CYTOKINES AND INTERFERONS.

Learning objectives:

- Classification and naming of cytokines.
- Properties and function of cytokines.
- Mode of action in immune response and regulation.
- Clinical applications of cytokines

What are Cytokines ?

- Low-molecular-weight regulatory proteins secreted by white blood cells and various other cells in response to a number of stimuli.

- Soluble proteins secreted by one cell that can alter the behaviour or properties of the same cell or of another cell.

What are Cytokines ?

- Secreted molecules that regulate the intensity and duration of the immune response by exerting a variety of effects on lymphocytes and other immune cells

- Cytokines = messengers of the immune system, just as hormones = messengers of the endocrine system

Classification of cytokines.

- classified into four groups based on structure:

➢ Haematopoietin family (e.g. IL-2, IL-4)

➢ Inteferon family (e.g. interferon-beta)

➢ Tumor necrosis factor family (e.g. TNF-alpha) and

➢ Chemokine family (e.g., IL-8, MCP-1)

Cytokines by any other name….

Lymphokines – cytokines secreted by lymphocytes

Monokines – cytokines secreted by monocytes/macrophages

Interleukins – secreted by leukocytes, act on leukocytes

Chemokines – cytokines that are chemotactic and play important roles in inflammation

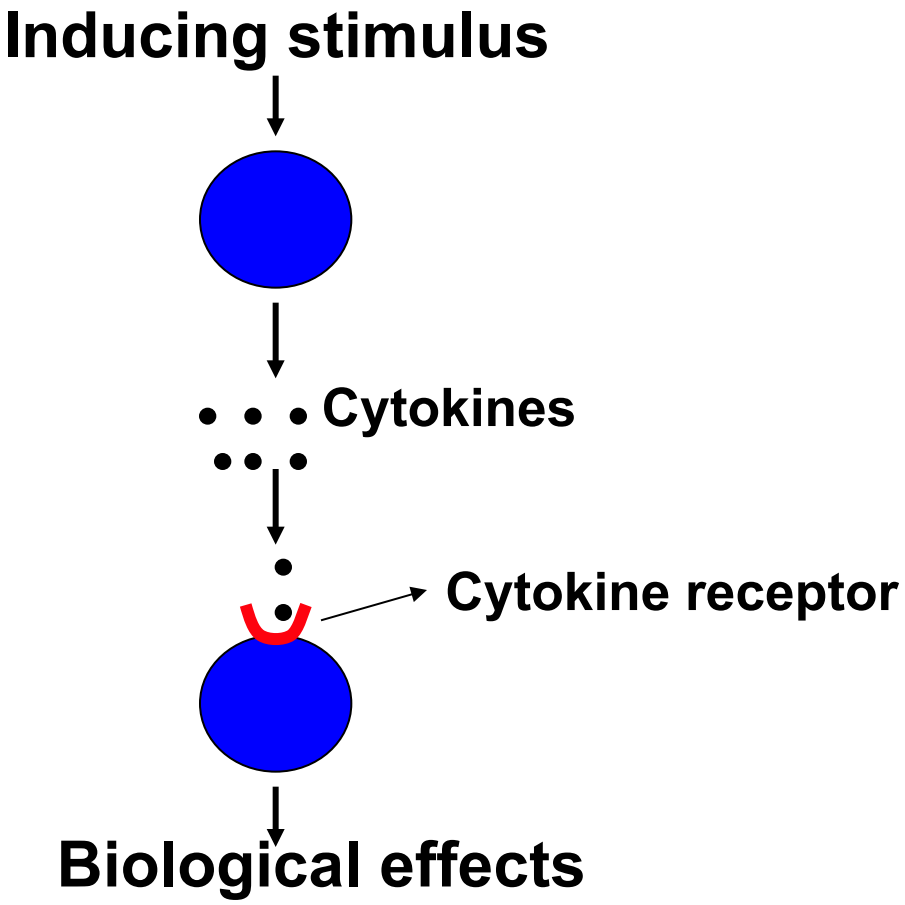
Interferons, CSFs, tumor necrosis factors.

