

Cytokines

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Inflammation

- The inflammatory process involves a series of events that can be elicited by numerous stimuli (e.g., infectious agents, ischemia, antigen-antibody interactions, and thermal, irradiation or other physical injury).
- Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation on a theme.
- At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain.

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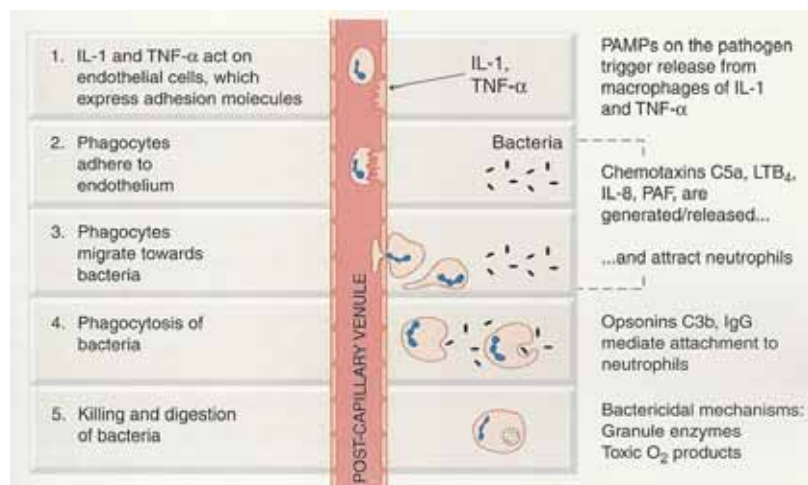
Phases of inflammatory responses

Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms:

1. An **acute transient phase**, characterized by local vasodilatation and increased capillary permeability.
2. A delayed, **subacute phase**, most characterized by infiltration of leukocytes and phagocytic cells.
3. A **chronic proliferative phase**, in which tissue degeneration and fibrosis occur.

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Mediators in acute inflammatory reaction



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Inflammatory processes

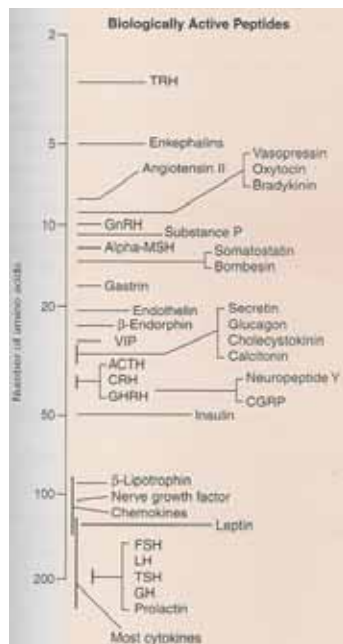
- Many different mechanisms are involved in the inflammatory process.
- The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens and injury.
- However in some situations and diseases the inflammatory response may be exaggerated and sustained for no apparent beneficial reason for the host.

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Cytokines

- Cytokines are peptides released from inflammatory tissue, connective tissue and immune system cells; they act by **autocrine** and **paracrine** mechanisms.
- Cytokines that are secreted from lymphocytes are termed **lymphokines**.
- Those secreted by monocytes or macrophages are termed **monokines**.
- A large family of cytokines are produced by various cells of the body.

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Biologically active peptides

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Interleukins

- Many of the lymphokines are also known as **interleukins (ILs)**, since they are not only secreted by leukocytes but also able to affect the cellular responses of leukocytes.
- Specifically, interleukins are growth factors targeted to cells of hematopoietic origin.

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The cytokine superfamily I

- More than 50 cytokines have been identified, and the cytokine superfamily includes **interleukins, chemokines, colony-stimulating factors, growth factors, interferons, and the transforming growth factor and tumour necrosis factor** families.
- Here we emphasize mainly the cytokines implicated in inflammatory and immune conditions. These cytokines are produced mainly from macrophages and lymphocytes but also from other leukocytes, endothelial cells and fibroblasts.

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The cytokine superfamily II

- Most are not produced **constitutively** but are synthesised **de novo** on cell activation (**inducible**).
- Most act locally by paracrine and/or autocrine mechanisms; exceptions being IL-1 and TNF- α .
- On the target cell, cytokines act on specific, high-affinity receptors, which, in most cases, are **upregulated** in the cell when it is stimulated.

