Cytokines

Definition: secreted, low-molecular-weight proteins that regulate the nature, intensity and duration of the immune response by exerting a variety of effects on lymphocytes and/or other cells.

- Cytokines bind to specific **receptors** on target cells.
  - **Lymphokines** produced only by lymphocytes.
  - **Monokines** secreted by monocytes and macrophages.
  - **Interleukin** produced by some leukocytes.
  - **Chemokines**, they are also considered cytokines promote chemotaxis.

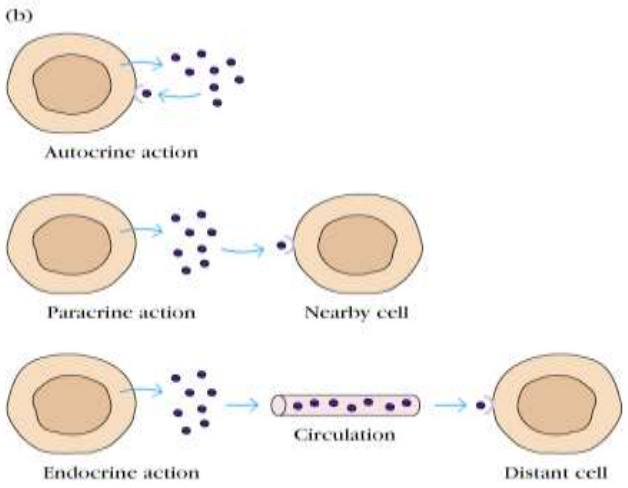
- Cytokines regulate the intensity and duration of the immune response by **stimulating or inhibiting the activation, proliferation, and/or differentiation** of various cells and by regulating their secretion of Abs or other cytokines.
- The cytokines secreted by a single **T lymphocyte following Ag activation** can influence the activity of various other cells involved in the immune response ie. B cells, Tc cells, NK cells, MOs, hematopoietic cells, ect.

Regulation of secretion

1:- **Autocrine action** by binding to receptor on the membrane of the same cell that secreted it.

2:- **Paracrine action** binding to receptors on a target cell in close proximity to the producer cell.

3:- **Endocrine activity** by traveling through circulation and acting on target cells in distant parts of the body.



Autocrine (same cell),

Paracrine (close proximity)

Endocrine (long distance)