Properties of Cytokines

- autocrine (binds receptors on the same cell that secreted the cytokine),
- paracrine (binds to receptors on a nearby cell, a variation on paracrine is "juxtacrine" meaning binds a neighboring cell) or in some cases,
- endocrine fashion (binds to receptors on distant target cell).

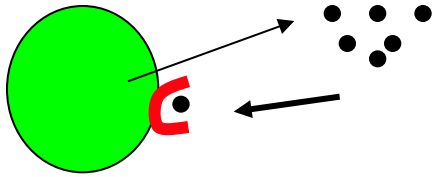
- Pleiotropy: a cytokine may have different biological effects on different target cell.
- Redundancy: two or more cytokines may have the same effect on a target cell (e.g. IL-2 and IL-15).
- Synergy: additive effect of cytokines used
- Antagonism: negate effect of another cytokine.
- cascade effect: stimulate other cytokines, forming cytokine networks.

Autocrine property of cytokines

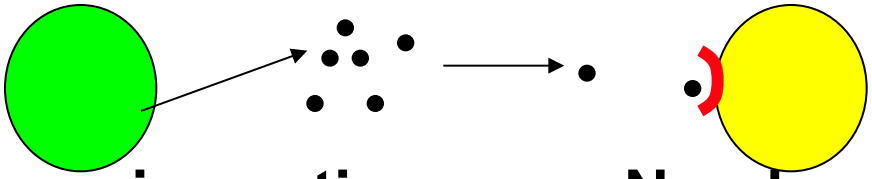


Cytokines bind to specific receptors on target cell membranes, trigger signal-transduction pathways and alter gene expression

