Cytokines:

In order to mount and coordinate an effective immune response, a mechanism by which lymphocytes, inflammatory cells and haematopoietic cells can communicate with each other is required. Cytokines perform this function. **Cytokines** are a large, diverse family of **small proteins** or **glycoproteins** (usually smaller than 30 kDa). Although initially described for their immunomodulatory capabilities, additional roles separate from the immune system in developmental processes are also documented, such as cell differentiation and directed migration. Influencing both innate and adaptive immune responses, the two principal producers of cytokines are **helper T cells** (Th cells) and **macrophages**, although they can be transiently induced and secreted by virtually all nucleated cells.

Cytokine is a general name; other names include **lymphokine** (cytokines made by lymphocytes), **monokine** (cytokines made by monocytes), **chemokine** (cytokines with chemotactic activities), and **interleukin** (cytokines made by one leukocyte and acting on other leukocytes).

The downstream effects of a particular cytokine occurs through its high-affinity binding of its **receptor** expressed on the surface of a target cell. This **action** may occur in an **autocrine** (acts on same cell), **paracrine** (acts on nearby cell) or **endocrine** (acts on distant cell; not the normal manner for cytokine responses) manner. Receptor engagement triggers intracellular signalling cascades leading to altered gene expression in the target cell, which lead to a biological effect (Figure - 1). Differentiation, proliferation and activation of the target cell are all effects which can be detected after cytokine stimulation.

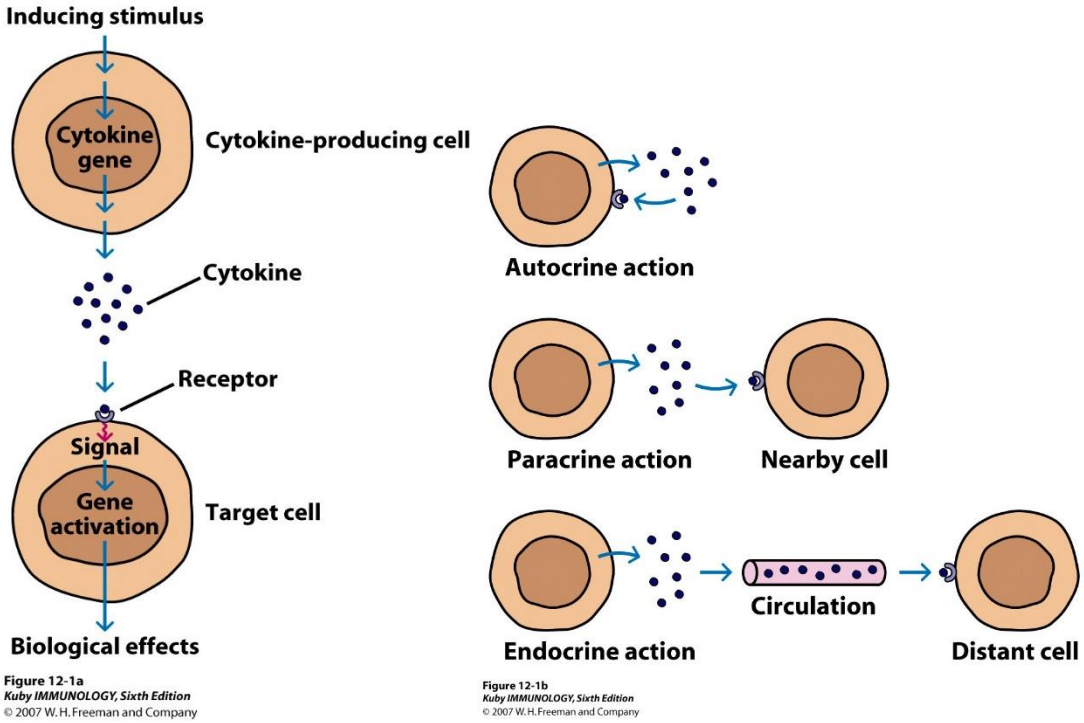
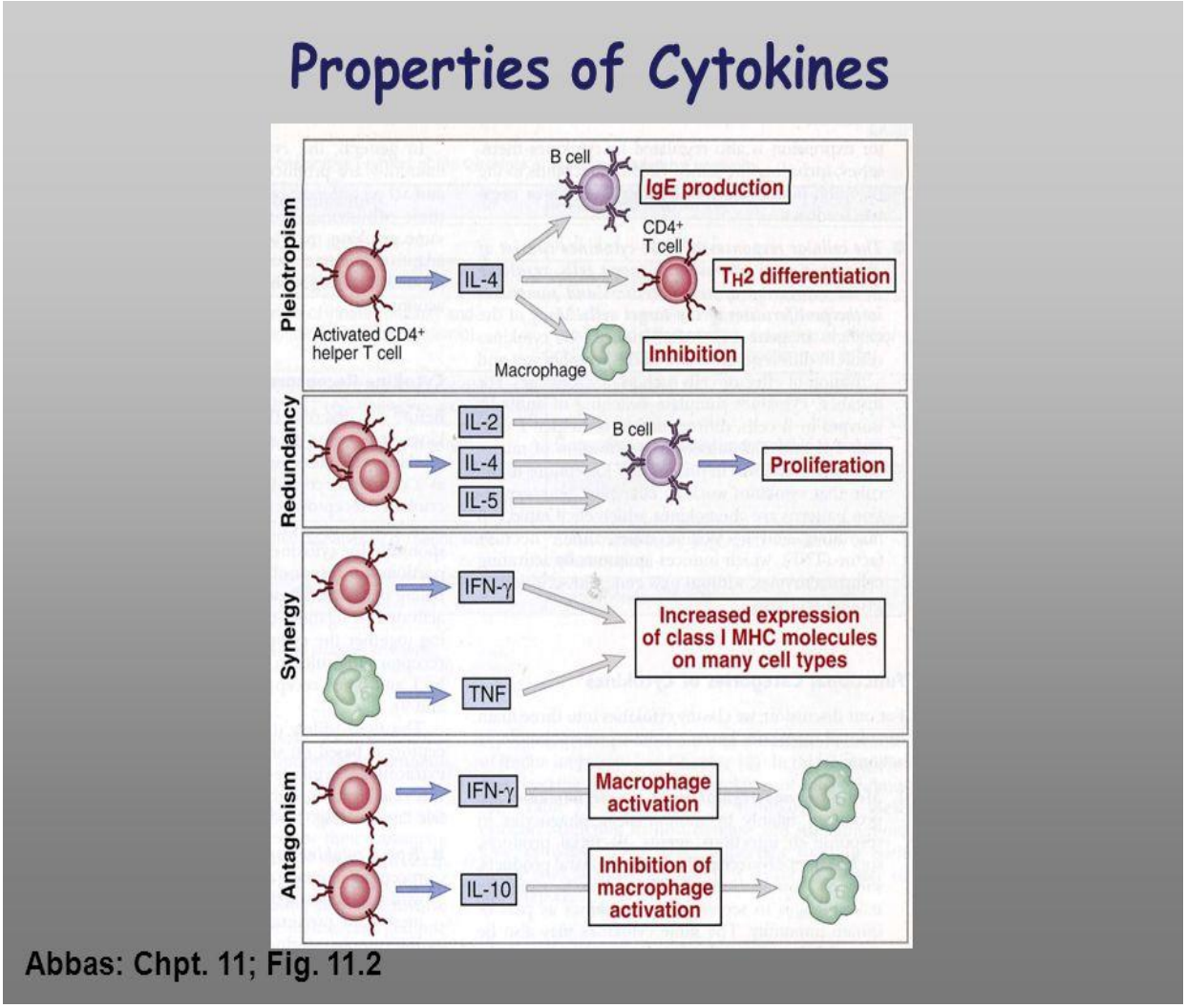


