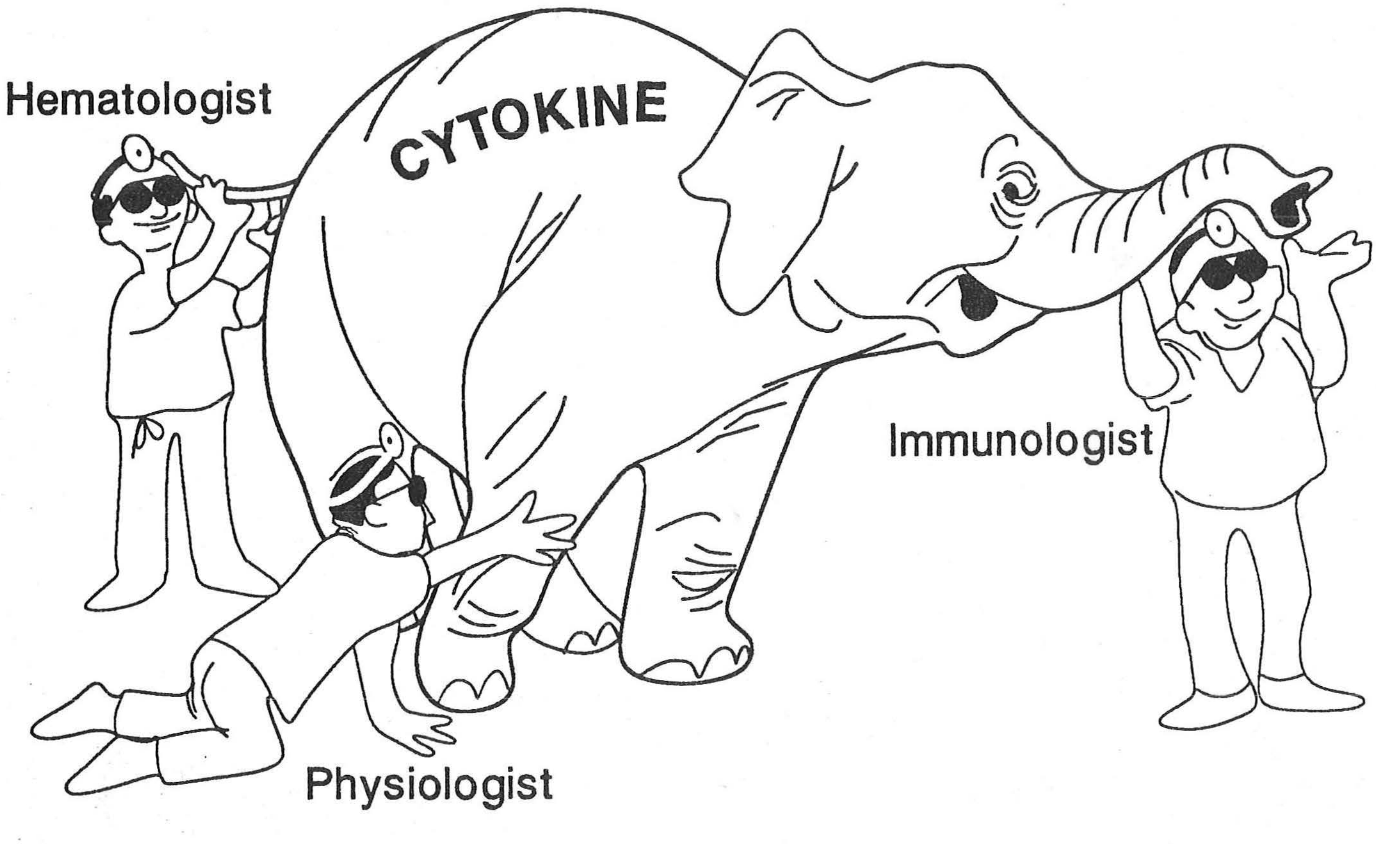
Immunol.

