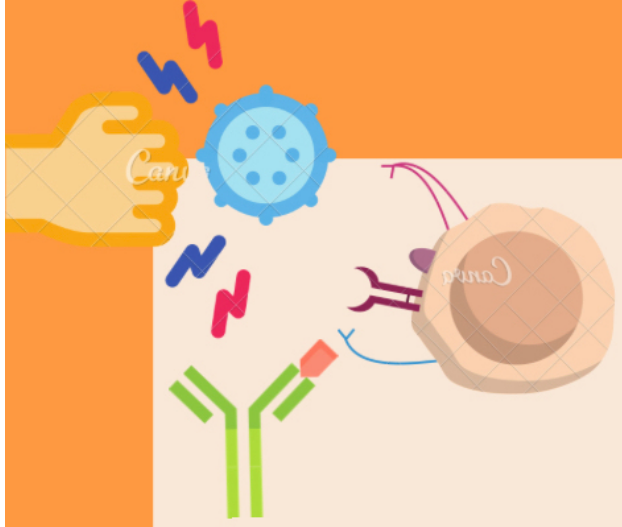
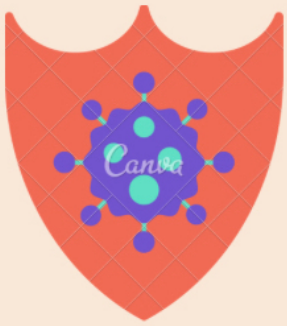


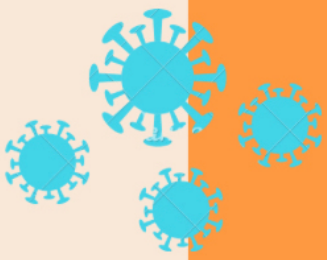
2nd year

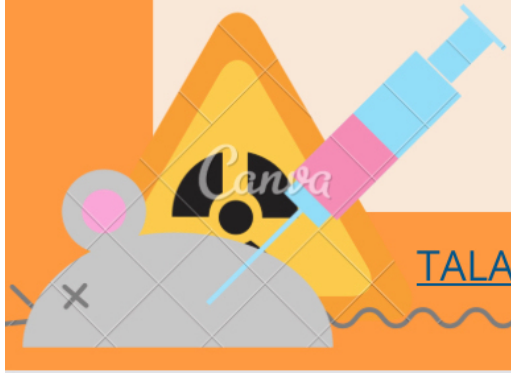


Immunology notes

Molecules of the immune system:

- complement
- cytokines
- MHC Molecules





TALA IYAD

2) cytokines:

IL8 IL1 TNF IL6

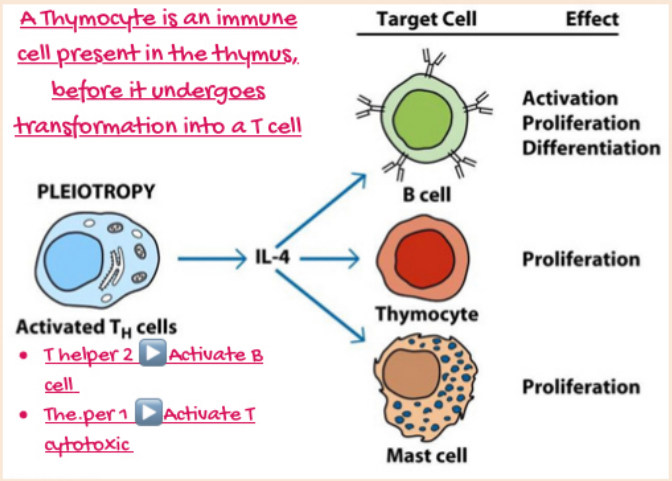
• Definition :

