NKMAX

Cytokine

Cytokines are a broad and loose category of small proteins that are important in cell signaling. It may act on the cells that secrete them (autocrine action), on nearby cells (paracrine action), or in some instances on distant cells (endocrine action). Cytokines affect nearly every biological process; these include embryonic development, disease pathogenesis, non-specific response to infection, specific response to antigen, changes in cognitive functions and progression of the degenerative processes of aging. For that reason, cytokines have become an important frontier in medicine in a vital place as diagnostic, prognostic and therapeutic agents in human disease.

Cytokine includes chemokines, interferons (IFN), interleukins (IL), lymphokines that are produced by a type of immune cell, etc. and it is produced by a broad range of cells, including a macrophage, B cells, T cells, and mast cells, as well as endothelial cells, fibroblast, and various stromal cells. Also, it is possible to classify cytokines based on the nature of the immune response such as pro-inflammatory signaling (IL-1α/β, IL-6, IL-12, IL-17/22, IL-18, TNF-α, IFN-γ, GM-SCF), and anti-inflammatory signaling (IL-1RA, IL-4, IL-5, IL-10, IL-11, IL-13, TGF-β), with individual cytokines, also performing specific roles dependent upon cell type and location.

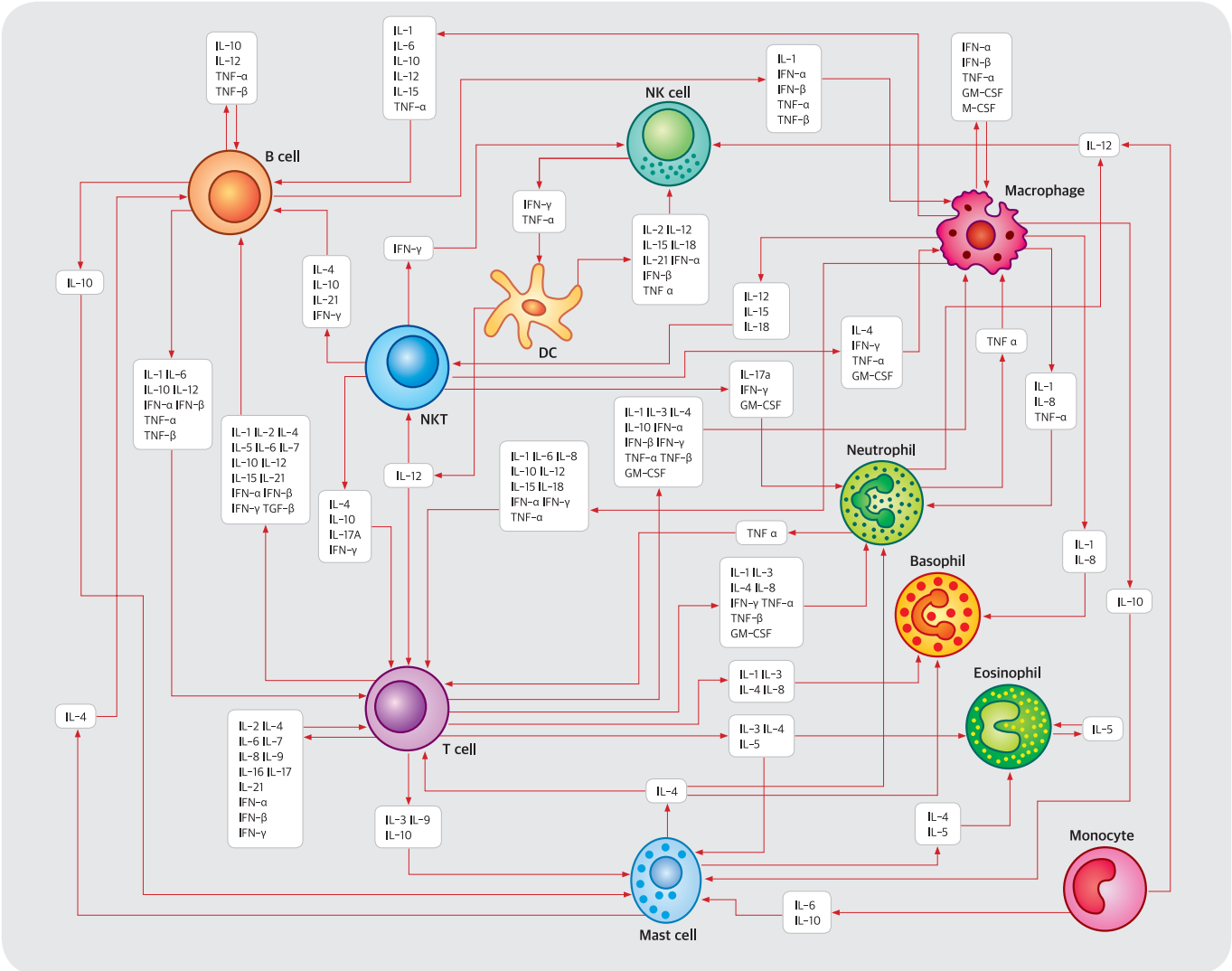


Table 1 Cytokines and their major functions

Cytokine	Main source	Target cell	Major function
Interleukins			
IL-1α, IL-1β	Macrophages, B cells, DCs	B cells, NK cells, T cells	Pro-inflammatory, proliferation and differentiation, BM cell proliferation
IL-1RA			IL-1 mediated anti-inflammatory
IL-2	T cells	Activated T and B cells, NK cells	Proliferation and activation
IL-3	T cells, NK cells	Stem cells	Hematopoietic precursor proliferation and differentiation
IL-4	Th cells	B cells, T cells, macrophages	Proliferation of B and cytotoxic T cells, enhances MHC class II expression, stimulates IgG and IgE production
IL-5	Th cells	Eosinophils, B cells	Proliferation and maturation, stimulates IgA and IgM production
IL-6	Th cells, macrophages, fibroblasts	Activated B cells, plasma cells	Differentiation into plasma cells, IgG production
IL-7	BM stromal cells, epithelial cells	Stem cells	B and T cell growth factor
IL-8	Macrophages	Neutrophils	Chemotaxis, pro-inflammatory
IL-9	T cells	T cells	Growth and proliferation
IL-10	T cells	B cells, macrophages	Inhibits cytokine production and mononuclear cell function, anti-inflammatory
IL-11	BM stromal cells	B cells	Differentiation, induces acute phase proteins
IL-12	T cells	NK cells	Activates NK cells
IL-13	Th cells, mast cells, NK cells	B cells, macrophages	Stimulates growth and differentiation of B cells, inhibits Th1 cells
IL-14	T cells, B cells	B cells	Growth and differentiation B cells, inhibits Ig secretion