Figure -1. Cytokine mode of action.

Properties of Cytokines

The multiple cytokines detected in the extracellular milieu at any given time during an immunological response can interact in **pleiotropic** (different effects on different types of target cells or for different cell types to secrete the same cytokine), **redundant** (multiple cytokines have same effect), **synergic** (cooperative effect of multiple cytokines or two or more cytokines acting together), **antagonistic** (inhibition of one cytokines effects by another or cytokines causing opposing activities) and **cascade induction** (multiple-step feed-forward mechanism for the amplified production of a particular cytokine or as one cytokine stimulates its target cells to make additional cytokines) manners. Activation by cytokines occurs in an antigen-non-specific manner and must, therefore, be regulated to avoid inappropriate responses in a host's system which would be detrimental to health. In healthy individuals, cytokine action is regulated by their transient

production only in response to either antigen or potent inflammatory stimuli, the short half-life of cytokines in extracellular fluids and compartments, and the restricted receptor expression profiles on the surface of both activated and unactivated target cells, as well as other mechanisms. Of course, there are examples of cytokine dysregulation which result in pathological disease. Such an example is the role of **tumour necrosis factor alpha** (**TNFα**) in the development of **rheumatoid arthritis**; blockade of this cytokine's effect through the administration of a **recombinant soluble TNF-receptor** also exemplifies how understanding these molecules can be exploited with medical benefits.



Cytokine Activities

Cytokines are made by many cell populations, but the predominant producers are helper T cells (Th) and macrophages.