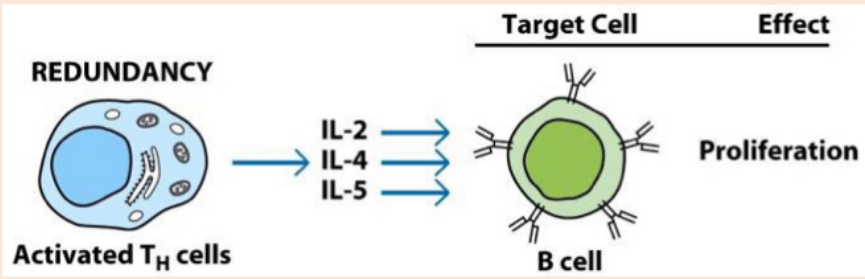
- Cytokines are low molecular weight, soluble proteins that are produced in response to an antigen and function as chemical messengers for regulating the innate and adaptive immune systems.
- They are produced by virtually all cells involved in innate and adaptive immunity.
- The cytokines, in turn, are then able to bind to specific cytokine receptors on other cells of the immune system and influence their activity.

• Properties of cytokines:

• cytokines are :

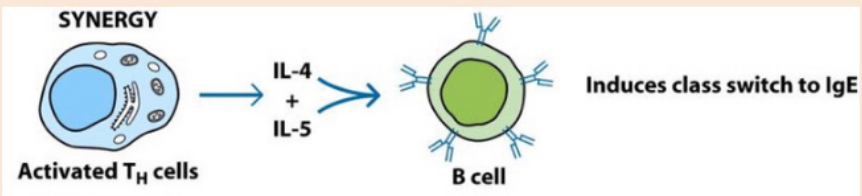
- Pleiotropic : → means that a particular cytokine can act on a number of different types of cells rather than a single cell type.





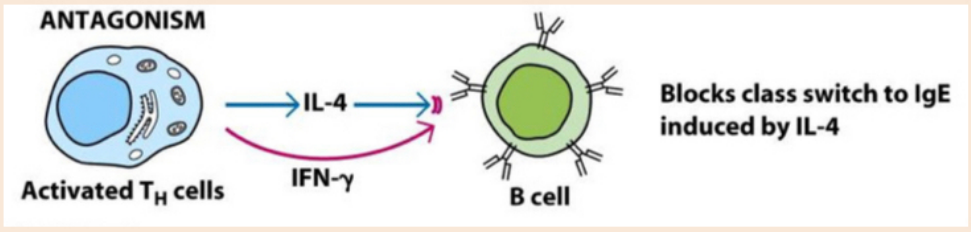
Actions are redundant
•(REDUNDANCY): different cytokines may have the same effect.

- 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.
  - For example : IL6 : induce fever , liver protein synthesis.
- SYNERGY : → 2 cytokines are together secreted and both carry out same function and this lead to increase their activity more than summation.



- Isotypes switching of Ig according to the secreted cytokines

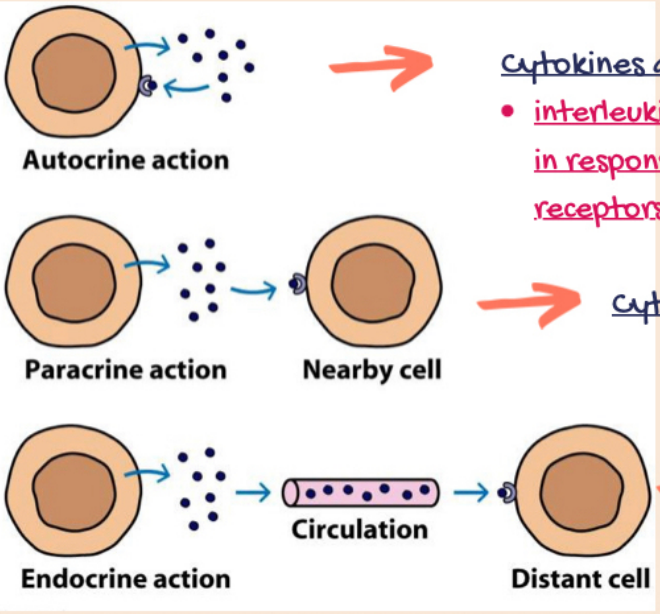
- ANTAGONISM : → 2 cytokines each carry out function antagonise the other.



• Properties of cytokines:

IL8 IL1 TNF IL6

- They can act locally or in a distance :



Cytokines are secreted by the cell and act on the same cell.