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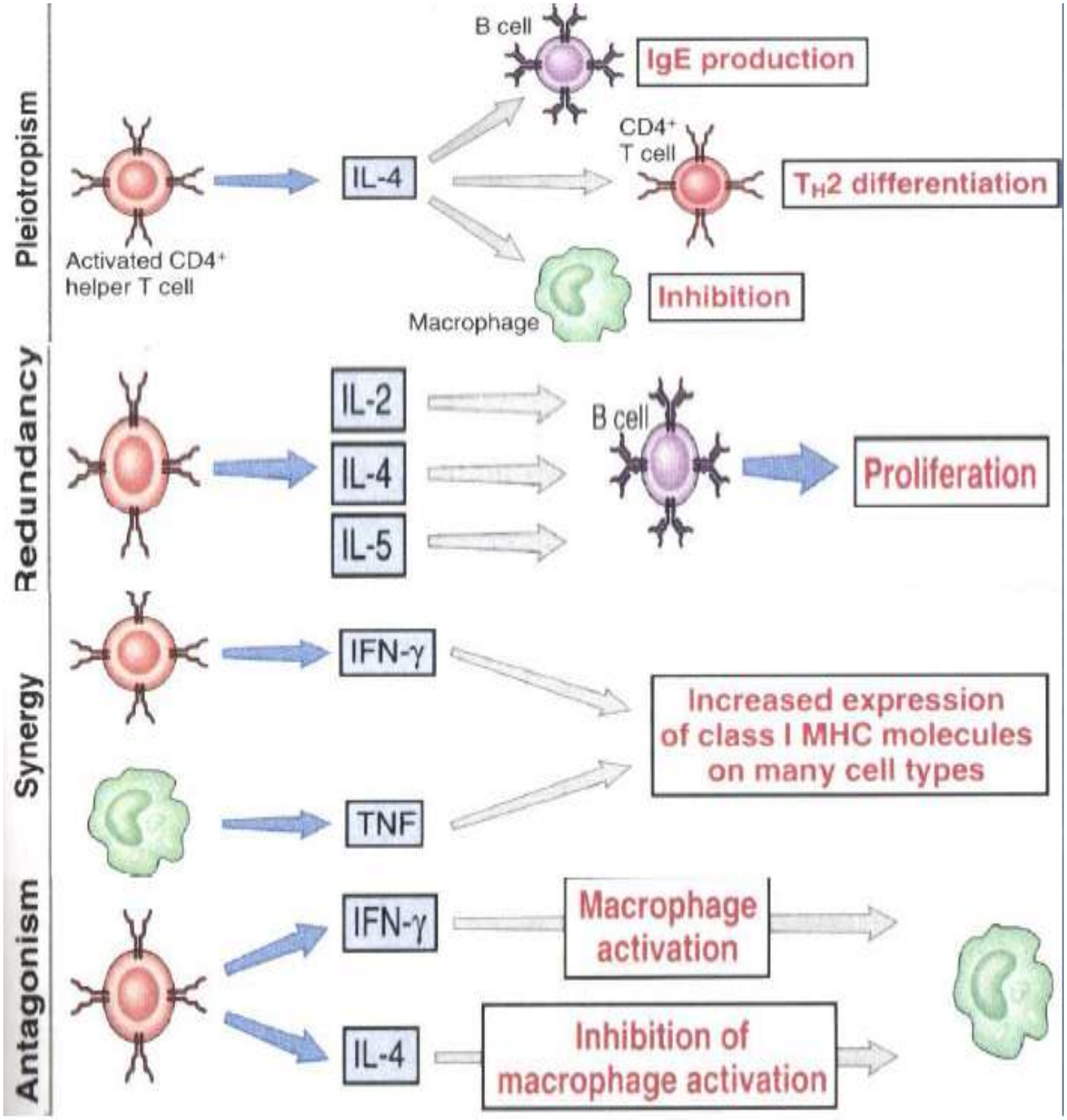
Cytokines can regulate cellular activity in a coordinated interactive way due to the following attributes:

1:- **Pleiotrophy**- one cytokine has many different functions.

2:- **Redundancy**- several different cytokines can mediate the same or similar functions.

3:- **Synergism**- occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of individual cytokines.

4:- **Antagonism**-the effects of one cytokine inhibits or offsets the effects of another cytokine.



Function of Cytokines

- Cytokines generally function as **intercellular messenger molecules** that evoke particular **biological activities** after binding to a receptor on a responsive target cell.
- Although a variety of cells can secrete cytokines, the two principal producers are the **Th cell and the macrophage.**

The main biological activities of cytokines include.

- Both cellular and humoral immune responses,
- Induction of inflammatory responses,
- Regulation of hematopoiesis,
- Control of cellular proliferation and differentiation,
- Induction of wound healing.

General properties of cytokines

- Not stored
- Have local and systemic effects
- One stimulates secretion of other
- High receptor affinity
- Change the level of gene transcription

