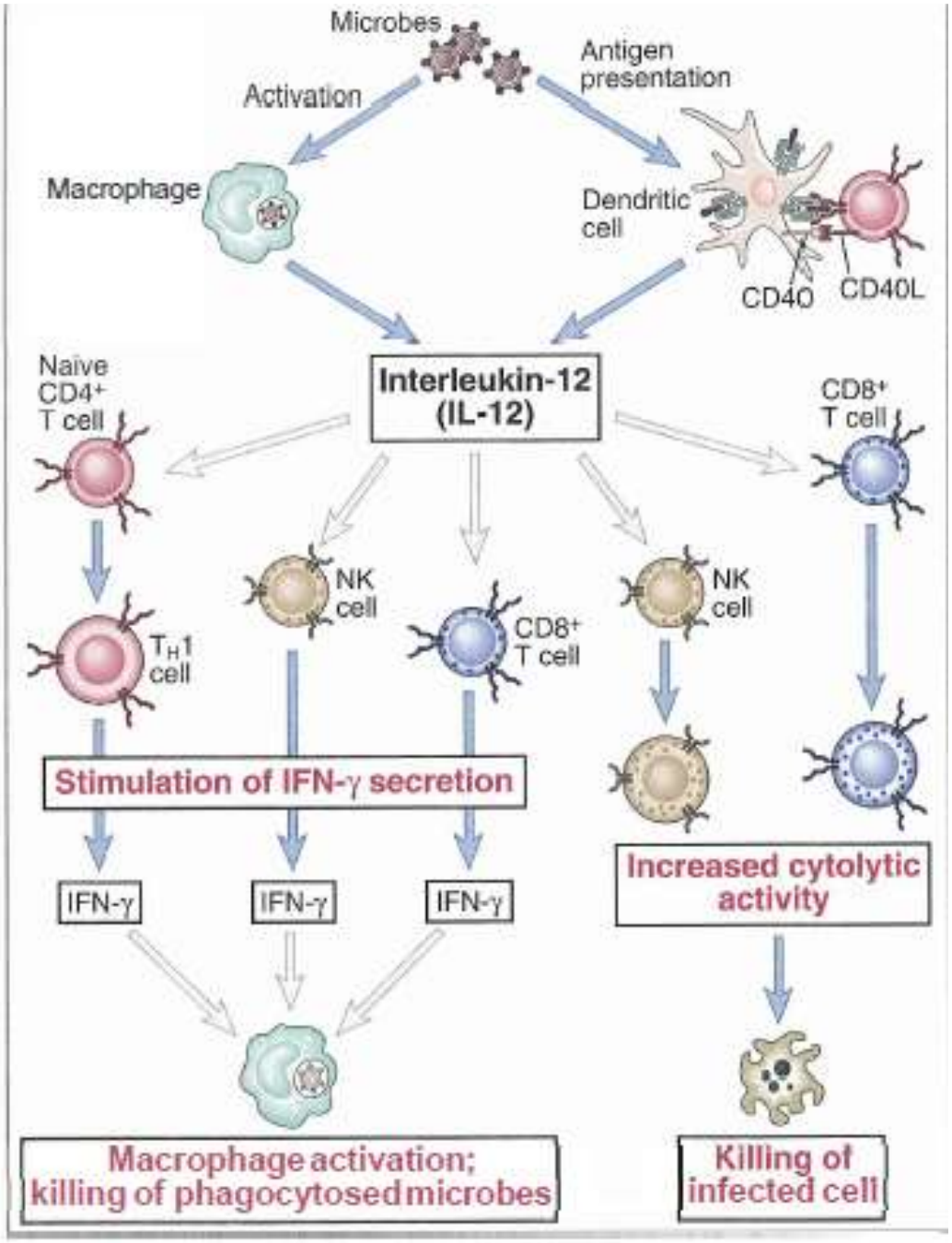

Microbes
Activation
Antigen presentation
Macrophage
Dendritic cell
CD40
CD40L
Naive CD4+ T cell
Interleukin-12 (IL-12)
CD8+ T cell
NK cell
NK cell
CD8+ T cell
TH1 cell
Stimulation of IFN-γ secretion
IFN-γ
IFN-γ
IFN-γ
Increased cytolytic activity
Macrophage activation; killing of phagocytosed microbes
Killing of infected cell