CYTOKINES: MESSENGER MOLECULES OF THE IMMUNE SYSTEM



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Medical Grand Rounds

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A BRIEF HISTORY OF THE CYTOKINES

I. The Age of Acronyms

1966 *David, Bloom & Bennett* - Macrophage migration inhibition factor (MIF) described

- small molecular substance that inhibited the migration of macrophages

1969 *Dumonde* - "Lymphokines"

- soluble antigen nonspecific products of lymphocytes that mediated the manifestations of delayed-type hypersensitivity reactions

1974 *Cohen* - "Cytokine"

- Soluble products from cells other than lymphocytes also effected immune responses

1979 *International Lymphokine Workshop* - "Interleukins"

- Substances that communicated signals between different populations of leukocytes

II. The Age of Molecular Biology

1982 *Gray & Goeddel* - Gene for gamma interferon cloned

1983—> present Gene for many cytokines cloned -

Interleukins 1α, 1β, 2, 3, 4, 5, 6
GM-CSF, G-CSF, M-CSF
TNFα, LT

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ACTIVITIES ATTRIBUTED TO CYTOKINES

AEF
BAF
BCDF
BCDFγ
BCGF-I
BCGF-II
BPA
BSF-1
BSF-2
CSF-1
CSF-2
CSFα
CSFβ
Cachectin
Catabolin
ECSF
EDF
EP
ETAF
Eo-CSF
GRF
HCGF
HPGF
HSF-II
Hemopoietin I
IFN-β2
IgA-EF
IL-HP1
Interferon α
Interferon β
Interferon γ
KHF
LAF
LEM
LDCF
LIF
Lymphotoxin
MAF
MCF
MCGF
MCGF-2
MFF
MIF
MP
Meg-CSF
Multi-CSF
NIF-T
OAF
PIF
PSF
Pluripoietin
SIRS
SMAF
SRF
TCGF
TCGF-2
T_HF
TNF
TRF
TRF_M
T_SF
Urinary CSF
26Kd protein

CYTOKINES WHOSE GENES HAVE BEEN CLONED AND EXPRESSED

A. Primarily Monocyte/Macrophage Derived

1. Interleukin 1α
2. Interleukin 1β
3. Tumor necrosis factor α

B. Primarily T Lymphocyte-Derived

1. Interleukin 2
2. Interleukin 4
3. Interleukin 5
4. Interleukin 6
5. Lymphotoxin
6. Interferon γ

C. Hemopoietic Growth Factors

1. Interleukin 3
2. Granulocyte Macrophage Colony Stimulating Factor
3. Macrophage Colony Stimulating Factor
4. Granulocyte Colony Stimulating Factor

D. Factors primarily produced by cells outside the immune system or whose major action is not immunologic

1. Interferon α
2. Interferon β
3. Transforming Growth Factor β
4. Platelet Derived Growth Factor

Interleukin 1α (IL1α)
Interleukin 1β (IL1β)

Other names:

Lymphocyte Activating Factor (LAF)
B Cell Activating Factor (BAF)
Leukocyte Endogenous Mediator (LEM)
Endogenous Pyrogen (EP)
Hemopoietin I
Catabolin
Mononuclear Cell Factor (MCF)
Osteoclast Activating Factor (OAF)
Epidermal Cell Derived Thymocyte Activating Factor (ETAF)

Natural Products:

IL1α	protein, Mr 17,000	pI=5.5
IL1β	protein, Mr 17,000	pI=7.0

Deduced Size of Mature Protein:

IL1α	159 amino acids	Mr 17,500
IL1β	153 amino acids	Mr 17,500

Gene:

Chromosome: single copy genes, chromosome 2
Organization: Seven exons, six introns
IL1α - 10.2 Kb
IL1β - 7.0 Kb

Cellular Sources:

Cell	Stimulus
Monocytes, macrophages	bacterial endotoxin, muramyl dipeptide immune complexes, C5a cytokines (M-CSF, TNFα, IFNγ)
Keratinocytes	muramyl dipeptide, bacterial endotoxin phorbol esters
Langerhans cells	bacterial endotoxin
Large granular lymphocytes	bacterial endotoxin
Endothelial cells	bacterial endotoxin, thrombin
Mesangial cells	-
Astrocytes	bacterial endotoxin

Glioma cell lines	-
Microglial cells	bacterial endotoxin

Receptors:

Specificity:	IL1α or IL1β, human material is active in mice		
Avidity:	Murine T cells -	high avidity: low avidity:	$Kd=5x10^{-12}M$; $Kd=4x10^{-10}M$
	Human fibroblasts -		$Kd=8x10^{-12}M$
	Human EBV transformed B cells-		$Kd=2\text{-}6x10^{-10}M$
Number:	Murine T cells -	resting:	high avidity, 12/cell low avidity, 180/cell
		activated:	high avidity, 23/cell low avidity, 580/cell
	Murine T cell tumors:		high avidity, 46-340/cell low avidity, 2550-17,700/cell
	Human fibroblasts:		3000/cell
	Human EBV transformed B cells:		110-220/cell
	Other cells:		20-5000/cell
Size:	Mr 80,000		
Organization:	Single chain		
Distribution:	T cells, B cell lines, fibroblasts, endothelial cells, melanoma cells, hepatoma cells, epithelial cells.		