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The cytokine superfamily III

- In addition to their own direct actions on cells, some cytokines induce formation of other cytokines (which could constitute a necessary **amplification cascade**), some induce the receptors for other cytokines.
- Some have complicated synergistic or antagonistic interactions with other cytokines.

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Signalling language for cytokines

- Cytokines have been linked to a **complex signaling language** with the final response of a particular cell involved being determined by a number of different messages received concurrently at the cell surface.
- The details of the functioning of this complex cytokine network are not yet fully understood. However, it is becoming clear that they are important pathophysiological mediators and are implicated in the pathogenesis of numerous disease states.

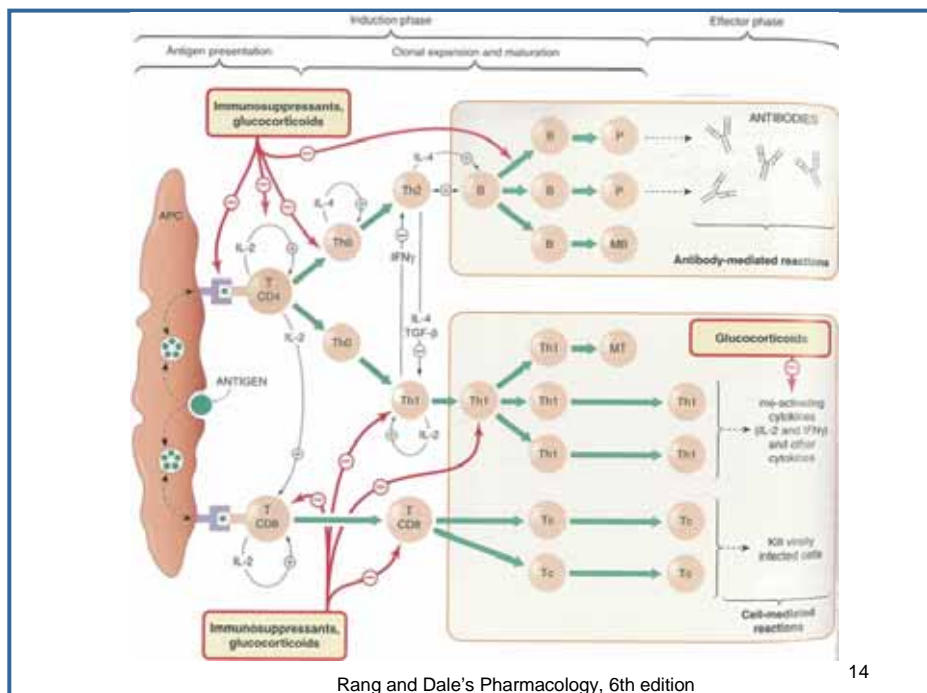
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Classification of cytokines

Although there are various classifications, for the purposes of this lecture we will divide cytokines into two main groups:

- Those involved in the **induction** of the immune response
- Those involved in the **effector** phase of the immune/inflammatory response

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Cytokines involved in effector phases

- The effector phase cytokines include both **proinflammatory** and **antiinflammatory** peptides.
- The primary proinflammatory cytokines are tumour necrosis factor- α (**TNF- α**) and interleukin-1 (**IL-1**).
- These are released from macrophages and many other cells and can start a cascade of **secondary cytokines** amongst which are the **chemokines** -a subfamily of cytokines that attract and activate motile inflammatory cells.

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Chemokines I

There are at least 28 chemokines, subdivided into two groups:

1. The α or C-X-C group in which the first two cysteine residues are separated by an intervening amino acid.
2. The β or C-C group in which they are not.

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Chemokines II

- The α chemokines (main example IL-8) act on neutrophils and are predominantly involved in **acute inflammatory responses**.
- The β chemokines [main examples being monocyte chemoattractant protein (MCP-1), and regulated upon activation normal T cell expressed and secreted, (RANTES)] act on monocytes, eosinophils and other cells, and are involved predominantly in **chronic inflammatory responses**.
- Various growth factors (e.g. platelet-derived growth factor, fibroblast growth factor, vascular endothelial growth factor) are important in **repair processes** and are also implicated in chronic inflammation.