The largest group of cytokines stimulates immune cell proliferation and differentiation. This group includes Interleukin 1 (IL-1), which activates T cells; IL-2, which stimulates proliferation of antigen-activated T and B cells; IL-4, IL-5, and IL-6, which stimulate proliferation and differentiation of B cells; Interferon gamma (IFNg), which activates macrophages; and IL-3, IL-7 and Granulocyte Monocyte Colony-Stimulating Factor (GM-CSF), which stimulate hematopoiesis. Other groups of cytokines include interferons and chemokines. **Interferons** IFNa and IFNb inhibit virus replication in infected cells, while IFNg also stimulates antigen-presenting cell MHC expression. **Chemokines** attract leukocytes to infection sites.

Table-1. Cytokine mode of action, with specific examples.

	Cytokines	Action
1-	Interferon family	Antiviral proteins
2-	Chemokine family	Direct cell migration, adhension and activation
3-	Tumour necrosis factor family	Regulate inflammatory and immune responses
4-	Interleukin family	Variety of actions dependent upon interleukin and cell type
5-	Haematopoietins	Promote cell proliferation and differentiation
6-	Transforming growth factor beta family	Regulation of immune cells

Functional

A classification that proves more useful in clinical and experimental practice outside of **structural biology** divides immunological cytokines into those that enhance **cellular immune responses, type 1** (TNFα, IFN-γ, etc.), and those that enhance **antibody responses, type 2** (TGF-β, IL-4, IL-10, IL-13, etc.). A key focus of interest has been that cytokines in one of these two sub-sets tend to inhibit the effects of those in the other. Dysregulation of this tendency is under intensive study for its possible role in the **pathogenesis** of **autoimmune disorders.** Several **inflammatory cytokines** are induced by **oxidative stress.** The fact that cytokines themselves trigger the release of other cytokines and also lead to increased oxidative stress makes them important in **chronic inflammation**, as well as other immunoresponses, such as fever and **acute phase proteins of the liver** (IL-1,6,12, IFN-a). Cytokines also play a role in anti-inflammatory pathways and are a possible therapeutic treatment for pathological pain from inflammation or peripheral nerve injury. There are both **pro-inflammatory** and **anti-inflammatory** cytokines that regulate this pathway.

Cytokine receptor family

Type I cytokine receptors

Type I cytokine receptors have certain conserved motifs in their extracellular amino-acid domain, and lack an intrinsic protein tyrosine kinase activity. This family includes receptors for IL2 (beta-subunit), IL3, IL4, IL5, IL6, IL7, IL9, IL11, IL12, GM-CSF, G-CSF, Epo, LIF, CNTF, and also the receptors for Thrombopoietin (TPO), Prolactin, and Growth hormone. Type I cytokine receptor family is subdivided into three subsets on the basis of the ability of family members to form complexes with one of three different types of receptor signaling components (gp130, common beta, and common gamma - the gamma-chain of the IL2 receptor).

Type II cytokine receptors

Type II cytokine receptors are multimeric receptors composed of heterologous subunits, and are receptors mainly for interferons. This family includes receptors for IFN-alpha, IFN-beta, IFN-gamma, IL10, IL22, and tissue factor. The extracellular domains of type II cytokine receptors share structural similarities in their ligand-binding domain. Several conserved intracellular sequence motifs have been described, which probably function as binding sites for the intracellular effector proteins JAK and STAT proteins.

Chemokine receptors

Chemokine receptors are G protein-coupled receptors with 7 transmembrane structure and couple to G-protein for signal transduction. Chemokine receptors are divided into different families: CC chemokine receptors, CXC chemokine receptors, CX3C chemokine receptors, and XC chemokine receptor (XCR1).

Tumor necrosis factor receptor (TNFR) family

Tumor necrosis factor receptor (TNFR) family members share a cysteine-rich domain (CRD) formed of three disulfide bonds surrounding a core motif of CXXCXXC creating an elongated molecule. TNFR is associated with procaspases through adapter proteins (FADD, TRADD, etc.) that can cleave other inactive procaspases and trigger the caspase cascade, irreversibly committing the cell to apoptosis.

TGF-beta receptors

TGF-beta receptors are single pass serine/threonine kinase receptors. TGF-beta receptors include TGFBR1, TGFBR2, and TGFBR3 which can be distinguished by their structural and functional properties.

Cytokine cross-regulation

• IFN-γ (Th-1) inhibits proliferation of Th-2

• IL-4 and IL-10 (Th-2) inhibits proliferation of Th-1 by decreasing IL-12 production

• INF-γ (Th-1) promotes IgG2a production and decreases IgE by B cells

• IL-4 (Th-2) promotes production of IgE and IgG1 by B cells and decreases IgG2a.

Cytokine & Diseases

• **Bacterial Septic Shock** – Due to several Gram (-) bacteria – Stimulation of Macrophages by LPS ↑ TNF-α, IL-1β – Drop in blood pressure, fever, diarrhea, systemic blood clotting in various organs

• **Bacterial Toxic Shock** – Caused by superantigens (wide variety of toxins) – Activation of T cells ↑ cytokines from T cells and activated macrophages.

• **Infectious Diseases** – Leprosy, Chagas Disease