Properties of Cytokines

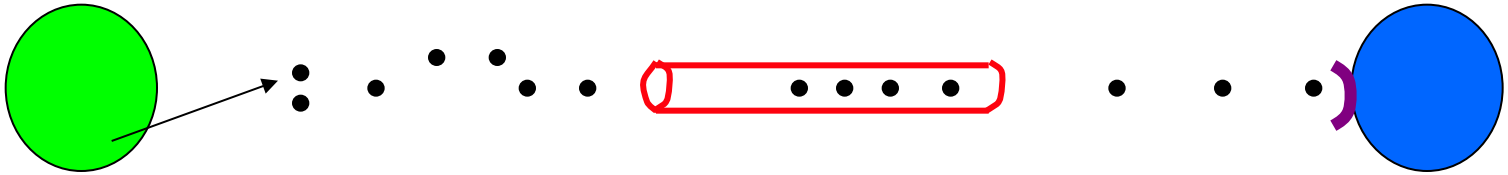


Autocrine action



Paracrine action

Nearby cell



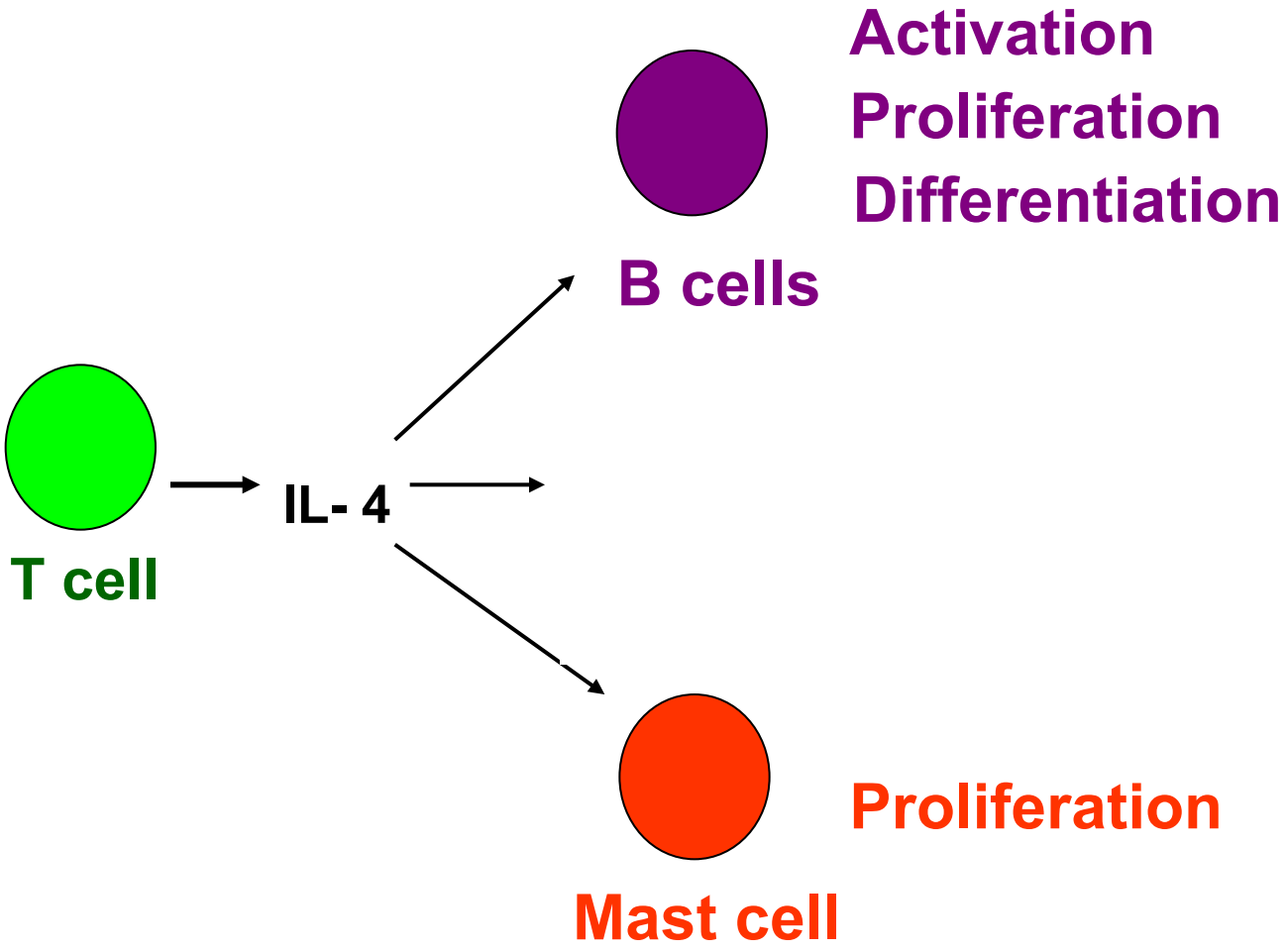
Endocrine action

Circulation

Distant cell