IL-15	Macrophages, DCs, fibroblasts	T cells, NK cells	Proliferation and activation
IL-16	T cells, eosinophils	$CD4^+$ T cells	Recruitment of $CD4^+$ T cells
IL-17A	Th17 cells, NK cells, NKT cells	Neutrophils, fibroblast, epithelial cells	pro-inflammatory, proliferation of T cells
IL-17B/C/D	Neuronal cells, epithelial cells, B and T cells	Monocytes, endothelial cells, epithelial cells	Anti-microbial, pro-inflammatory
IL-17F	Th17 cell, NK cells, NKT cells, T cells	Epithelial cells, endothelial cells, lymphocytes	Pro-inflammatory, recruitment and activation of neutrophils
IL-18	Monocytes, DCs	T cells, NK cells, macrophages, epithelial cells	pro-inflammatory, enhances NK cell cytotoxicity, differentiation of T cells
IL-19	Monocytes	Keratinocytes	Pro-inflammatory
IL-20	Monocytes, Keratinocytes	Keratinocytes	Proliferation and differentiation of keratinocytes
IL-21	T cells, NKT cells	Lymphocytes, DCs	Proliferation of T cells, promotes differentiation of B cells, NK cell cytotoxicity
IL-22	Th17 cells	Fibroblasts, epithelial cells	Pathogen defense, wound healing, tissue reorganization
IL-23	Macrophages, DCs	Lymphocytes	Pro-inflammatory, enhancement of T cell proliferation, and NK cell activation
IL-24	Melanocytes, keratinocytes, monocytes, T cells	Cancer cells	Tumor suppression, wound healing
IL-25 (IL-17E)	T cells, mast cells, epithelial cells	T cells, fibroblasts, NKT cells, macrophages	Promotes Th2 differentiation and proliferation
IL-26	T cells, NK cells	Epithelial cells	Activation and regulation of epithelial cells
IL-27	DCs, macrophages, epithelial cells	T cells, NK cells	Promotion of Th1 cell differentiation, inhibition of Th17 cell response
IL-28A/B, IL-29	DCs	Monocytes, DCs, $CD4^+$ T cells	Downregulation of Th2 and upregulation of Th1 response
IL-30	Monocytes	Lymphocytes, mast cells, endothelial cells	Prevention and treatment of cytokine-induced liver injury
IL-31	T cells, monocytes, macrophages, DCs,	Keratinocytes, epithelial cells	Pro-inflammatory
IL-32	Monocytes, macrophages, NK cells, T cells, epithelial cells	Macrophages, DCs, T cells, PBMCs, monocytes	Pro-inflammatory
IL-33	Mast cells, Th2 cells	DCs, T cells, B cells	Induction of Th2 response
IL-34	Phagocytes, epithelial cells	Monocytes, macrophages,	Regulator of myeloid lineage differentiation, microglial proliferation
IL-35	Treg cells, monocytes, endothelial cells, epithelial cells	NK cells, T cells	Immune suppression
IL-36	Endothelial cells	Keratinocytes, DCs, T cells	Pro-inflammatory
IL-37	Monocytes, Cancer cells	DCs	Regulation of innate immunity, pro-inflammation
IL-38	Epithelial cells	T cells	Inhibition of Th17 response
IL-39	B cells	Neutrophils	Induction of differentiation and proliferation
IL-40	BM cells, B cells	unknown	Development of humoral immune response