- interleukin-1 in monocytes. When interleukin-1 is produced in response to external stimuli, it can bind to cell-surface receptors on the same cell that produced it.

Cytokines secreted by. A cell and affec a nearby cells.

- cytokines at inflammatory site .

cytokines act on a distant cells.

- IL1 secreted at inflammatory site and migrate to brain to induce fever.

- 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.

• Innate vs adaptive cytokines:

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

1) cytokines that produced by innate immune responses :

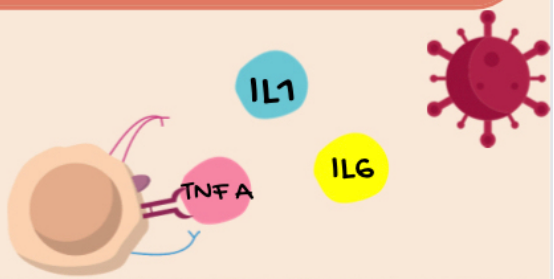
- Definition:

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

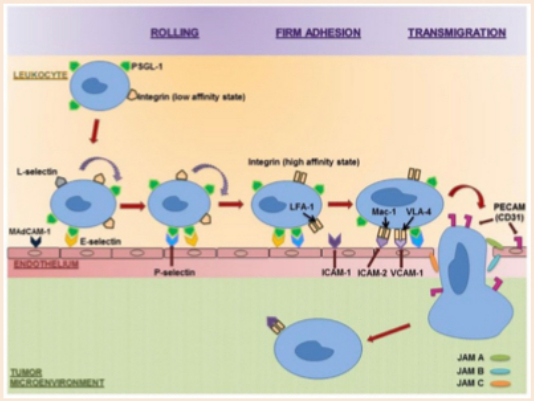
1) cytokines that produced by innate immune responses :

• pro-inflammatory cytokines: (IL1 ,TNF alpha , IL6)

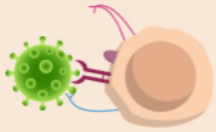
IL-1 function similarly to TNF in that it mediates acute inflammatory responses. It also works synergistically with TNF to enhance inflammation



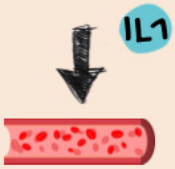
- They are both produced primarily by local activated monocytes, macrophages and by neutrophils.
- They stimulate the synthesis of adhesion factors on endothelial cells and leukocytes that help in cell migration
- they produced in high quantity affecting on hypothalamus to increase prostaglandin syn. causing fever (endogenous pyrogens) (this is inhibited by aspirin) mainly IL 1
- stimulate the production of acute phase proteins from liver mainly IL6



Mechanism of fever :



IL1



Fever

1) Exogenous pyrogens

2) endogenous pyrogens (IL1)

3) circulate to hypothalamus

4) bind receptors and stimulate expression of PGE2

5) reset the thermostat to higher point

6) increase body temperature (fever)

Exogenous pyrogens are substances, which originate outside the body and which are capable of inducing interleukins

Liver :

Acute-phase proteins (APPs) are a class of proteins whose concentrations in blood plasma either increase (positive acute-phase proteins) or decrease (negative acute-phase proteins) in response to inflammation

- Examples:
  1) C reactive protein
  2) mannose binding lectin
  3) complement factor
- Function:

Activation of complement opsonisation

MBL

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1) cytokines that produced by innate immune responses

TA

Bone marrow, endothelium

Human bone marrow stromal cells respond to stimulation by the monokines IL-1 and TNF by producing colony-stimulating factors such as GM-CSF and G-CSF

↓

Neutrophils mobilisation

↓

Phagocytosis

hypothalamus

- Increase body temperature

↓

- decrease bacterial and virus replication by disturbing step in process
- increase antigen processing
- increase specific immune response

Fat , muscle

- protein and energy mobilisation To increase body temperature

↓

dendritic cells

Dendritic cells TNF alpha stimulate migration to lymph nodes and maturation

↓

Initiation of adaptive immune response

TNF alpha

• IL-12 :(secreted by both innate and adaptive cells):

• Notes :