Known Activities:

Cell	Activity
T Lymphocytes	Co-mitogenic with lectins Increase lymphokine production (IL2, IFNγ) Augment activity of cytotoxic T cells Increase receptors for IL-2
B Lymphocytes	Maturation of pre-B cells Cofactor in clonal expansion Promote differentiation of antibody forming cells
NK Cells	Enhance killing and synergistically enhance killing with IFN-γ

Macrophages	Increase production of prostaglandin Increase tumoricidal activity
Hemopoietic Cells	Facilitate response of immature precursors to colony stimulating factors
Smooth Muscle Cells	Stimulate growth Stimulate prostaglandin production
Endothelial Cells	Increase proliferation Increase prostacyclin, prostaglandin, platelet activating factor, GM-CSF, G-CSF production Increase adhesiveness for polymorphonuclear leukocytes, monocytes, lymphocytes Increase procoagulant and plasminogen activator activity Induce new surface antigens
Fibroblasts	Increase PGE_2 production Increase collagenase production Increase proliferation Increase production of GM-CSF, G-CSF, IL6
Chondrocytes	Increase production of collagenase, neutral proteases, plasminogen activator Increase production of PGE_2
Non-neuronal cells of nerves	Stimulate production of Nerve Growth Factor
Hepatocytes	Increase synthesis of complement factors B and C3, metallothionen, α_1- antichymotrypsin, α_1 acid glycoprotein, inter-α_1-trypsin inhibitor, serum amyloid associated protein Decrease synthesis of albumin, transferrin, fibrinogen Decrease activity of cytochrome P-450
Mesangial Cells	Increase proliferation
Osteoblasts	Increase proliferation
Osteoclasts	Increase bone resorption Decrease alkaline phosphatase
Epidermal Cells	Increase synthesis of collagen type IV
Adipocytes	Decrease lipoprotein lipase activity

Tumor Cells	Cytostasis
Glial Cells	Increase proliferation
Pancreatic Cells	Cytotoxicity
Thyroid Cells	Cytotoxicity
Pituitary Cells	Stimulate secretion of ACTH, LH, GH, TSH

Activity *in vivo*:

Animals

1. Fever
2. Induce acute phase reactants from liver
3. Slow wave sleep
4. Anorexia
5. Induce colony stimulating activity
6. Accelerate recovery from Listeriosis
7. Protect granulocytopenic mice from lethal gram-negative infection
8. Protect from lethal irradiation
9. Protect from oxygen damage (with TNFα)
10. Downregulate hepatic steroid receptors, reduce gluconeogenesis and decrease plasma glucose
11. Stimulate secretion of corticotropin-releasing factor from the hypothalamus
12. Intra-articular injection causes loss of cartilage matrix and synovitis.

Man

1. Found in synovial fluid of patients with various forms of arthritis
2. Found in gingival fluid of patients with periodontal disease

Tumor Necrosis Factor α (TNFα)

Other Names:

Cachectin

Natural Product:

Protein, Mr 17,000

Deduced Size of Mature Protein:

157 amino acids, Mr 17,300

Gene:

Chromosome: Single copy gene, chromosome 6 (p23-q12)
Organization: No information

Cellular Sources:

Macrophages activated by bacterial endotoxin, M-CSF, IFN-γ
Activated T cells, mast cells

Receptors:

Specificity: TNFα or LT, human material is active in rodents

Avidity: $Kd=2x10^{-10}M$

Number: 200-7500/cell, increased by IFN-γ

Size: Mr 140,000

Organization: 2 polypeptides: Mr 80,000 and Mr 60,000

Distribution: Fibroblasts
Activated T lymphocytes
Activated B lymphcytes
Many tumor cells

Known Activities

Cell	Activity
T Cells	Enhance proliferation, IL2 receptor expression
B Cells	Enhance proliferation and differentiation of activated B cells into antibody forming cells

NK Cells	Enhance cytolytic potential, synergize with IL2
Hepatocytes	Increase production of complement factors B, C3, α1 antichymotrypsin Decrease production of albumin, transferrin
Hemopoietic Stem Cells	Inhibition of proliferation and differentiation
Endothelial Cells	Enhance production of IL1, GM-CSF, G-CSF, platelet activating factor, procoagulant activity, neutrophil adherence, new antigen expression
Fibroblasts	Stimulate production of PGE_2, collagenase, GM-CSF, G-CSF, membrane IL1, IL6
Adipocytes	Inhibit lipoprotein lipase
Osteoclasts	Increase bone resorption, decrease alkaline phosphatase
Neutrophils	Stimulate phagocytosis, respiratory burst, degranulation and production of platelet activating factor
Tumor Cells	Cytotoxicity
Macrophages	Induce IL1, PGE_2 and platelet activating factor production Chemotactic