Cytokine receptors

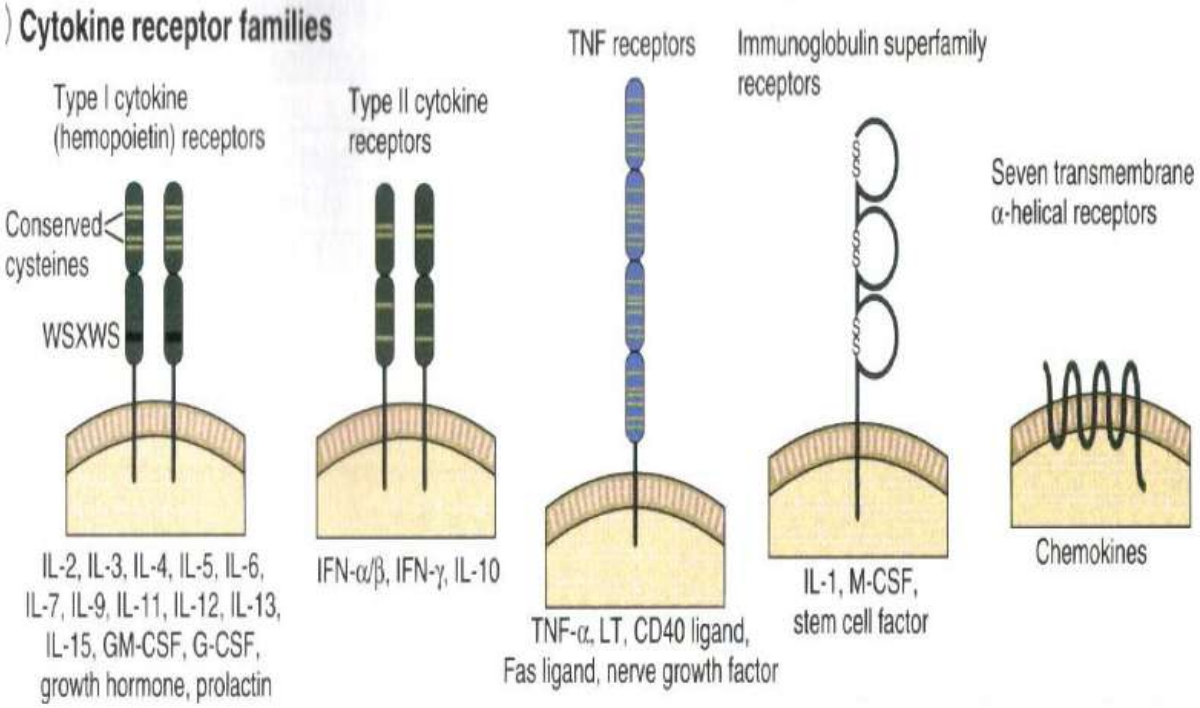
Cytokines exert their biological effects through specific receptors expressed on the membrane of responsive target cells.

There are 5 families of receptor proteins:

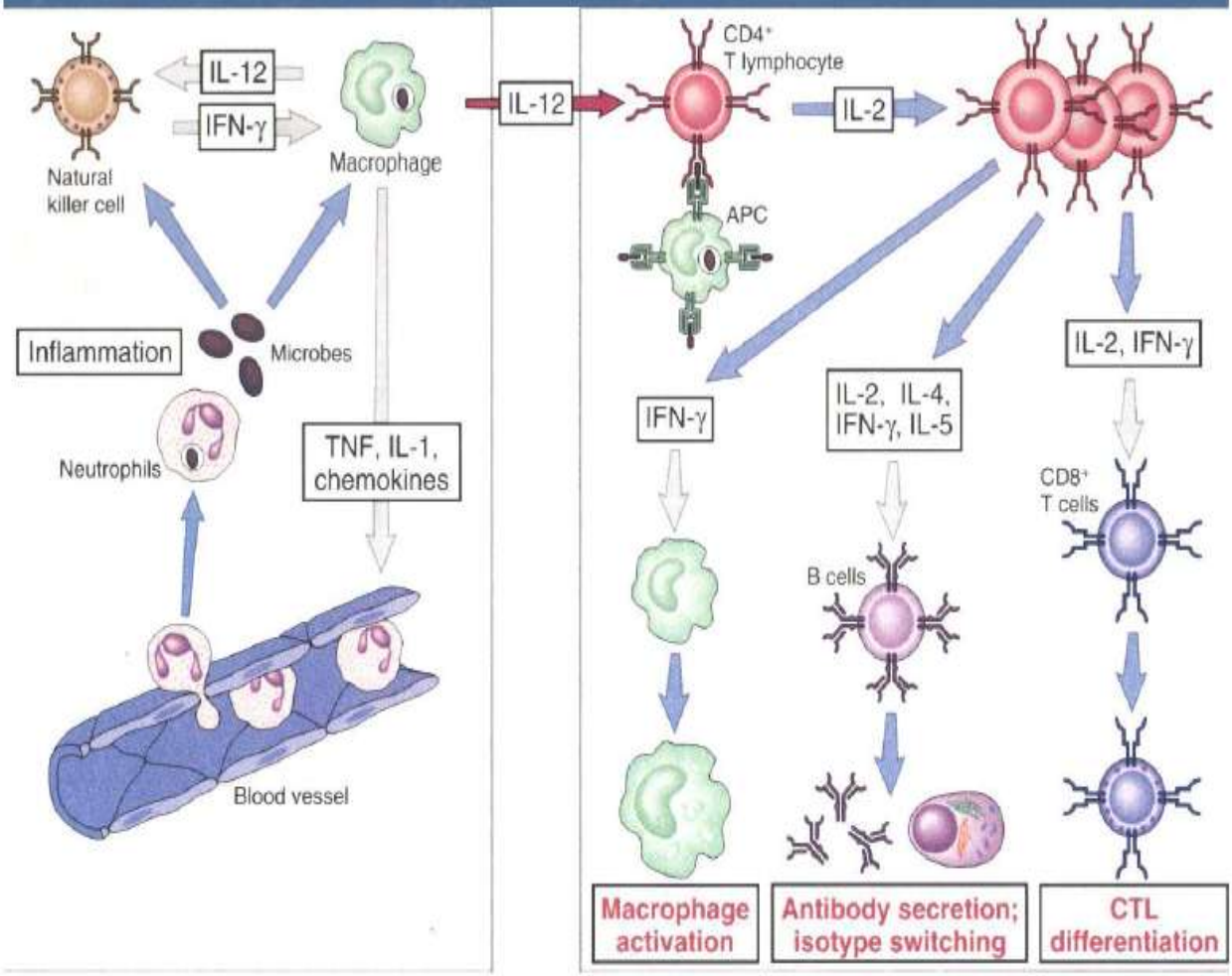
1. Ig superfamily receptors (**IL1, M-CSF**)
2. Hematopoietin receptor family (class I cytokine receptor family) * most belong to this group (**IL2,3,4,5,6,7,9,11,12,13,15, GM-CSF, G-CSF**)
3. Interferon receptor family (class II cytokine receptor family) (**IFN**α, β, γ)
4. TNF receptor family (**TNF**α,β **Fas**)
5. Chemokine receptor family (**IL8, rantes**)

• All cytokine receptors have at least one extracellular domain, a membrane spanning domain, and a cytoplasmic tail.

Cytokine receptor families



Innate and adaptive immunity



Cytokine classification

- innate immunity cytokines
- adaptive immunity cytokines
- hematopoietic cytokines
- immunosuppressive cytokines

Innate immunity cytokines

- Secreted by macrophages
- Stimmulated by LPS, nucleic acids, immunocomplexes those are:
- **TNF-α, IL-1, IL-12, If**α, β.
- IL-6, IL-8, IL-18, IL-23, IL-27,…

Other innate immunity cytokines

- **IL-10**

Inhibits IL-12 and TNF-α production, as well as MHC –class II (immunosuppression)

- **IL-6**

Stimulates acute-phase proteins and lymphocyte T/B growth (adaptive immunity)

- **IL-15**

Stimulates NK cell proliferation

- **IL-8, IL-18, IL-23, IL-27**

Adaptive immunity cytokines

- Secreted by T-lymphocytes
- Stimulated by antigenes

Those are:

- **IL-2, IL-4, IL-5, IF-γ**
- IL-6, IL-11, IL-13, IL-17,…

Immunosuppression cytokines

- produced by CD4+T-ly, macrophages
- Suppress macrophages and Th1

Those are:

- **TGF-β, IL-10**
- IL-4, IL-13,…

TGF-ß

- Inhibits lymphocyte T and macrophages
- Stimulates IgA secretion
- Stimulates production of extracellular
- matrix (healing and reparation)