- T helper 2 ▶ Activate B cell
- T heper 1 ▶ Activate T cytotoxic
- Intracellular pathogens which resist phagocytosis inside macrophage and dendritic cells (listeria, mycobacteria, virus)

⏬

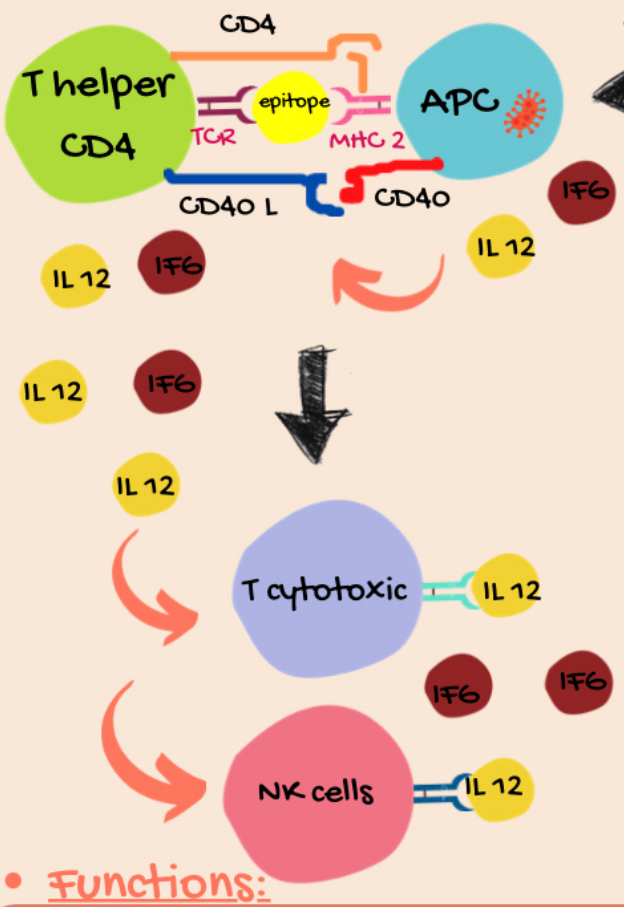
- DC when phagocytise a pathogen secrete Many cytokines include IL 12

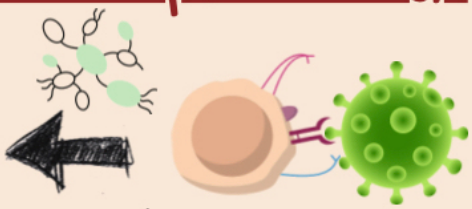
⏬

- IL 12 insuce differentiation of T helper into T helper 1

⏬

- Th1 activate T cytotoxic and help NK cell





1)inflammation and phagocytosis by dendritic cells

migration to closet lymph node (induced by TNF ALPHA)

2)APC (DC for TH1) bind The per and activate it and secrete IL12 for differentiation into TH 1

3) IL12 activate NK cells and T cytotoxic, and kill infected cells

• Functions:

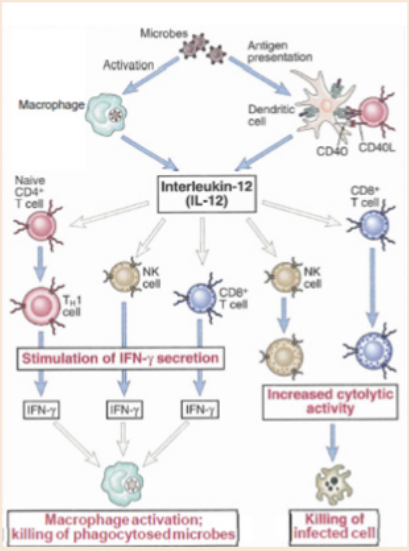
It is an activator CD8 T cells differentiation,

2. TH1 cell differentiation when binding CD4 and APC include intracellular pathogen and CD40 and CD40L ligation

3. NK activation

4. It also stimulates interferon-gamma production from these cells

1) cytokines that produced by innate immune responses :