Activity *in vivo*:

Animals

1. Fever
2. Induce colony stimulating activity
3. Shock
4. Wasting
5. Necrosis of certain transplantable tumor
6. Protect from oxygen damage (with IL1)
7. Prevent nephritis in $(NZBxNZW)F_1$ mice
8. Antibody to TNFα prevents:
    a. Skin and gut lesions in acute graft versus host disease
    b. Neurological manifestations of malaria (murine cerebral malaria)
    c. Death from lethal doses of endotoxin

<u>Man</u>

1. Identified in synovial fluid of patients with rheumatoid arthritis

Interleukin 2 (IL2)

Other Names:

T cell growth factor (TCGF)

Natural Product:

Glycoprotein (O-linked sugar only): Mr 15-17,000

Deduced Size of Mature Protein:

133 amino acids, Mr 15,400

Gene:

Chromosome: Single copy gene, chromosome 4 (q26-q28)
Organization: 4 exons, 3 introns (5 Kb)

Cellular Sources:

Activated T cells
Some activated B cells

Receptors:

Specificity: IL2 only, human material is active in the mouse

Avidity:

Low avidity: Kd = $1\text{-}3\times10^{-8}$M

Intermediate avidity: Kd = 1×10^{-9}M

High avidity: Kd = $2\text{-}20\times10^{-12}$M

Number:

Low avidity: $3\text{-}6\times10^{4}$/activated T cell, 0/resting T cell

Intermediate avidity: 0/activated T cell, 700/resting T cell, 2000/NK cell

High avidity: $3\text{-}4\times10^{3}$/activated T cell, 0/resting T cell

Size:

Low avidity: Mr 55,000

Intermediate avidity: Mr 70,000

High avidity: Mr 125,000

Organization:

Low avidity: single chain (p55)

Intermediate avidity: single chain (p70)

High avidity: heterodimer (p55 + p70)

Gene: p55 - chromosome 10 (p14-p15)
8 exons, 7 introns (>25Kb)
p70 - no information

Distribution:

Low avidity: Activated T cells, activated B cells, IFN-γ activated macrophages

Intermediate avidity: Resting T cells, NK cells

High avidity: Activated T cells, activated B cells

Known Actions:

Cell	Action
T Cells	Stimulate the growth of activated T cells Stimulate functional differentiation of activated T cells to cytotoxic effector cells
B Cells	Stimulate the growth of activated B cells Stimulate functional differentiation of activated B cells to antibody secreting cells
NK Cells	Enhance lytic potential
Macrophages	Functional activation

Activity *in vivo*

Animals

1. Protect mice from lethal gram negative infection
2. Polyclonal activation of T and B cells
3. Promote the generation of specific cytotoxic T cells

Man

1. Found in synovial fluid of patients with rheumatoid arthritis
2. Results of intravenous administration
   a) Two to sixteen-fold increase in circulating T lymphocytes (CD4+ and CD8+)
   b) Increase circulating T cells with IL2 receptors
   c) Increase plasma levels of γ interferon

Interleukin 4 (IL4)

Other Names:

B cell stimulatory factor 1 (BSF-1)
B cell growth factor I (BCGF-I)
B cell differentiation factor γ (BCDFγ)
T cell growth factor 2 (TCGF-2)
Mast cell growth factor-2 (MCGF-2)

Natural Product:

Mouse:	Glycoprotein, Mr 20,000
Human:	No information

Deduced Size of Mature Protein:

129 amino acids, Mr 15,000

Gene: No information

Cellular Sources:

Activated T cells
Mast cells (mouse)

Receptors:

Specificity:	IL4 only, species specific
Avidity:	$Kd = 0.5\text{-}1.0 \times 10^{-10} M$
Number:	100-2500/cell
Size:	Mr 139,000
Organization:	Single chain
Distribution:	T lymphocytes, B lymphocytes, Mast cells, Macrophages, Myeloid precursors, Erythroid precursors, Fibroblasts, Melanocytes, Keratinocytes, Brain cells, Muscle cells, Hepatocytes, Pancreatic cells, Bladder cells

Known Actions:

Cell	Activity
B Cells	Enhance proliferation of activated cells Increase expression of class II MHC molecules on murine B cells Increase expression of low affinity receptors for IgE (CD23)