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The antiinflammatory cytokines

- The antiinflammatory cytokines include **TGF- β** , **IL4**, **IL-10** and **IL-13**; these can inhibit the production of chemokines and the last three can inhibit responses mediated by Th1 cells.

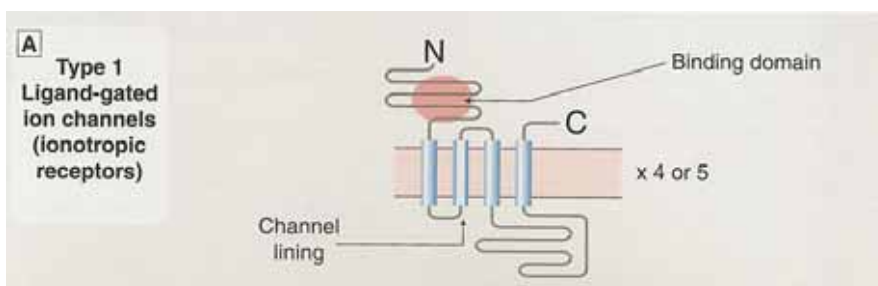
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Signal transduction pathways

- Most **cytokines** the signal transduction mechanisms in the target cell involve the **Jak/Stat pathway**.
- The **chemokines** act through **G-protein-coupled receptors**.
- The **growth factors** act through **Ras/Raf pathway**.

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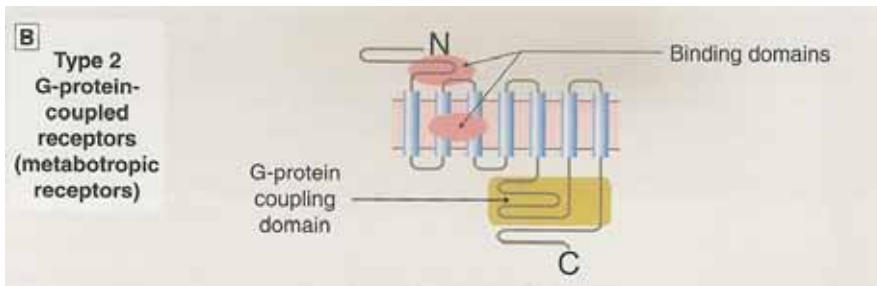
Ionotropic receptors (ligand gated channels)



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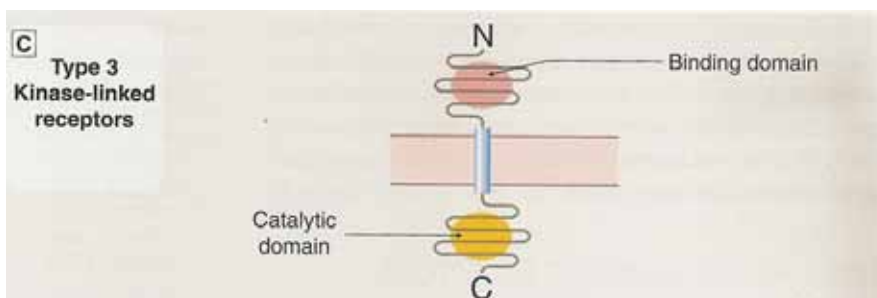
Metabotropic receptors (G-protein coupled)



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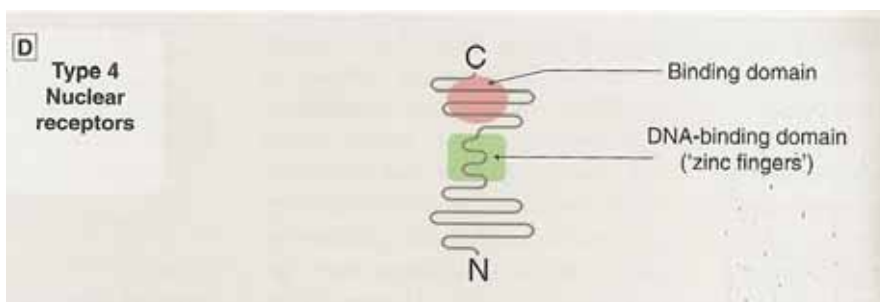
Kinase linked receptors