3. Chemokines

- Although there are exceptions, recruitment of neutrophils is mainly mediated by CXC chemokines, monocyte recruitment is more dependent on CC chemokines, and lymphocyte recruitment is mediated by both CXC and CC chemokines.
- Chemokines are required for the migration of immune cells from sites of infection into draining lymph nodes CC-chemokine receptor 7 (CCR7).
- Neutrophils express receptors for (IL-8) CXCL8 produced by tissue resident macrophages , the major chemokine supporting neutrophil migration into tissues.
- classical monocytes, express CCR2. This receptor binds chemokines for monocyte recruitment being CCL2

4. Type 1 interferon

- **Type I Interferons,** include 13 subtypes of interferon-alpha, interferon-beta and others. (There is only one **type II interferon**, interferon-gamma, which is involved in the innate and adaptive immune response.)

- The **most powerful stimulus for type I interferons is the first immune reaction against viral infection**
- Produced by any virus-infected cell; act paracrine; **induce uninfected cells to produce enzymes capable of degrading viral mRNA**.(becomes virus resistant)ِ .Also as autocrine; **blocks viral protein synthesis** and replication in side the cell.
  - it also help in CD4 differentiation to TH1cells
  - and help in activation of CD8 cell in killing virus infected cells
  - Activate NK to act against the virus
  - Stimulates production of IFN-gamma by activated T cells

1-Interferon-alpha (leukocyte) is produced by monocytes/macrophages;
2- interferon-beta (fibroblast) by virus-infected cells, and fibroblasts

Cytokines that produced by Adaptive Immune Responses (Humoral Immunity and Cell-Mediated Immunity)

- Cytokines that regulate adaptive immunity are produced primarily by T-lymphocytes Examples include:

1. Interleukin-2 (IL-2) IL-2 (growth factor)
    1. Is produced by DC and T and B cells, it is a growth factor for Th1, Th2 and CD8 -lymphocytes upon activation (3rd signal),
    2. B7 ligates T cell CD28, activating the T cell to produce IL-2 and its receptor (IL-2R). The cytokine acts in an autocrine fashion. The cell divides and differentiates into an effector T cell
2. Interleukin-4 (IL-4) IL-4 is
    1. B cell growth major stimulus for production of IgE in B cells
    2. It also antagonizes the effects of interferon-gamma and thus inhibits cell-mediated immunity.
    3. IL-4 is produced mainly by Th2 cells and B cells.
3. Interleukin-5 (IL-5) IL-5 is
    1. A growth and activating factor for eosinophils as a defense against helminths.
    2. It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes
    3. IL-5 is produced mainly by Th2 cells.
4. IL-13 by Th2 cells act on B cells

4. **Interferon-gamma (IFN-gamma).** Type II interferon is produced by both innate and adaptive; macrophages and DC in intracellular infection and by activated TH1 , NK and CD8 to promote the activity of the cell-mediated immune system.against intracellular pathogen

-IFN-gamma is the principal cytokine for activating macrophages. It also promote cell-mediated immunity by activating CD8 and NK

- IFN-gamma inhibits the proliferation of Th2 cells;
- Stimulates the production of IgG subclasses that activate the complement pathway and promote opsonization.

5. **Transforming growth factor-beta (TGF-beta)**

- Regulatory cytokine functions to inhibit the proliferation and effector function of T-lymphocytes; inhibit the proliferation of B-lymphocytes; and inhibits macrophage function .

-TGF-beta is produced by T-reg.

- The generation of some regulatory T cells from CD4 cells requires the cytokine TGF-β. And IL-2

-TGF beta with IL-6 lead to differentiation of TH17

6. .**Lymphotoxin (TNF beta).** LT plays a role in the **recruitment and activation of neutrophils** and in lymphoid organogenesis. Being chemically similar to TNF, LT is also pro-**inflammatory responses** .LT is made by T-lymphocytes.