Table 1 Cytokines and their major functions (continued)

Cytokine	Main source	Target cell	Major function
Tumor necrosis factors (TNF) superfamily			
TNF-α	Macrophages, NK cells, T cells, B cells	Neutrophils, macrophages, monocytes, endothelial cells	Regulation of immune cells, inflammation, apoptosis, inhibition of tumorigenesis and viral replication
TNF-β	T cells, B cells	Many cell types	Induction of inflammation, anti-viral response, development of secondary lymphoid organs, tumorigenesis
TNF-γ	T cells, B cells	Myeloid cells, other cell types	Induction of inflammation, anti-viral response, development of secondary lymphoid organs, tumorigenesis
OX40L	T cells, B cells, DCs, monocytes	T cells, B cells, DCs	Activation of T cell immune response
CD40L	T cells, B cells, DCs, monocytes	B cells, APCs	Regulation of adaptive immune response
FasL	T cells, B cells, NK cells	APCs, many other cell types	Regulation of T cell homeostasis
CD27L	T cells, B cells, DCs, monocytes	T cells, B cells	Regulation of B cell activation and T cell homeostasis
CD30L	Neutrophils, B cells, macrophages, T cells	T cells, B cells, DCs	Induction of apoptosis of T and B cells, prevention of autoimmunity
4-1BBL	T cell, B cells, DCs, monocytes, macrophages	T cells, B cells, DCs	Promotes activation and migration of monocytes
TRAIL	NK cells, T cells	Many cell types	Inhibition of tumorigenesis, induction of apoptosis
RANKL	T cells, Osteoprotegerin	Osteoclasts, many cell types	Tissue growth, DCs maturation
TWEAK	Monocytes, macrophages, endothelial cells	Tissue progenitors, epithelial cells, endothelial cells	Regulation of angiogenesis, induction of apoptosis
APRIL	Macrophages, DCs	B cells	Regulation of B cell development and plasma cell survival
BAFF	Macrophages, DCs, astrocytes	B cells	Stimulation of B cell proliferation and differentiation
LIGHT	T cells, monocytes, DCs	B cells, NK cells, DCs, other tissue	Stimulation of T cell proliferation, apoptosis regulation
TL1A	Macrophages, endothelial cells	T cells	Inhibition of angiogenesis
GITRL	DCs, macrophages, B cells	Treg cells, T cells	Regulation of T cell survival
Tumor Growth Factor (TGF) β superfamily			
TGF-βs; TGF-β1, β2, β3	Epithelial cells, fibroblasts, eosinophils, macrophages, T cells	Various	Balance of pro-inflammatory and anti-inflammatory, differentiation of Th cell subsets, induction of Treg maintenance, epithelial-mesenchymal transition
Activins/ Inhibins	Monocytes, macrophages,	T cells, macrophages, microglial cells, DCs, mast cells, B cells	Regulation of menstrual cycle, Metabolism, hemostasis, immune response, wound repairs
BMPs/GDFs	Thymic stromal cells, cardiomyocytes, macrophages	Monocytes, fibroblasts, cardiomyocytes	Fetal and embryonic development, cartilage development, adipogenesis, pro-fibrotic, anti-hypertrophic, promotes cardiomyocyte survival, immune response
Interferons (IFN)			
IFN-α	Leukocytes	Various	Anti-viral, promotes activation of NK cells and T cells, inhibits megakaryocyte stem cell differentiation and proliferation
IFN-β	Fibroblasts	Various	Anti-viral, promotes the expression of MHC-I on NK cells and T cells, suppresses inflammation
IFN-γ	Th1 cells, NK cells	Various	Anti-viral, macrophage activation, increases neutrophil and monocyte function, MHC-I and -II expression on cells
Colony stimulating factors (CSF)			
G-CSF	Fibroblasts, endothelium	Stem cells in BM	Granulocyte production
GM-CSF	T cells, macrophages, fibroblasts	Stem cells	Granulocyte, monocyte, eosinophil production
M-CSF	Fibroblast, endothelium	Stem cells	Monocyte production and activation
Erythropoietin	Endothelium	Stem cells	Red blood cell production

Abbreviations: BM, bone marrow; DCs, dendritic cells; NK cell, natural killer cell; G-CSF, granulocyte-colony stimulating factor; M-CSF, macrophage-colony stimulating factor; Th, T helper cell; Treg, regulatory T cell; APC, antigen presenting cell.