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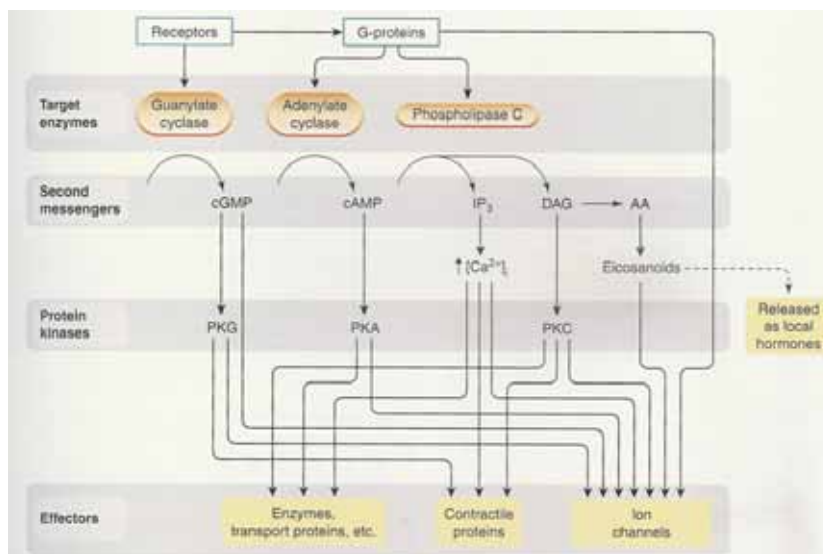
Steroid receptors



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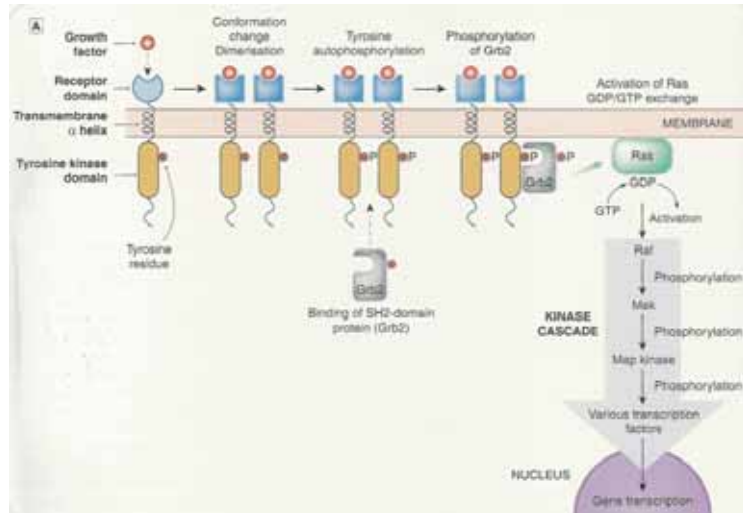
G protein coupled cellular events



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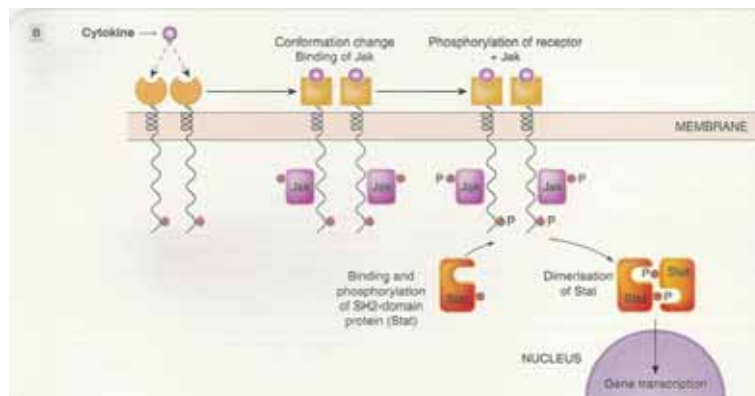
Growth factor (Ras/Raf) pathway



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Cytokine (Jak/Stat) pathway



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Table 56-2. The cytokines.