5. IL-6 and IL-10

- **IL-6 produced by both innate and adaptive functions to**
  - IL-6 is produced by macrophages, monocytes.(PRO-INFLAMMATORY CYTOKINE) **stimulate the liver to produce acute phase proteins**
  - **From TH2 to stimulates the differentiation and growth of B-lymphocytes .**
  - Help in differentiation of TH17 if TGF beta present
- **IL-10 (pan-regulatory cytokine) is**
  - **An inhibitor of activated macrophages and dendritic cells and as such, inhibit production of IL-12 and co-stimulator molecules like MHC2 (inhibit TH1, TH2 and CD8)**
  - **regulates innate immunity and cell-mediated and humoral immunity**
  - IL-10 is produced mainly by Treg, and Th2 cells.

Other....

Type-1 & Type-2

- Type-1 cytokines are cytokines produced by Th1 T-helper cells.
- Include IL-2 (IL2), IFN-gamma (IFN-G), IL-12 (IL12) & TNF-beta (TNF-b).
- Type-2 cytokines are those produced by Th2 T-helper cells.
- Include IL-4 (IL4), IL-5 (IL5), IL-6 (IL6), IL-10(IL10), and IL-13 (IL13).

Mediators of natural immunity.

- TNF-α, IL-1, IL-10, IL-12, type I interferons (IFN-α and IFN-β), IFN-γ, and chemokines.

Mediators of adaptive immunity.

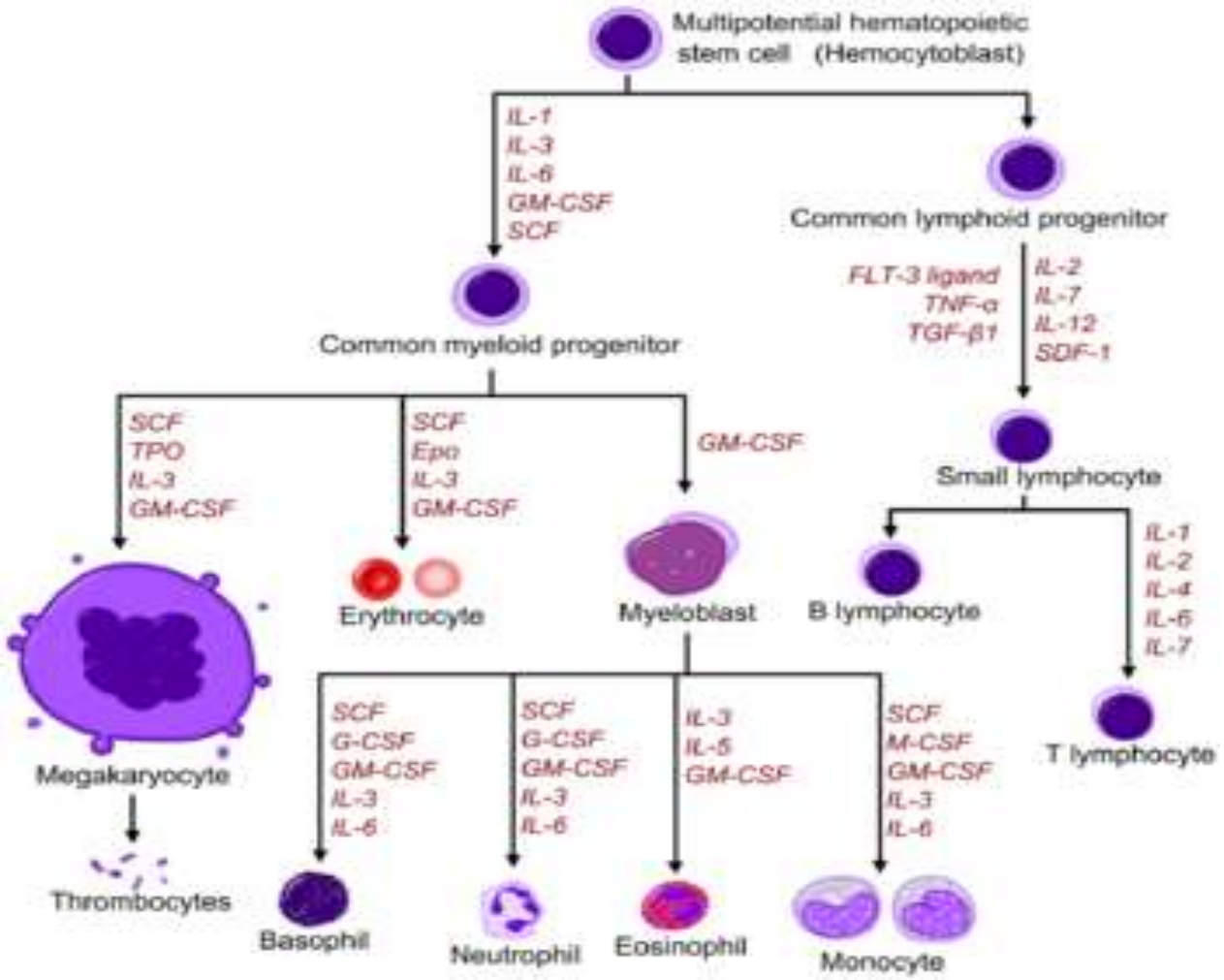
- IL-2, IL-4, IL-5, TGF-β, IL-10 and IFN-γ.