- Summarisation

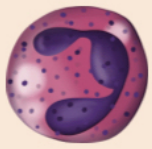
- **chemokine :**
- Definition:

CXC CC CX3C XC

Chemokines, or chemotactic cytokines, are a family of small cytokines or signaling proteins secreted by cells that induce directional movement of leukocytes, as well as other cell types, including endothelial and epithelial cells

- Types :
- homeostatic : → are constitutively produced in certain tissues and are responsible for basal leukocyte migration.
- Inflammatory: → these are formed under pathological conditions (on pro-inflammatory stimuli, such as IL-1, TNF-alpha, LPS, or viruses)

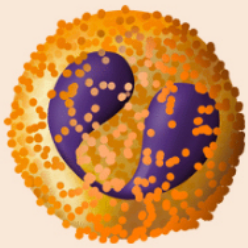
- CXC chemokines → Recruitment of neutrophils



- CC chemokines → Recruitment of macrophage

- and both type for lymphocytes recruitment

- Chemokines are required for the migration of immune cells from sites of infection into draining lymph nodes CC-chemokine receptor 7 (CCR7) • macrophage
- 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

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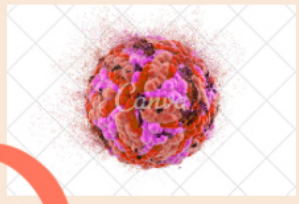
1) cytokines that produced by innate immune responses :

- ## Type 1 interferons:



Interferons:

β

α

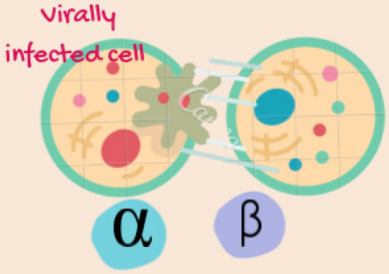
Class 1 :
- 13 subtypes:
- alpha : by macrophage
- beta :by fibroblasts and virally infected cells

Class 2 :
- 1 subtype
- gamma
- for cell mediated immunity

γ

The most powerful stimulus for type I interferons is the first immune reaction against viral infection

- ## class 1 interferons:



Interferons b secreted by infected cell to act on non infected cell to :
- reduce level of protein synthesis
- degrade mRNA

- 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.)
- 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 by increase expression of IL-12
- —and help in activation of CD8 cell in killing virus infected cells
- —Activate NK to act against the virus

- ## IL-6 and IL-10:

IL6 :
- 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 .
- and to differentiate TH to TH17 if TGF beta present

IL-10 (regulatory cytokine) :
- an inhibitor of activated macrophages and dendritic cells and as such, inhibit production of IL-12 and co-stimulator molecules like MHC2 (inhibit TH1, CD8)
- regulates innate immunity and cell-mediated immunity
- IL-10 is produced mainly by Treg, and Th2 cells

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

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

- **Interleukin-2 (IL-2) IL-2 (growth factor)** → is produced by DC and T cells, it is a growth factor for Th1, Th2 and CD8 - lymphocytes upon activation (3rd signal)

IL 2

- **Interleukin-4 (IL-4 :)** → a B cell growth major stimulus for production of IgE in B cells It also antagonizes the effects of interferon-gamma and thus inhibits cell-mediated immunity.
- IL-4 is produced mainly by Th2 cells and mast cells.

note :
- mast cell for allergy require IgE
- Th2 activate B cells to produce IgE

IL4

- **Interleukin-5 (IL-5) :** → a growth and activating factor for eosinophils as a defense against helminths .
- It also stimulates the proliferation and differentiation of antigen-activated B-lymphocytes
- IL-5 is produced mainly by Th2 cells.