Cytokine	Properties
Interferon- α (IFN- α)	Antiviral, oncostatic, activates NK cells
Interferon- β (IFN- β)	Antiviral, oncostatic, activates NK cells
Interferon- γ (IFN- γ)	Antiviral, oncostatic, secreted by and activates or up-regulates Th1 cells, NK cells, CTLs, and macrophages
Interleukin-1 (IL-1)	T cell activation, B cell proliferation and differentiation
Interleukin-2 (IL-2)	T cell proliferation, Th1, NK, and LAK cell activation
Interleukin-3 (IL-3)	Hematopoietic precursor proliferation and differentiation
Interleukin-4 (IL-4)	Th2 and CTL activation, B cell proliferation
Interleukin-5 (IL-5)	Eosinophil proliferation, B cell proliferation and differentiation
Interleukin-6 (IL-6)	HCF, Th2, CTL, and B cell proliferation
Interleukin-7 (IL-7)	CTL, NK, LAK, and B cell proliferation, thymic precursor stimulation
Interleukin-8 (IL-8)	Neutrophil chemotaxis, proinflammatory
Interleukin-9 (IL-9)	T cell proliferation
Interleukin-10 (IL-10)	Th1 suppression, CTL activation, B cell proliferation
Interleukin-11 (IL-11)	Megakaryocyte proliferation, B cell differentiation
Interleukin-12 (IL-12)	Th1 and CTL proliferation and activation
Interleukin-13 (IL-13)	Macrophage function modulation, B cell proliferation
Interleukin-14 (IL-14)	B cell proliferation and differentiation
Interleukin-15 (IL-15)	Th1, CTL, and NK/LAK activation, expansion of T cell memory pools
Interleukin-16 (IL-16)	T lymphocyte chemotaxis, suppresses HIV replication
Interleukin-17 (IL-17)	T cell proliferation
Interleukin-18 (IL-18)	Th1 suppression, CTL activation, B cell proliferation
Interleukin-19 (IL-19)	Megakaryocyte proliferation, B cell differentiation
Interleukin-20 (IL-20)	Th1 and CTL proliferation and activation
Interleukin-21 (IL-21)	Macrophage function modulation, B cell proliferation
Interleukin-22 (IL-22)	B cell proliferation and differentiation
Interleukin-23 (IL-23)	Th1, CTL, and NK/LAK activation, expansion of T cell memory pools
Interleukin-24 (IL-24)	T lymphocyte chemotaxis, suppresses HIV replication
Interleukin-25 (IL-25)	Neutrophil chemotaxis, proinflammatory
Interleukin-26 (IL-26)	Induces Th1 response
Interleukin-27 (IL-27)	Proinflammatory
Interleukin-28 (IL-28)	Immunity, anti-differentiation
Interleukin-29 (IL-29)	Immunity, proliferation of activated T cells, induction of NK cells
Interleukin-30 (IL-30)	Regulation of Th2 cells
Interleukin-31 (IL-31)	Immunity, proliferation of Th1 memory cells
Interleukin-32 (IL-32)	Induces tumor apoptosis, induces Th1 response
Interleukin-33 (IL-33)	Immunity, naive CD4 cells to produce Th1
Interleukin-34 (IL-34)	Antiviral, oncostatic, like interferon
Interleukin-35 (IL-35)	Anti-tumor, anti-IL-1
Interleukin-36 (IL-36)	Contributes to type 1 hypersensitization and Th2 response
Interleukin-37 (IL-37)	Inhibits inflammation
Tumor necrosis factor- α (TNF- α)	Shocklike, macrophage activation, proinflammatory
Tumor necrosis factor- β (TNF- β)	Shocklike, proinflammatory, chemotaxis
Granulocyte colony-stimulating factor	Granulocyte production
Granulocyte-macrophage colony-stimulating factor	Granulocyte, monocyte, macrophage production
Macrophage colony-stimulating factor	Macrophage production, activation
Erythropoietin receptor (EPO)	Red blood cell production
Thrombopoietin (TPO)	Platelet production
AC1, hematopoietic cytokine LAK, lymphokine-activated killer cell	

Table 56-2. The cytokines.