Pleiotropy

A single cytokine can have different effects

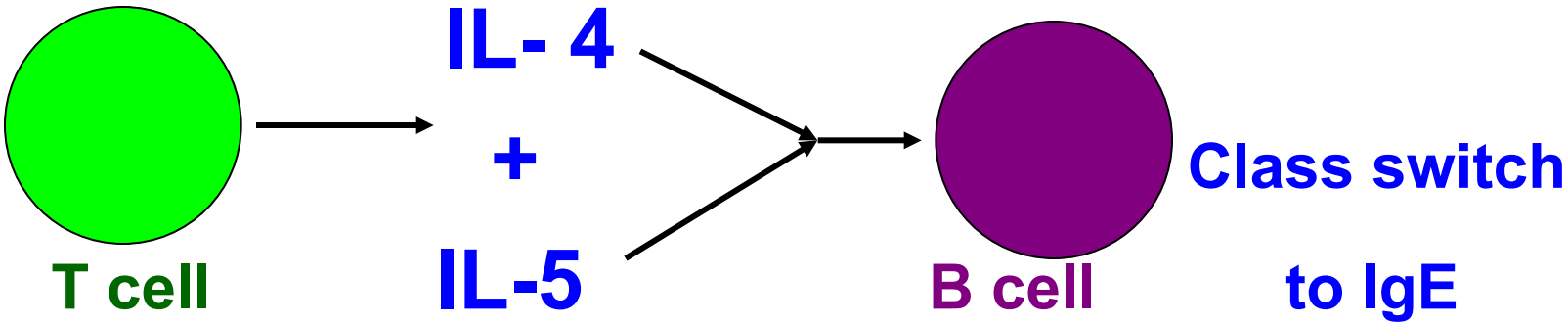


Redundancy

- ***Different cytokines can have the same effect (redundancy- e.g., IL-2 and IL-15)***