	Promote production of IgGI, IgE from stimulated murine B cells
T Cells	Promote growth of activated T cells Promote generation of antigen specific cytotoxic T cells
Mast Cells	Support proliferation of murine mast cells
Macrophages	Enhance tumoricidal activity Increase expression of class II MHC molecules on murine macrophages Enhance antigen presenting capacity of murine macrophages Induce giant multinucleated cells from murine macrophages
Hemopoietic precursors	Costimulate growth of murine erythroid, macrophage, granulocyte and mast cell colonies

Activity *in vivo*:

Animals

1. Antibody to IL4 abrogates the induction of IgE responses in the mouse

Man

No information

Interleukin 5 (IL-5)

Other Names:

B cell growth factor II (BCGF-II)
T cell replacing factor (TRF)
Killer helper factor (KHF)
Eosinophil differentiation factor (EDF)
Eosinophil-colony stimulating factor (Eo-CSF)
IgA-enhancing factor (IgA-EF)

Natural Product:

Glycoprotein oligomer: Mr 50-60,000

Deduced Size of Mature Protein:

115 amino acids, Mr 13,000

Gene:

Chromosome: No information
Organization: 4 exons, 3 introns (2.1 Kb)

Cellular Sources:

Activated T cells

Receptors:

No information

Known Actions:

Cell	Activity
B Cells	Induce the differentiation of activated B cells into antibody secreting cells Facilitate the production of IgA from activated B cells
T cells	Facilitate the generation of murine cytotoxic T cells
Homopoietic Precursors	Induce immature precursors to differentiate into eosinophils

Activity *in vivo*:

No information

Interleukin 6 (IL-6)

Other Names:

Interferon β_2 (IFN-β_2)
B Cell Stimulatory Factor 2 (BSF-2)
Hepatocyte Stimulatory Factor II (HSF-II)
Hybridoma Plasmacytoma Growth Factor (HPGF, IL-HP1)
Myeloma Cell Growth Factor (MCGF)
26 Kd Protein

Natural Product:

Glycoprotein: Mr 26,000

Deduced Size of Mature Protein:

184 amino acids, Mr 21,000

Gene:

Chromosome: Single copy gene, chromosome 7
Organization: 5 exons, 4 introns

Cellular Sources:

Activated T cells	
Fibroblasts:	constitutive, increased by poly(I)poly(C), IL1, TNFα, IFNβ_1, PDGF
Monocytes:	constitutive, increased by bacterial endotoxin
EBV-transformed B lymphoblastoid cells:	constitutive
Myeloma cells:	constitutive
Atrial myxoma cells:	constitutive
Carcinoma cell lines:	constitutive, increased by TNFα, lymphotoxin

Receptors:

Specificity:	IL6 only, human IL6 is active on murine cells
Avidity:	Kd = 3.4×10^{-10}M
Number:	140-890/cell (fresh myeloma cells); 2700/cell (CESS EBV-transformed B lymphoblastoid cells)
Size:	No information
Organization:	No information
Distribution:	Resting T cells, activated B cells, plasma cells, myeloma cells, myeloid precursors, astrocytes, hepatocytes, fibroblasts

Known Actions:

Cell	Activity
B Cells	Stimulate terminal maturation of activated B cells or EBV transformed B cells into antibody secreting cells Promote growth of murine hybridomas and plasmacytomas Promote growth of myeloma cells
T Cells	Enhance production of IL2 from murine T cells Enhance differentiation of murine cytotoxic T cells Stimulate murine thymocyte proliferation
Hemopoietic Stem Cells	Stimulate growth of granulocyte-macrophage progenitors Stimulate growth of multipotential hemopoietic progenitors
Fibroblasts	Inhibit growth Enhance expression of class I MHC molecules
Hepatocytes	Induce production of haptoglobin, fibrinogen, α_1 antitrypsin

Activity *in vivo*:

Animals

1. Induce fever

Man

1. High levels in blood and synovial fluid of patients with inflammatory arthritis

Lymphotoxin (LT)

Other Names:

Tumor necrosis factor β (TNFβ)

Natural Product:

Glycoprotein: Mr 25,000
Glycoprotein trimer: Mr 60-70,000

Deduced Size of Mature Protein:

171 amino acids, Mr 18,600

Gene:

Chromosome: single copy gene, chromosome 6 (p23-q12)
Organization: No information

Cellular Sources:

Activated T cells
B lymphoblastoid cell lines

Receptors:

Specificity:	LT or TNFα, human material is active in rodents
Avidity:	Kd = 2×10^{-10}M
Number:	200-2000/cell, increased by IFN-γ
Size:	Mr 140,000
Organization:	2 polypeptides - Mr 80,000 and Mr 60,000
Distribution:	Same as receptors for TNFα