Cytokines that Stimulate Hematopoiesis

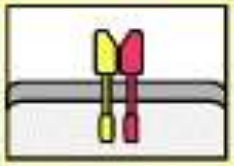
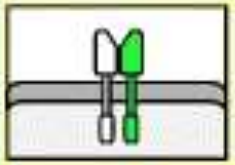
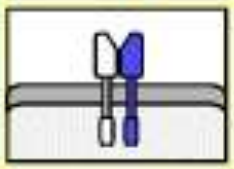
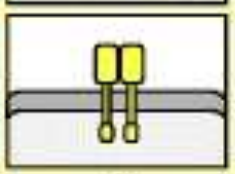
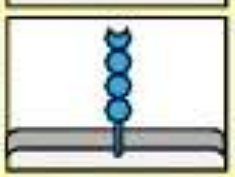
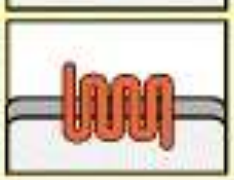
- Produced by bone marrow stromal cells, these cytokines stimulate the growth and differentiation of immature leukocytes .Examples include:

1. Colony-stimulating factors (CSF) Promote the production of colonies of the different leukocytes in the bone marrow and enhance their activity .Examples include granulocyte macrophage colony stimulating factor (GM-CSF) granulocytes (neutrophils, eosinophils, and basophils) and monocytes. , granulocyte colony stimulating factor (G-CSF), and macrophage colony stimulating factor (M-CSF)
2. Stem cell factor. Stem cell factor makes stem cells in the bone marrow more responsive to the various CSFs

3. Interleukin-3 and IL-7, supports the growth of multi-lineage bone marrow stem cells .


Multipotential hematopoietic stem cell (Hemocytoblast)
IL-1
IL-3
IL-6
GM-CSF
SCF
Common lymphoid progenitor
FLT-3 ligand
TNF-α
TGF-β1
IL-2
IL-7
IL-12
SDF-1
Common myeloid progenitor
Small lymphocyte
SCF
TPO
IL-3
GM-CSF
SCF
Epo
IL-3
GM-CSF
GM-CSF
IL-1
IL-2
IL-4
IL-6
IL-7
Erythrocyte
Myeloblast
B lymphocyte
T lymphocyte
Megakaryocyte
SCF
G-CSF
GM-CSF
IL-3
IL-6
SCF
G-CSF
GM-CSF
IL-3
IL-6
IL-3
IL-5
GM-CSF
SCF
M-CSF
GM-CSF
IL-3
IL-6
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte

Cytokines receptors

Class I cytokine receptor (Hematopoietin-receptor family)		Receptors for erythropoietin, growth hormone, and IL-13
		Receptors for IL-3, IL-5, and GM-CSF share a common chain, CD131 or β_c (common beta chain)
		Receptors for IL-2, IL-4, IL-7, IL-9 and IL-15 share a common chain CD132 or γ_c (common gamma chain). IL-2 receptor also has a third chain, a high-affinity subunit IL-2Rα (CD25)
Class II cytokine receptor		Interferon-α, -β, and -γ receptor, IL-10 receptor
TNF-receptor family		Tumor necrosis factor (TNF) receptors I and II CD40, Fas (Apo 1), CD30, CD27, nerve growth factor receptor
Chemokine-receptor family		CCR1–5, CXCR1–4

Cytokine Receptors

- 5 Major Families
  - Immunoglobulin Superfamily
  - Hematopoietin Receptor Family (Class I)
  - Interferon Receptor Family (Class II)
  - TNF Receptor Family
  - Chemokine Receptor Family
- Class I and II (Majority Of Receptors)

- **Immune modulation** aims to alter the balance between different subsets of responding **T cells** such that helpful responses are promoted and damaging responses are suppressed. **As a therapy for autoimmunity (INCREASE TH2 RESPONSE) or in allergy (increase in TH1)** it has the advantage that one might not need to know the precise nature of the autoantigen or allergen. However, the drawback of this approach is the unpredictability of the results.