IL-10

- Inhibits macrophages

IL-4 and IL-13

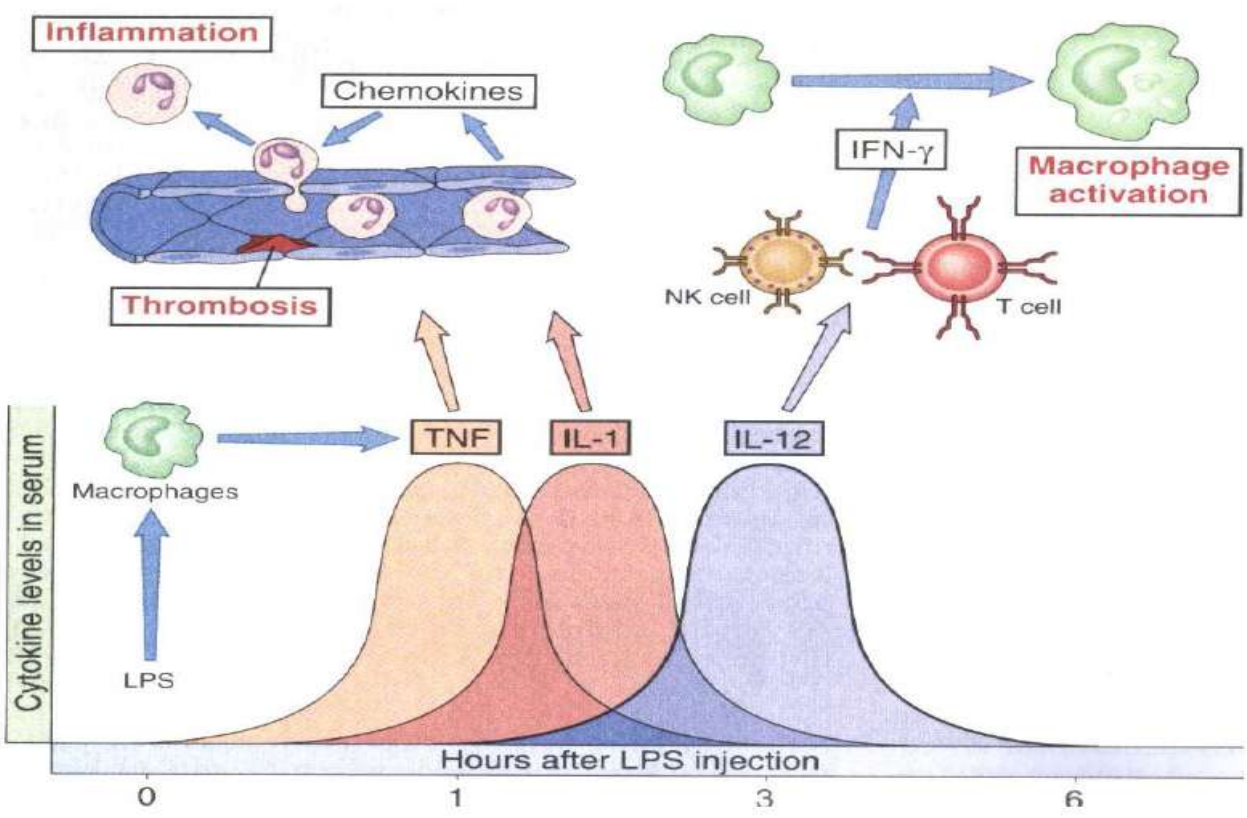
- Inhibit cell-mediated and stimulate humoral immunity.