IL13

IL5

- **Interleukin-13 (IL-13) :** → IL-13 by Th2 cells act on B cells

- **Interferon-gamma (IFN-gamma) :** → Type II interferon is produced 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

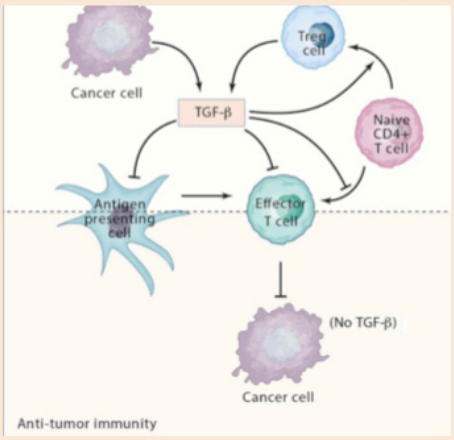
IFN-gamma inhibits the proliferation of Th2 cells; —stimulates the production of IgG subclasses that activate the complement pathway and promote opsonization

IF6

TGF B

- **Transforming growth factor-beta (TGF-beta):** →
  - TGF-beta is produced by T-reg
  - The generation of some regulatory T cells requires the cytokine TGF-β. And IL-2
  - TGF beta with IL-6 lead to differentiation of Th17
  - regulatory cytokine functions to inhibit the proliferation and effector function of T-lymphocytes; inhibit the proliferation of B-lymphocytes; and inhibits macrophage function

Note :
cytokines that activate cell type also secreted by the same type and inhibit other immune responses (th1 & th2)



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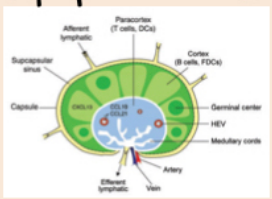
2) Cytokines that produced by Adaptive Immune Responses (Humoral Immunity and Cell-Mediated Immunity)

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

- Lymphotoxin (LT)



LT

- 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.

- IL - 17 :

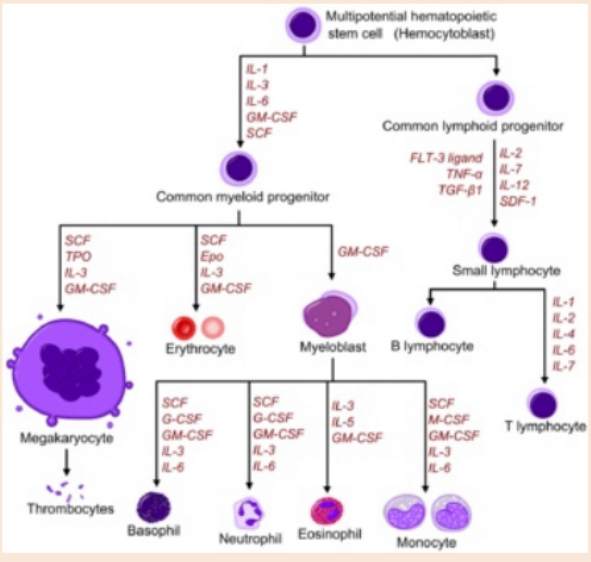
IL17

- The TH17 subset is primarily produce IL-17 that involved in
- •recruiting neutrophils and macrophages to site of infection,
- •inducing inflammation

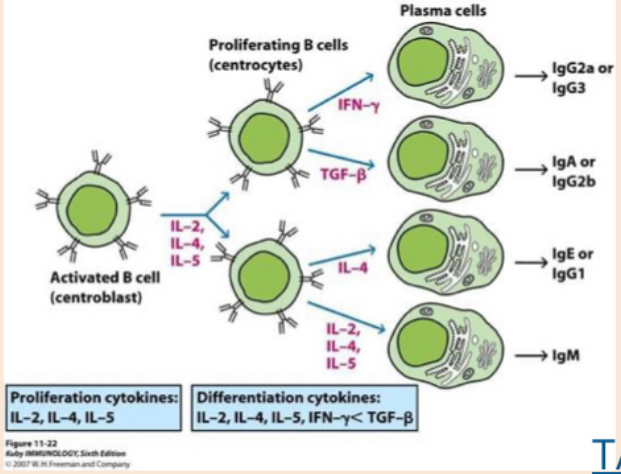
3) Cytokines that Stimulate Hematopoiesis :

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

- 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)
- Stem cell factor. Stem cell factor makes stem cells in the bone marrow more responsive to the various CSFs
- Interleukin-3 and IL-7, supports the growth of multi-lineage bone marrow stem cells.