Cytokine as a biologic therapy

- Suppression of TH1 and Tc in auto-immune diseases by
  - Blocking antibodies against IL-2R
  - Or IL-2 analogue that prevent IL-2 binding
- using IL2 to activate lymphocytes to attack a cancer in a patient

Autoreactive T cell destruction

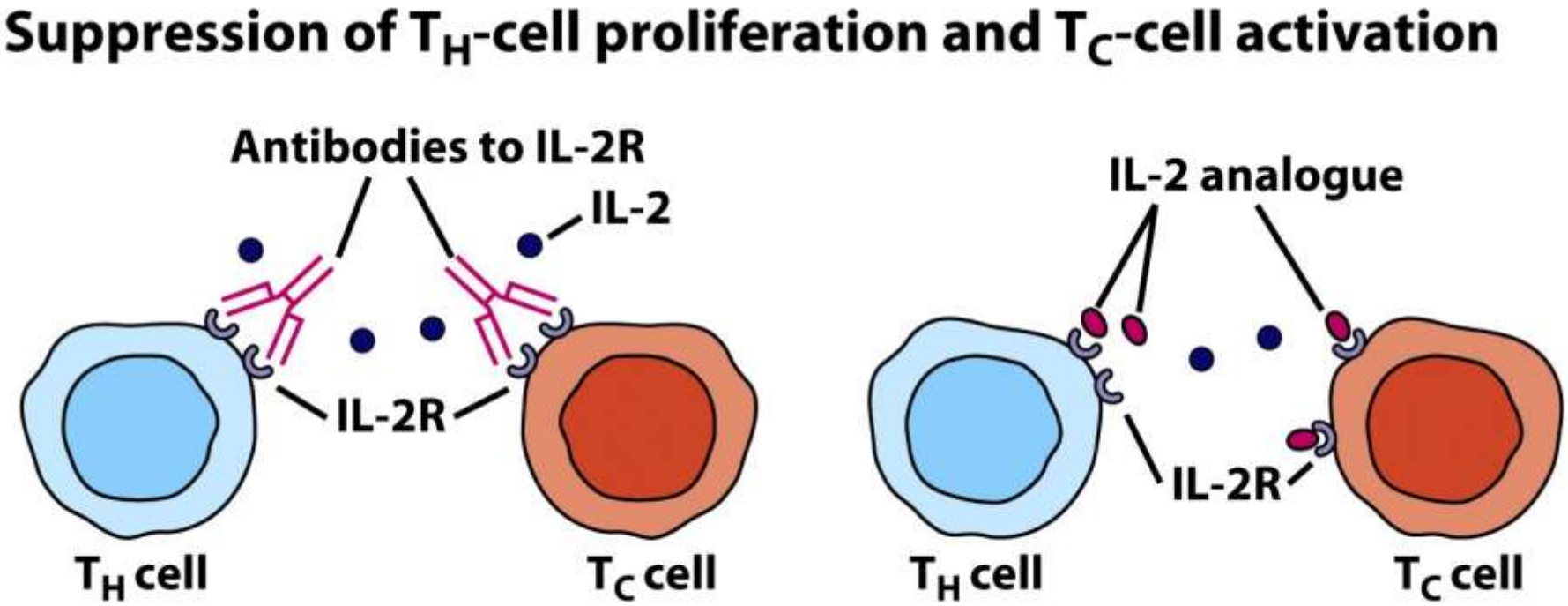


Figure 12-15a
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Autoreactive T cell destruction