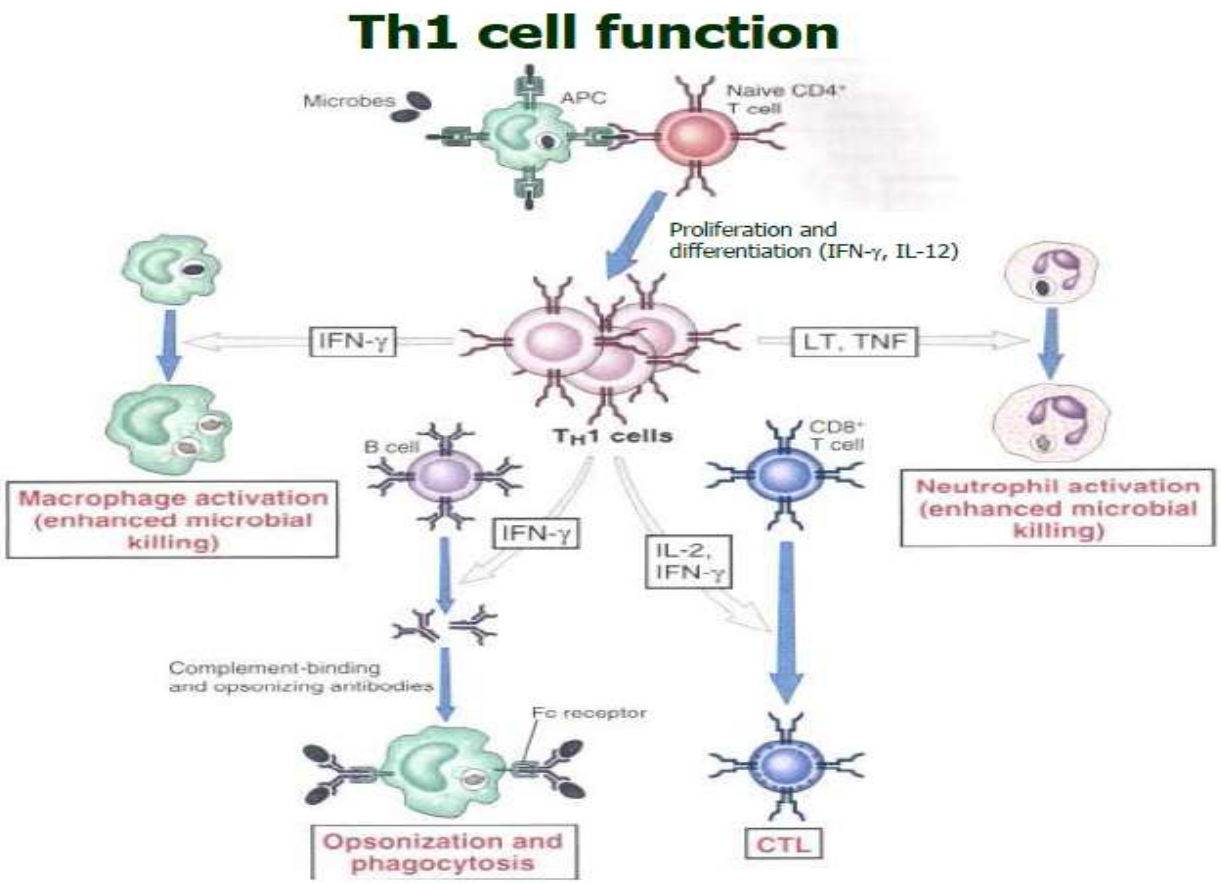
Hematopoietic cytokines