- Cytokines and Ab differentiation:



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• Cytokines 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)

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

• Autoimmune disease and cytokines:

- the TH1 cytokines, which secrete interferon (IFN)-γ, and the TH2 cells, which secrete IL-4, IL-5, IL-10.
- •autoimmune disease is associated with the activation of TH1cytokines, which activate macrophages and drive an inflammatory immune response. In animal models of experimentally induced autoimmune disease, the relative activation of the TH1 is more than TH2 subsets of T lymphocytes .TH2 response that confers protection against disease can be manipulated by cytokines immunotherapy
- • The preferential activation of TH 1or TH2 cells can be achieved by direct manipulation of the cytokine environment or by administering antigen by particular routes, for example by feeding

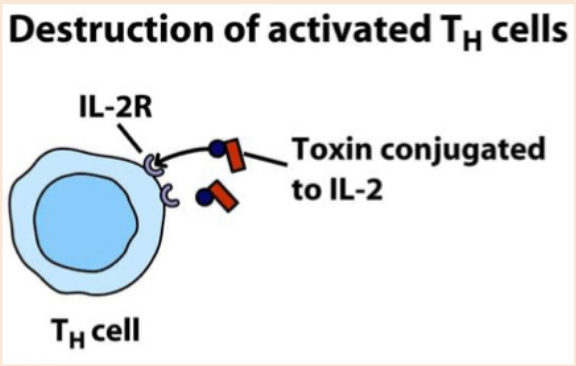
- Immune modulation aims to alter the balance between different subsets of responding T cellssuch that helpful responses are promoted and damaging responses are suppressed. As a therapy for autoimmunity (INCREASE TH2 RESPONSE) or in allergy (increase in TH1) it has the advantage that one might not need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

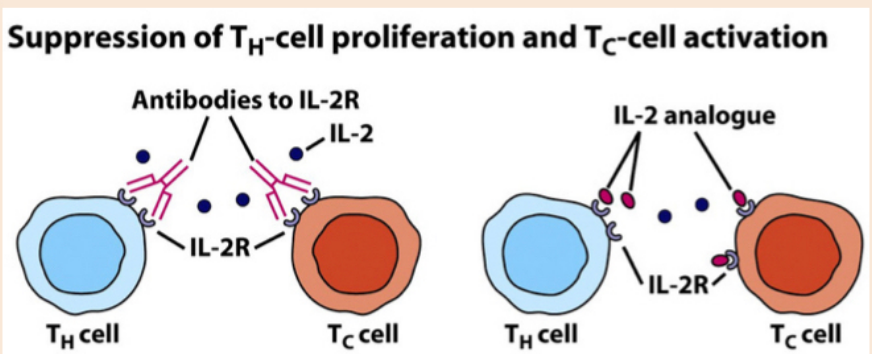
• cytokines as therapy:

1) suppression of Th & Tc in outdo immune disease :

- blocking Ab against IL2 R or analogue of IL2 that bind its receptor

2) using IL2 to activate lymphocytes to attack a cancer patients.





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78) Global T cell growth Factor

Select one:

a) IL-4
b) IL-10
c) Interferon-gamma
d) IL-2
e) Tumor necrosis factor beta

101) Which combinations of cytokines most influence whether at CD4+ T cell becomes a TH1 or TH2? Select one:

a. IL-4 and IL-5.

b. IL-8 and IFN-gamma.

C. IL-4 and IL-12.

d. IL-17 and IFN-beta

e. IL-2 and IL-5

37) Promotes lgE synthesis

Select one:

a) IL-4
b) IL-10
c) Interferon-gamma
d) IL-2
e) Tumor necrosis factor beta

55) Activate immune action against worms

Select one:

a) IL-5
b) IL-10
c) Interferon-gamma
d) IL-2
e) Tumor necrosis factor beta

- MCQ :

39) Which of the following cytokines is associated with inducing fever?

Select one:

a) IL-1
b) IL-2
c) IL-5
d) IL-10
e) IL-5

56) Anti- fever Aspirin inhibits

Select one:

a) IL-1 and TNF
b) IL-2 and TNF
c) IL-8 and IL-1
d) T cells
e) B Cells