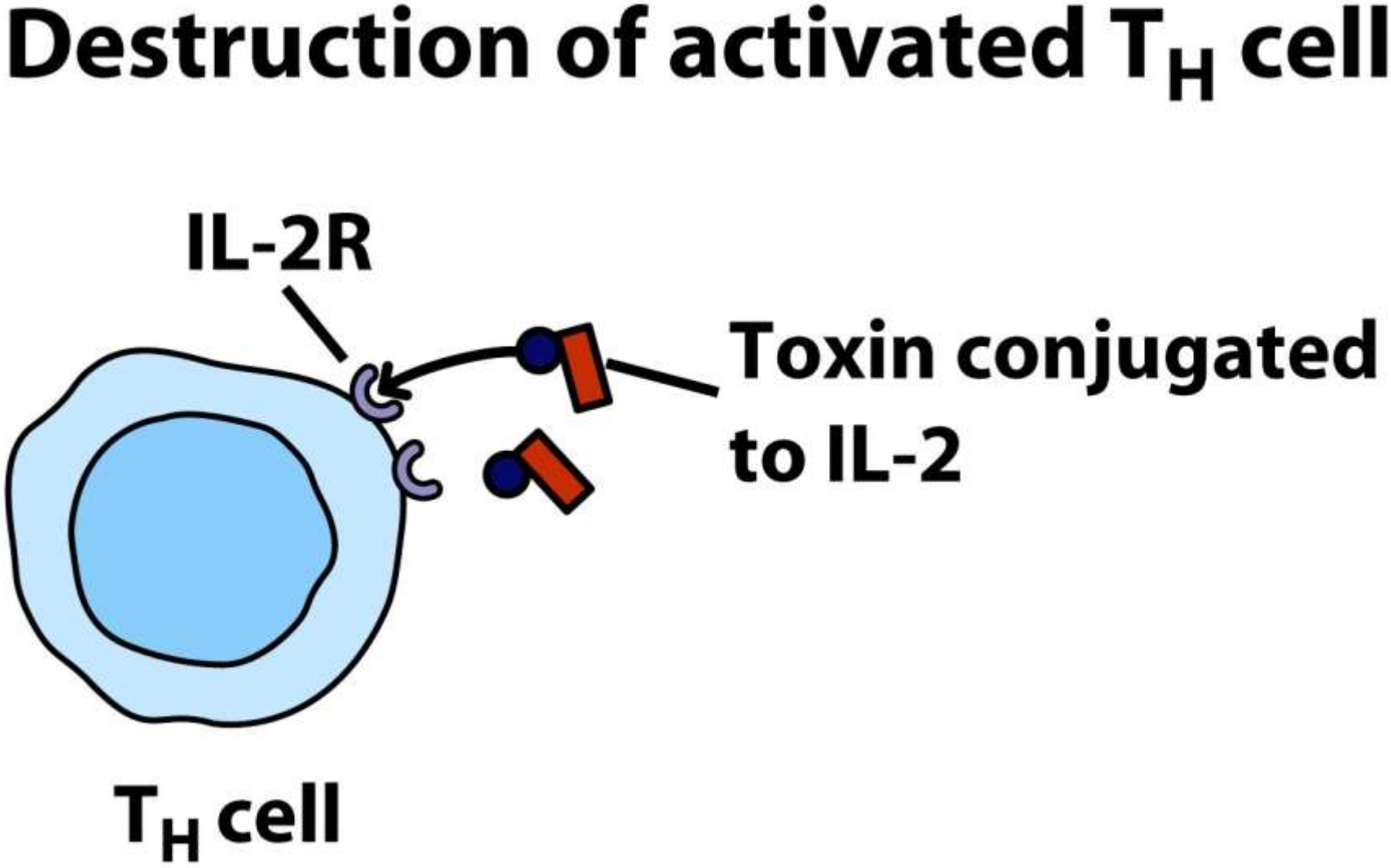

Figure 12-15b
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Therapeutic Uses of Cytokines

1) Interferon in treatment of viral diseases, cancer.

2) Several cytokines are used to enhance T-cell activation in immunofideficency diseases, e.g. IL-2, IFN-γ,TNF-α.

3) IL-2 and lymphokine activating killer cells (LAK) in treatment

4) Anti-cytokines in management of autoimmune diseases :
   a)- Anti-TNF in treatment rheumatoid arthritis
   b)- Anti-IL2R to reduce graft rejection.

5) Anti-TNF antibodies in treating septic shock.

6) Anti-IL-2R α in treating adult T-cell leukemia.

7) Anti-IL-4 is under trial for treatment of allergies.