Cytokine	Properties
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Interleukin-4 (IL-4)	Th2 and CTL activation, B cell proliferation
Interleukin-5 (IL-5)	Eosinophil proliferation, B cell proliferation and differentiation
Interleukin-6 (IL-6)	HCF, Th2, CTL, and B cell proliferation
Interleukin-7 (IL-7)	CTL, NK, LAK, and B cell proliferation, thymic precursor stimulation
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Interleukin-14 (IL-14)	B cell proliferation and differentiation
Interleukin-15 (IL-15)	Th1, CTL, and NK/LAK activation, expansion of T cell memory pools
Interleukin-16 (IL-16)	T lymphocyte chemotaxis, suppresses HIV replication

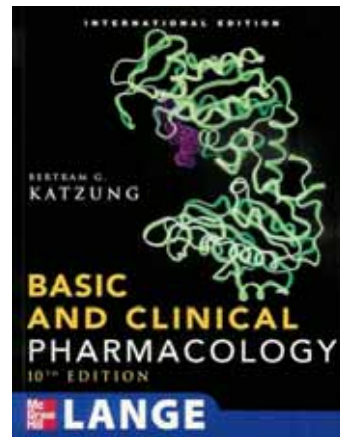
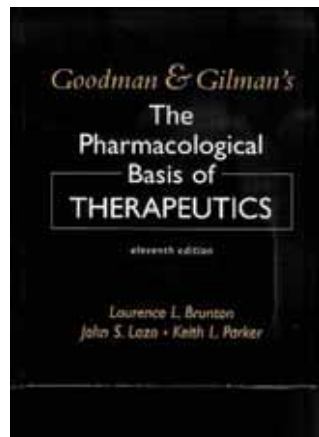
Interleukin-17 (IL-17)	Stromal cell cytokine production
Interleukin-18 (IL-18)	Induces Th1 responses
Interleukin-19 (IL-19)	Proinflammatory
Interleukin-20 (IL-20)	Promotes skin differentiation
Interleukin-21 (IL-21)	Promotes proliferation of activated T cells, maturation of NK cells
Interleukin-22 (IL-22)	Regulator of Th2 cells
Interleukin-23 (IL-23)	Promotes proliferation of Th1 memory cells
Interleukin-24 (IL-24)	Induces tumor apoptosis, induces Th1 responses
Interleukin-27 (IL-27)	Stimulates naive CD4 cells to produce IFN- γ
Interleukin-28 and 29 (IL-28, IL-29)	Antiviral, interferon-like properties
Interleukin-30 (IL-30)	p28 subunit of IL-27
Interleukin-31 (IL-31)	Contributes to type I hypersensitivities and Th2 responses
Interleukin-32 (IL-32)	Involved in inflammation
Tumor necrosis factor- α (TNF- α)	Oncostatic, macrophage activation, proinflammatory
Tumor necrosis factor- β (TNF- β)	Oncostatic, proinflammatory, chemotactic
Granulocyte colony-stimulating factor	Granulocyte production
Granulocyte-macrophage colony stimulating factor	Granulocyte, monocyte, eosinophil production
Macrophage colony-stimulating factor	Monocyte production, activation
Erythropoietin (epoetin, EPO)	Red blood cell production
Thrombopoietin (TPO)	Platelet production

HCF, hematopoietic cofactor; LAK, lymphokine-activated killer cell.
Note: Many interleukin activities overlap and are influenced by each other.

Program for chemotherapeutics

05.03.2008	Basic principles of chemotherapy, and sulphonamides
12.03.2008	Penicillins and cephalosporins
19.03.2008	Other cell wall synthesis inhibitors and flouroquinolones
26.03.2008	Agents that effect protein synthesis
02.04.2008	Antimycobacterial agents
30.04.2008	Disinfectants, antiseptics, urinary antiseptics, and miscellaneous antibacteriels
07.05.2008	Antifungal agents
14.05.2008	Antiviral agents
21.05.2008	Antiprotozoal agents
28.05.2008	Anthelmintic agents
04.06.2008	Clinical use of antibiotics

Major English Pharmacology Textbooks



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Thank you...



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