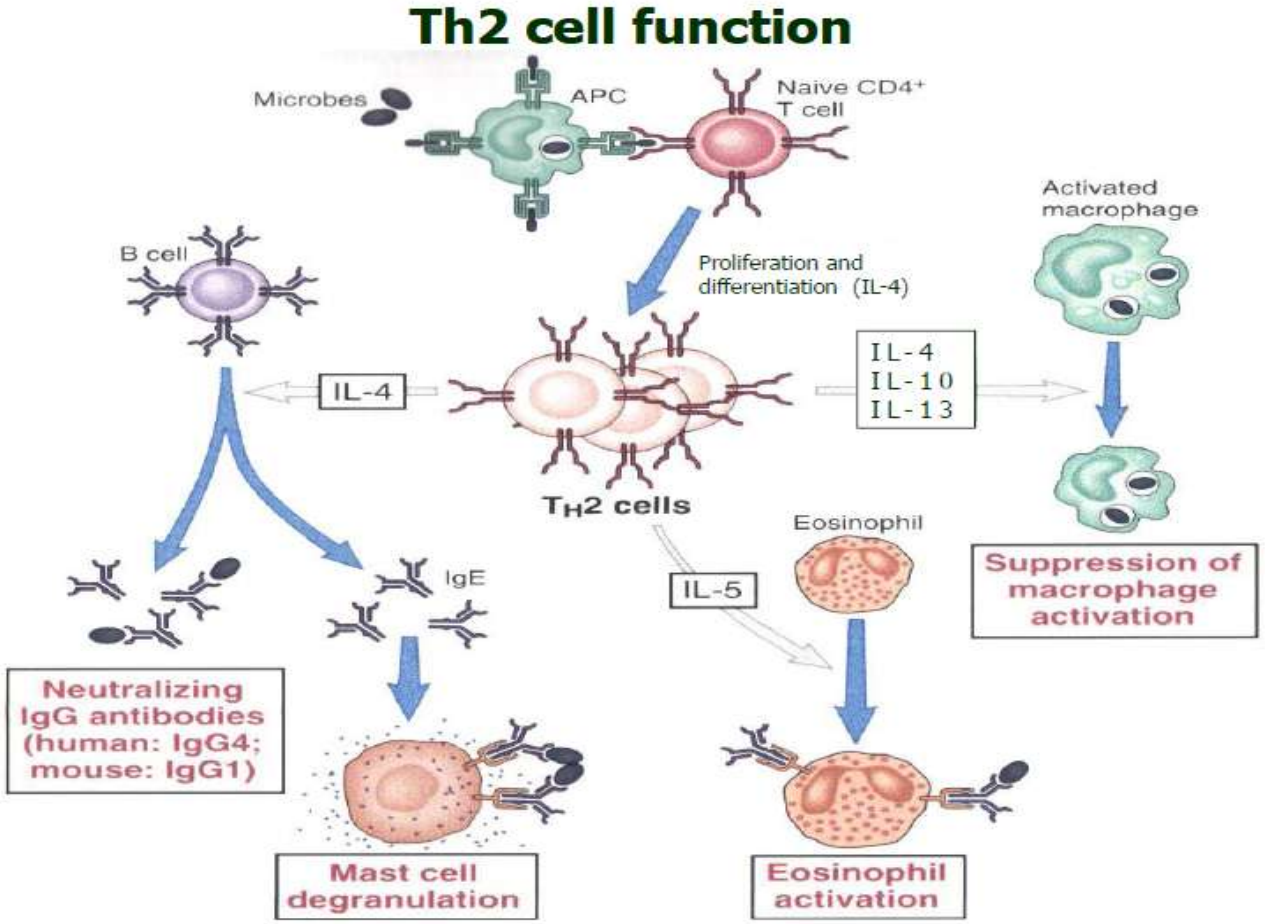
Produced by bone marrow cells and leukocytes