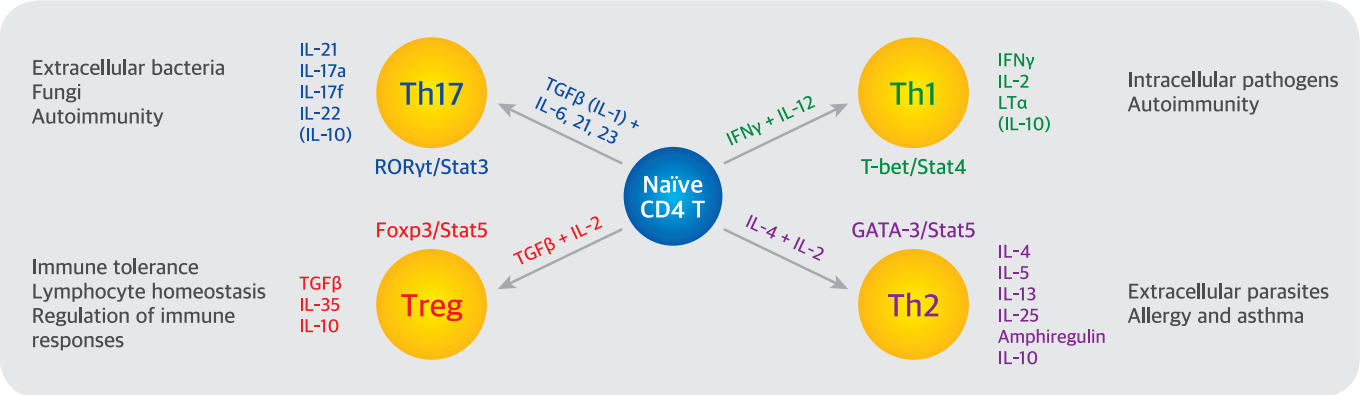
Table 2 Cytokine families

Family	Members
Hematopoietic	
- Common γ chain	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
- Shared β chain (CD131)	IL-3, IL-5, GM-CSF
- Shared IL-2β chain (CD122)	IL-2, IL-15
- Other hematopoietic	IFN-γ, IL-7, IL-13, IL-21, IL-31, TSLP
IL-1 family	IL-1α, IL-1β, IL-1RA, IL-18, IL-33, IL-36, IL-37
IL-6 family	IL-6, IL-11, IL-27, IL-31, CNTF, CT-1, LIF, OSM, OPN
IL-12 family	IL-12, IL-23, IL-27, IL-35
IL-10 superfamily	IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28, IL-29
IL-17 family	IL-17A-F, IL-25 (IL-17E)
Interferons	
- Type I interferons	IFN-α, IFN-β, IFN-ω
- Type II interferons	IFN-γ (also a hematopoietic cytokine)
- Type III interferons	IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B)
TNF superfamily	TNF-α, TNF-β, BAFF, APRIL

Abbreviations: GM-CSF, granulocyte-macrophage-colony stimulating factor; IFN, interferon; TSLP, thymic stromal lymphopoietin.; CNTF, ciliary neurotrophic factor; CT-1, ardiotrophin-1; LIF, leukemia inhibitory factor; OSM, oncostatin M; OPN, osteopontin; TNF, tumor necrosis factor.

Characteristics of Th1, Th2, Th17 and Treg cells

Th cells, also known as naïve $CD4^+$ T cells, are activated by antigen-presenting cells and proceed to clonal expansion and cytokine secretion. The cytokine profile secreted at this stage will determine the cell differentiation into any of the several subsets of Th cells and so define the type of immune response. These subsets include the Th1, Th2, Th17, and Treg cells.
Th1 cells are regarded as critical for immunity to intracellular microorganisms and Th2 cells for immunity to many extracellular pathogens. Abnormal activation of Th1 cells was seen as the critical event in most organ-specific autoimmune diseases while Th2 cells were responsible for allergic inflammatory diseases and asthma. Th17 cells play a critical function in protection against microbial challenges, particularly extracellular bacteria and fungi. Further, Th17 cells have been implicated in the pathogenesis of most common autoimmune diseases, including psoriasis, rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and multiple sclerosis (MS). Regulatory T cells (Tregs) play a critical role in maintaining self-tolerance as well as in regulating the immune response. Increasing Treg numbers and/or enhancing their suppressive function may be beneficial for treating autoimmune disease and for preventing allograft rejection.



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