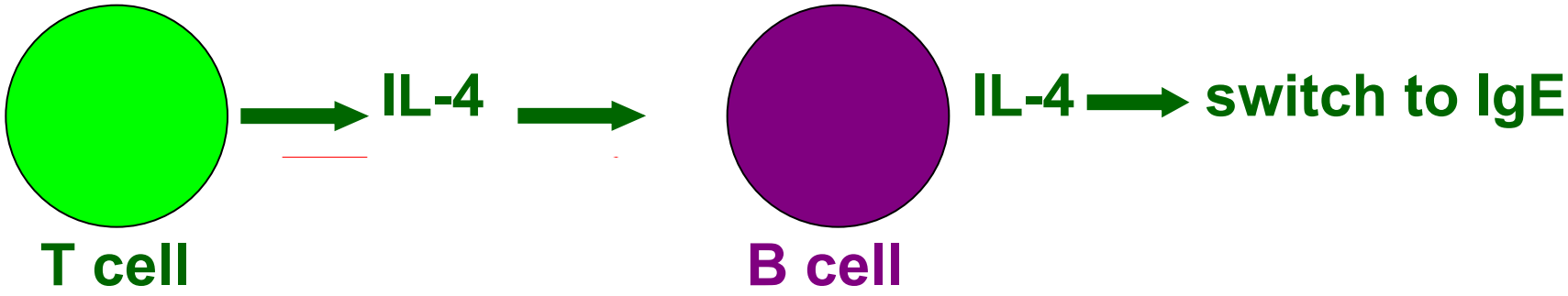
Synergy

Cytokines can work in synergy

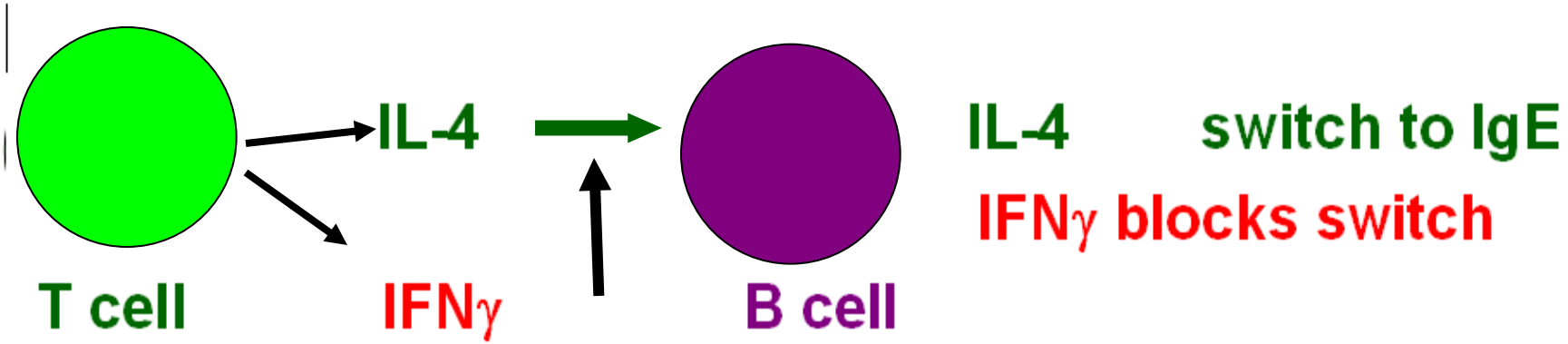


Inhibition

The effect of one cytokine can inhibit another

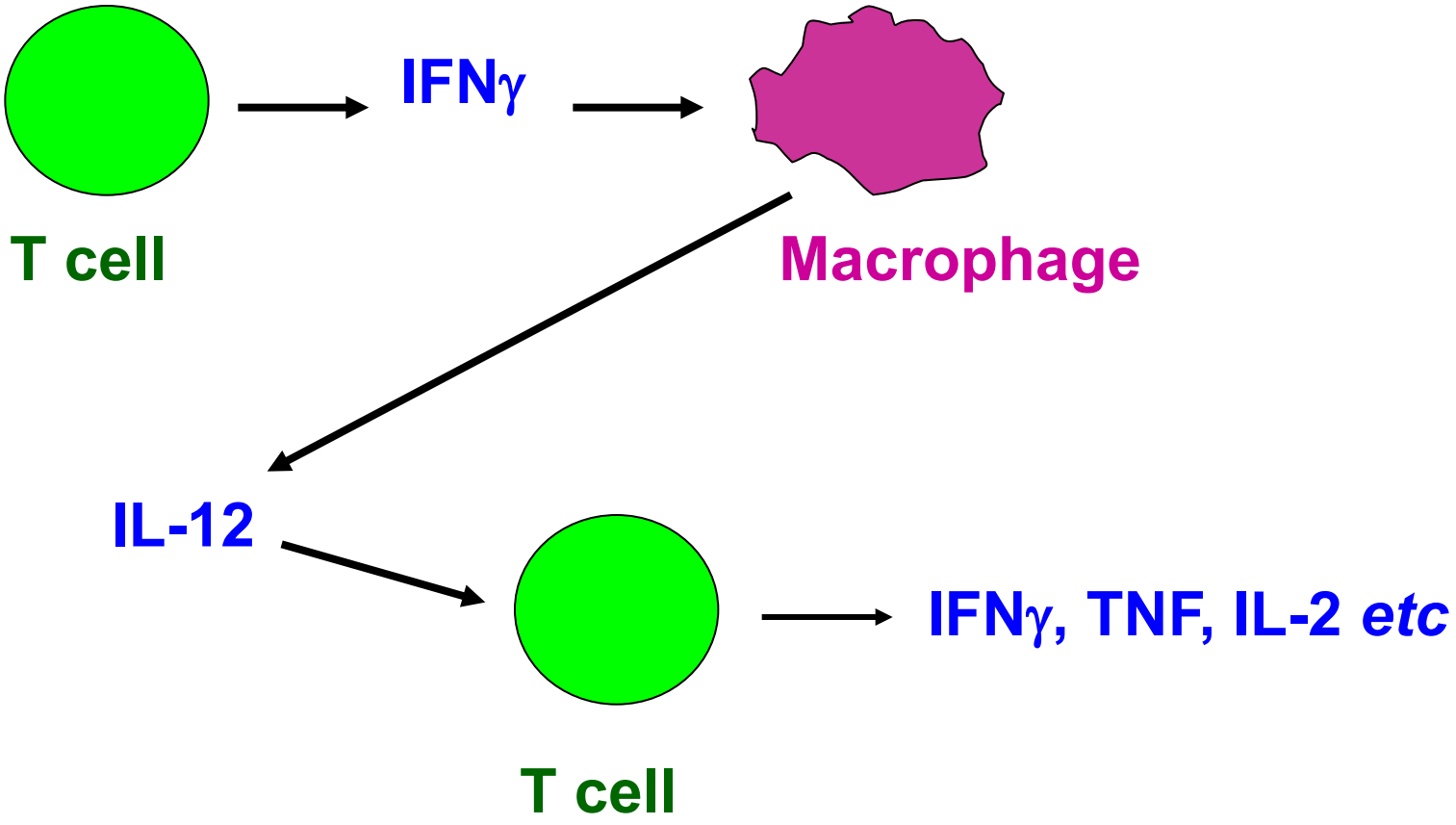


The effect of one cytokine can inhibit another



Cascade

Cytokines can network



Cytokines as intercellular messenger molecules

1. **Development of cellular & humoral responses**
1. **Induction of inflammatory responses**
2. **Regulation of hematopoiesis**
3. **Cellular proliferation and differentiation**
4. **Growth inhibition, apoptosis**
5. **Wound healing**

- Cytokines, despite being **antigen nonspecific:**

  regulate the intensity and duration of the inflammatory/immune response;

  by stimulating/inhibiting:

  - activation,
  - proliferation and/or differentiation and
  - migration of multiple cell types and
  - by regulating the synthesis and secretion of immunoglobulins.

How do nonspecific cytokines maintain the specificity of the immune response?

- Limited production of the cytokine: often cytokines are only made following some stimulus, for example

  – a macrophage phagocytosing bacteria,

  – a T cell engaging the T cell antigen receptor, or

  – some other cell-cell or pathogen-cell contacts.

- Limited radius of effectiveness, i.e., only those cells in physical contact with or in the immediate vicinity of the cytokine-secreting cell will be exposed to an effective concentration of the cytokine.

- Short half lives mean that cytokines can only act for a limited period of time.

- Regulation of cytokine receptor expression. For example, only lymphocytes which have interacted with antigen may express particular cytokine receptors.

- Antagonism, includes shedding receptors which may occupy a cytokine in solution preventing it from binding another receptor. Examples of shed receptors becoming antagonists are IL-1, IL-2, IL-4, -6, and -7, IFN-α, -γ, TNF-β, and leukemia inhibitory factor (LIF).

Cytokine secretion by Th1 and Th2 cells

- T_H cells (CD4+ lymphocytes) can be divided into Th1 and Th2 subsets, each with distinct cytokine secretion profiles.
- The Th1 subset is involved in response to intracellular pathogens including the production of opsonizing antibodies.
- Th1 cytokines promote the differentiation of CD8+ cells to become cytotoxic