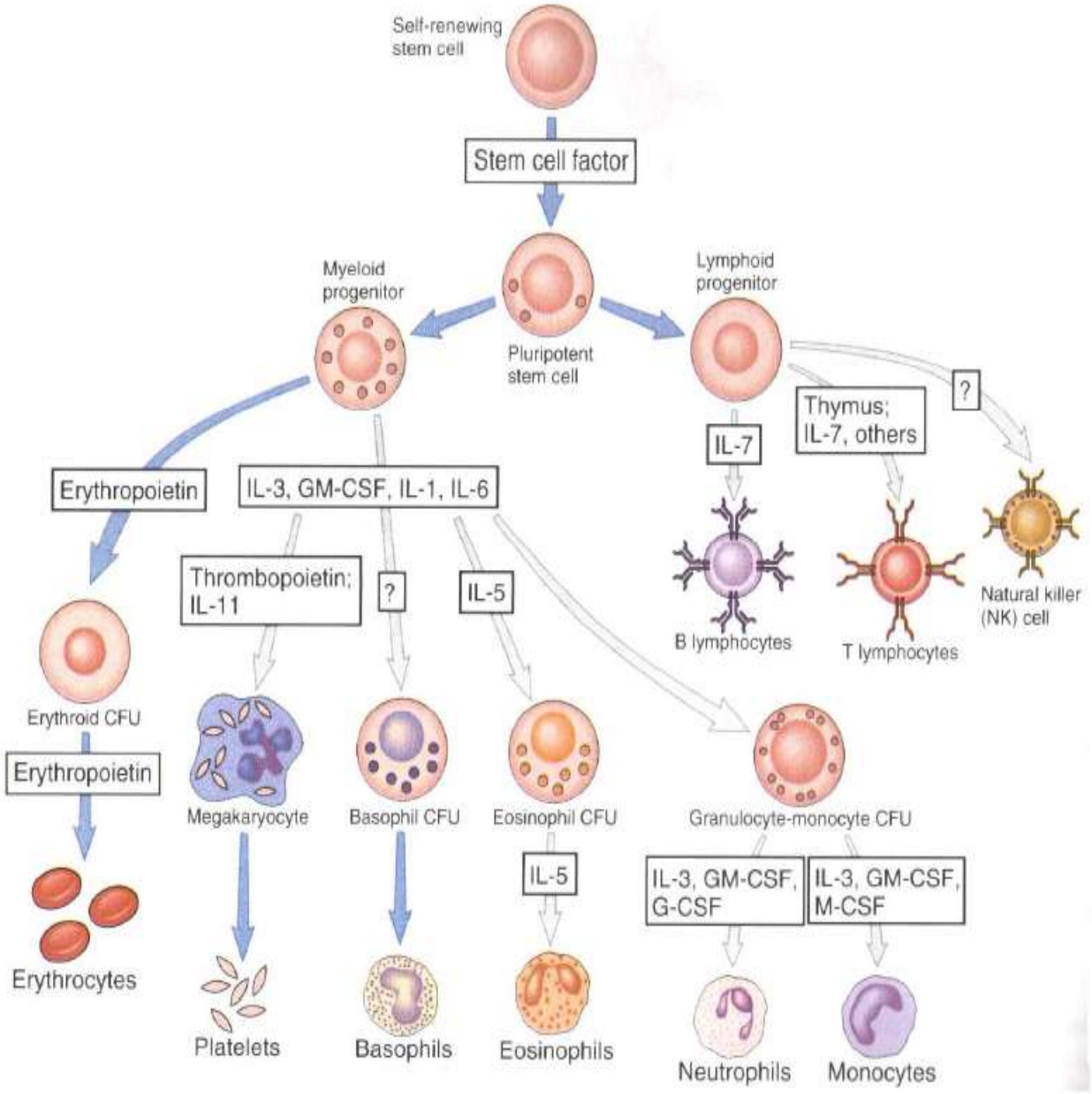
Those are:

- **CSF**
- **IL-7**
- **IL-3 (multi CSF)**
- **IL-1, IL-5, IL-6, erythropoietin, …**




Th1 cell function
Microbes
APC
Naive CD4+ T cell
Proliferation and differentiation (IFN-γ, IL-12)
IFN-γ
LT, TNF
TH1 cells
B cell
CD8+ T cell
Macrophage activation (enhanced microbial killing)
Neutrophil activation (enhanced microbial killing)
IFN-γ
IL-2, IFN-γ
Complement-binding and opsonizing antibodies
Fc receptor
Opsonization and phagocytosis
CTL


Th2 cell function
Microbes
APC
Naive CD4+ T cell
Activated macrophage
B cell
Proliferation and differentiation (IL-4)
IL-4
IL-4
IL-10
IL-13
TH2 cells
Eosinophil
IgE
IL-5
Suppression of macrophage activation
Neutralizing IgG antibodies (human: IgG4; mouse: IgG1)
Mast cell degranulation
Eosinophil activation


Self-renewing stem cell
Stem cell factor
Myeloid progenitor
Pluripotent stem cell
Lymphoid progenitor
Erythropoietin
IL-3, GM-CSF, IL-1, IL-6
IL-7
Thymus; IL-7, others
?
Thrombopoietin; IL-11
?
IL-5
B lymphocytes
T lymphocytes
Natural killer (NK) cell
Erythroid CFU
Erythropoietin
Megakaryocyte
Basophil CFU
Eosinophil CFU
Granulocyte-monocyte CFU
IL-5
IL-3, GM-CSF, G-CSF
IL-3, GM-CSF, M-CSF
Erythrocytes
Platelets
Basophils
Eosinophils
Neutrophils
Monocytes