Known Activities:

Presumably the same as TNFα

Activity *in vivo*:

Presumably the same as TNFα

Interferon Gamma (IFNγ)

Other Names:

Macrophage activating factor (MAF)

Natural Product:

Glycoprotein: Mr 20,000, Mr 25,000

Deduced Size of Mature Protein:

146 amino acids, Mr 17,100

Gene:

Chromosome:	single copy gene, chromosome 12
Organization:	4 exons, 3 introns

Cellular Sources:

Activated T cells
Natural killer cells

Receptors:

Specificity:	IFNγ only, species specific
Avidity:	Kd = $5\text{-}10 \times 10^{-10}$M
Number:	2,000 - 10,000/cell
Size:	Mr 70,000 - 80,000
Organization:	Single protein
Gene:	Encoded by gene on chromosome 6 (long arm)
Distribution:	Monocyte/macrophages, fibroblasts, endothelial cells, T lymphocytes, B lymphoblasts

Known Actions

Cell	Activity
Macrophages	Activation, enhanced production of reactive oxygen species Increase expression of MHC molecules Increase production of IL1, TNFα
Fibroblasts	Inhibit collagen synthesis, induce expression of class II MHC molecules

	Inhibit heparin releasable lipoprotein lipase activity Increase resistance to intracellular pathogens
Adipocytes	Inhibit heparin releasable lipoprotein lipase activity
T Cells	Enhance differentiation of cytotoxic effectors Increase production of LT
Endothelial Cells	Induce expression of class II MHC antigens Increase resistance to intracellular pathogens
NK Cells	Augment killing
B Cells	Enhance generation of immunoglobulin secreting cells from activated murine B cells (IgM, IgG2a) Counteract the effects of IL4
Hemopoietic Stem Cells	Inhibit growth and differentiation
Tumor Cells	Increase expression of receptors for TNFα
Hepatocytes	Increase resistance to replication by exoerythrocytic stages of Plasmodium
Many Cells	Increase expression of class II MHC antigens

Activity *in vivo*:

Animals

1. Activate macrophages to produce reactive oxygen species and kill microorganisms
2. Protect from Listeria monocytogenes infection
3. Promote killing of intracellular pathogens - *Toxoplasma gondii, Leishmania donovani, Listeria monocytogenes, Mycobacterium intracellulare*
4. Accelerate fatal glomerulonephritis in $(NZBxNZW)F_1$ mice
5. Antibodies to IFNγ
   a) cause remission in $(NZBxNZW)F_1$ mice
   b) inhibit allograft rejection
   c) prevent many of the toxic effects of bacterial endotoxin

Man

1. Local injection into lepromatous leprosy lesions ——> T cell and

monocyte infiltration, increased HLA-DR antigen expression

2. Induce hypertryglyceridemia and inhibit lipoprotein lipase activity
3. Ameliorate rheumatoid arthritis, psoriatic arthritis
4. Exacerbate multiple sclerosis

Colony Stimulating Factors

Interleukin 3 (IL3)

Other Names:

Multipotential Colony Stimulating Factor (Multi-CSF)
Hematopoietic Cell Growth Factor (HCGF)
P-Cell Stimulating Factor (PSF)
Mast Cell Growth Factor (MCGF)
Erythroid Colony-Stimulating Factor (ECSF)
Megakaryocyte Colony Stimulating Factor (Meg-CSF)
Eosinophil Colony Stimulating Factor (Eo-CSF)
Burst-Promoting Activity (BPA)

Natural Product:

Glycoprotein, Mr 20-26,000

Deduced Size of Mature Protein:

133 amino acids, Mr 15,000

Gene:

Chromosome: Single copy gene, chromosome 5 (long arm)
Organization: 5 exons, 4 introns

Cellular Source:

Activated T Cells

Receptors:

Specificity:	IL-3 only, species specific
Avidity:	*Kd = $2\text{-}5 \times 10^{-11}$M
Number:	*1000-5000/cell
Size:	*Mr 135,000
Organization:	*Heterodimer (Mr 75,000 + Mr 60,000)
Distribution:	Hemopoietic precursors, neutrophils, eosinophils, macrophages, mast cells

* Murine IL3 receptor

Known Actions:

Cell	Activity
Hemopoietic Precursors	Stimulate proliferation and differentiation of precursors of all cell lineages
Mast Cells	Stimulate growth of mast cell lines
Myeloid Cells	Stimulate growth of myeloid cell lines

Activity *in vivo*:

No information

Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF)

Other Names:

Colony Stimulating Factor α (CSFα)
Pluripoietin
Colony Stimulating Factor 2 (CSF2)
Neutrophil migration inhibitory factor from T cells (NIF-T)

Natural Product:

Glycoprotein: Mr 22,000

Deduced Size of Mature Protein:

127 amino acids, Mr 14,300

Gene:

Chromosome: Single copy gene, chromosome 5 (q21-q32)
Organization: 4 exons, 3 introns (4Kb)

Cellular Sources:

Activated T cells
HTLV-I infected lymphoblastoid cell lines
Endothelial cells, fibroblasts stimulated by TNFα, IL1
Myeloid leukemia cells
Bladder carcinoma cells

Receptors:

Specificity: GM-CSF only, species specific

Avidity: $Kd = 1\text{-}3 \times 10^{-11} M$

Number:	*70 high avidity receptors, 350 low avidity receptors per cell
Size:	*Mr 50,000
Organization:	Single protein
Distribution:	Myeloid leukemia cells, mature neutrophils, monocytes, eosinophils

Known Actions:

Cell	Activity
Hemopoietic Stem Cells	Stimulate monocyte and neutrophil colonies Stimulate pure neutrophil colonies Stimulate eosinophil colonies Facilitate growth of erythroid progenitors (BFU-E)
Mature Neutrophils	Inhibit migration Prime for responses to other stimuli Enhance phagocytosis, antibody dependent cellular cytotoxicity Increase expression of the LFA-1 family of adhesion molecules
Eosinophils	Enhance leukotriene production Increase antibody-dependent cellular cytotoxicity
Monocytes	Enhance tumoricidal activity Enhance functional activity

Activity *in vivo*

Animals

Mice

1. Evidence of tissue macrophage expansion and activation in transgenic mice expressing a GM-CSF transgene.

Monkeys

1. Leukocytosis (neutrophils, eosinophils)
2. Priming of neutrophils
3. Enhance recovery of neutrophils, platelets after bone marrow transplantation

Man

1. Dose dependent increase in neutrophils, eosinophils in AIDS patients

2. Increase in neutrophils, monocytes, eosinophils and lymphocytes in patients with myelodysplastic syndromes

Macrophage Colony Stimulating Factor (M-CSF)

Other Names:

Colony stimulating factor-1 (CSF-1)
Urinary colony stimulating factor

Natural Product:

Glycoprotein dimer: Mr 70-90,000

Deduced Size of Mature Protein:

224 amino acids, Mr 26,000

Gene:

Chromosome: Single copy gene, chromosome 5 (long arm)
Organization: No information

Cellular Sources:

Fibroblasts:	Constitutive
Endothelial cells:	Constitutive
Monocytes:	Constitutive, increased by bacterial endotoxin, interferon-γ, phorbol esters

Receptors:

Specificity:	M-CSF only, human M-CSF is active on mouse cells
Avidity:	*Kd = $4x10^{-10}$M
Number:	*3,000-15,000/cell
Size:	Mr 165,000
Organization:	Single protein with tyrosine kinase activity Related (possibly identical) to the product of the c-fms protooncogene encoded on the long arm of chromosome 5
Distribution:	Cells of monocyte/macrophage lineage Choriocarcinoma cells

* Murine M-CSF

Known Actions:

Cell	Activities
Monocytes/Macrophages	Increase antibody dependent cellular cytotoxicity Increase PGE_2 production Increase cytokine production (IL1, TNF) Increase tumoricidal activity
Hemopoietic Precursors	Stimulate growth of monocyte colonies

Activity *in vivo*:

Animals

1. Leukocytosis
2. Prevent meylosuppression induced by interferons

Man

1. No information

Granulocyte-Colony Stimulating Factor (G-CSF)

Other Names:

Colony stimulating factor β (CSF_{β})
Pluripoietin

Natural Product:

Glycoprotein (O-linked sugar only): Mr 19,600

Deduced Size of Mature Protein:

177 amino acids, Mr 19,000

Gene:

Chromosome: Single copy gene, chromosome 17
Organization: 5 exons, 4 introns

Cellular Sources:

Fibroblasts, endothelial cells - after stimulation with IL1, TNFα
Monocytes - after stimulation by bacterial endotoxin, interferon-γ phorbol esters

Receptors:

Specificity:	G-CSF only, human G-CSF is active on mouse cells
Avidity:	*Kd = $6\text{-}8 \times 10^{-11}$M
Number:	*50-500/cell
Size:	*Mr 150,000
Organization:	*Single protein
Distribution:	*Monomyelocytic cell lines Mature neutrophils

* Murine G-CSF

Known Actions:

Cells	Activity
Hemopoietic Precursors	Induce differentiation of myelocytic cell lines Induce growth of pure neutrophil colonies
Mature neutrophils	Enhance antibody dependent cellular cytotoxicity Prime for enhanced response to other signals

Activity *in vivo*:

Animals

1. Increase circulating neutrophils, T cells and phagocytic activity of neutrophils in monkeys, mice

Man

No information

ADDITIONAL CYTOKINES PRODUCED BY CELLS OF THE IMMUNE SYSTEM OR ACTING ON CELLS OF THE IMMUNE SYSTEM

1. Interferon α
2. Interferon β
3. Transforming Growth Factor β
4. Platelet Derived Growth Factor

ACTIVITIES IN SEARCH OF GENE PRODUCTS

1. Migration Inhibition Factor (MIF)
2. Soluble Immune Response Suppressor (SIRS)
3. Allogeneic Effect Factor (AEF)
4. Antigen Specific Helper Factor (T_HF)
5. Antigen Specific Suppressor Factor (T_SF)
6. Skin Reactive Factor (SRF)
7. Genetically-related Factor of Macrophages (GRF)
8. Specific Macrophage Arming Factor (SMAF)
9. Interleukin 4a
10. IgT
11. Proteolysis Inducing Factor (PIF)

SUMMARY OF THE CYTOKINES

1. Small protein or glycoprotein mediators produced by a wide variety of cells

   a) Monocyte/macrophages - IL1, TNFα, IL6, GF-CSF, M-CSF, G-CSF

   b) T lymphocytes - TNFα, IL2, IL4, IL5, IL6, LT, IFNγ, IL3, GM-CSF

   c) B lymphocytes - IL2, IL6, LT

   d) NK cells - IL1, IFNγ

   e) Fibroblasts - IL6, GM-CSF, M-CSF, G-CSF

   f) Endothelial cells - IL1, GM-CSF, M-CSF, G-CSF

   g) Mast cells - IL4, TNFα

2. Active at low concentrations on a variety of cells expressing small numbers of high avidity specific receptors

   a) Macrophage activation - IFN-γ, M-CSF, GM-CSF, IL-4, IL-2, IL-1, TNFα, LT

   b) T lymphocyte growth and differentiation - IL-1, TNFα, IL-2, IL-4, IL-5, IL-6, LT

   c) B lymphocyte growth and differentiation - IL-1, TNFα, IL-2, IL-4, IL-5, IL-6, LT, IFNγ

   d) Natural killer cell function - IL-1, TNFα, IL-2, LT

   e) Connective tissue - IL-1, TNFα, LT, IFNγ

   f) Hepatocytes - IL-1, TNFα, LT, IL-6

   g) Hemopoietic precursors - stimulation - IL-3, GM-CSF, G-CSF, M-CSF, IL-1, IL-4, IL-5, IL-6; inhibition - TNFα, IFNγ

3. Production of cytokines and responsiveness to cytokines are tightly regulated by environmental stimuli and other cytokines

   a) Cytokine regulation of cytokine production

Cytokine	Target Cell	Product
IL1	Endothelial cell	GM-CSF, G-CSF
	Fibroblast	GM-CSF, G-CSF, IL6
	T cell	IL2, IFNγ
TNFα	Monocyte	IL1
	Endothelial cell	IL1, GM-CSF, G-CSF

	Fibroblast	GM-CSF, G-CSF, IL6
IL6	T cells	IL2
IFNγ	Monocyte T cell	IL1, TNFα LT
M-CSF	Monocyte	IL1, TNFα

b) Cytokine regulation of cytokine receptors

Cytokine	Target Cell	Receptor
IL1	T cells Hemopoietic stem cells	IL2 CSFs
TNFα	T cells	IL2
IL4	T cells	IL2
IFNγ	Monocytes Tumor cells	IL2 TNFα

4. Many manifestations of inflammation can be accounted for by the action of multiple cytokines

a) Acute phase response

1. IL1 - increase: complement factor B, C3, serum amyloid associated protein, α_1-antichymotrypsin, α_1 acid glycoprotein, inter-α-trypsin inhibitor
   decrease: albumin, transferrin, fibrinogen

2. TNFα - increase: complement factor B, C3, α_1 antichymotrypsin
   decrease: albumin, transferrin

3. IL6 - increase: haptoglobin, fibrinogen, α_1 antitrypsin

b. Fever:

1. IL1
2. TNFα
3. IL6

c. Hypertriglyceridemia

1. TNFα
2. IL2
3. IFNγ

d. Neutrophilia

1. IL1
2. TNFα
3. GM-CSF
4. G-CSF

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