- The Th2 subset mediates the responses to extra cellular pathogens, including

➢ eosinophil activation and promoting production of IgM and IgE and

➢ non-complement-activating IgG isotypes,

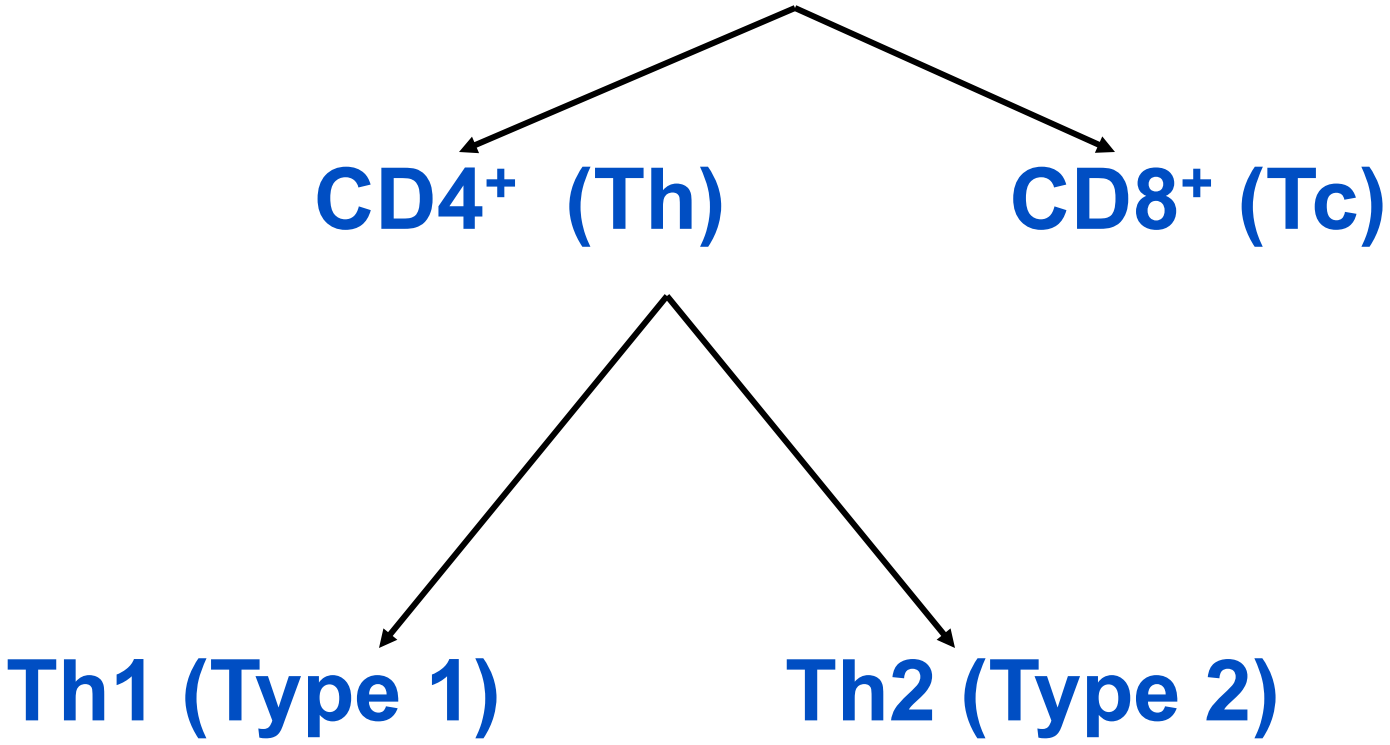
much of which contributes to allergic reactions.

- Cytokines produced by Th1 and Th2 cells exhibit cross-regulation.

➢ IFN-γ inhibits Th2 proliferation while IL-10 indirectly (by acting on antigen presenting cells) downregulates IFN-γ and IL-2 production by Th1 cells (required for Th1 proliferation).

➢ IL-4 directly antagonizes IFN-γ activity.

T cells



Th1 and Th2 cells

Th1: IFNγ, TNFβ, TNFα, IL-2

Mϕ activation, CTL activation, DTH → CMI

Th2: IL-4, IL-5, IL-9, IL-10, IL-13

Most IgG subclasses

IgE

IgA (mucosal immunity)

Eosinophil stimulation

} **Humoral immunity**

Cytokine receptors.

- Based on conserved structural features:

i. Class I, or hematopoietin receptor family

ii. Class II (IFN/IL-10) cytokine receptor family

iii. Tumor necrosis factor receptor superfamily (TNFRSF), the IL-1 receptor family.

iv. The TGF-β receptor family

v. The chemokine receptor family.

Therapeutic Uses of Cytokines

1) Interferon used in treatment of viral diseases, cancer

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

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

4) GM-CSF induces increase in white cell count, it is used:

a- To restore leukocytic count after cytotoxic chemotherapy induced neutropenia

b- After bone marrow transplantation

C- To correct AIDS-associated leukopenia

Therapeutic Uses of Cytokines

5) Anti-cytokines antibodies in management of autoimmune diseases and transplant rejection:
   a- Anti-TNF in treatment rheumatoid arthritis
   b- Anti-IL2R to reduce graft rejection

6) Anti-TNF antibodies in treating septic shock

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

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