

Crispian Scully[†] Eleni A Georgakopoulou Yazan Hassona

The Immune System: Basis of so much Health and Disease: 6. Cytokines

Abstract: The immune system is the body's primary defence mechanism against infections, and disturbances in the system can cause disease if the system fails in defence functions (in immunocompromised people), or if the activity is detrimental to the host (as in auto-immune and auto-inflammatory states). A healthy immune system is also essential to normal health of dental and oral tissues. This series presents the basics for the understanding of the immune system; this article covers the cytokines.
Clinical Relevance: Modern dental clinicians need a basic understanding of the immune system as it underlies health and disease.
Dent Update 2017; 44: 753–761

The immune system employs a wide array of soluble mediators that facilitate communication between immune cells, regulate the inflammatory response, and induce development and maturation of immune cells. Soluble mediators of the immune system are often produced by immune cells, and exert their effects through binding to specific receptors on target cells.

The main soluble mediators of the immune system are cytokines; low molecular weight secreted proteins that have a specific effect on the interactions and communications between cells. Cytokine is a general term, and the nomenclature describing different types of cytokines is sometimes confusing (Table 1).

Crispian Scully, CBE, DSc, DChD, DMed (HC), Dhc(multi), MD, PhD, PhD (HC), FMedSci, MDS, MRCS, BSc, FDS RCS, FDS RCPS, FFD RCSI, FDS RCSEd, FRCPath, FHEA, **Eleni A Georgakopoulou,** PhD, MD, MSc, DDS, Research Fellow, University of Athens and Dental Practitioner, 4 Fokaias Str, 14232 N Ionia, Greece and **Yazan Hassona,** BDS, FFD RCSI, PhD, Assistant Professor and Consultant in Oral Medicine and Special Needs Dentistry, The University of Jordan, Amman.

General properties of cytokines

Cytokines are produced by many cell populations, but the predominant producers are helper T-cells (Th) and macrophages. Some cytokines (eg type 1 interferons [IFN] and tumour necrosis factor [TNF]) are also produced by non-immune cells (ie epithelial cells).

It is common for different cell types to secrete the same cytokine or for a single cytokine to act on several different cell types (pleiotropy) (Figure 1). Cytokines are redundant in their activity, meaning that similar functions can be stimulated by different cytokines (Figure 2). They are often produced in a cascade, as one cytokine stimulates its target cells to make additional cytokines. Cytokines act in a network, and can also act synergistically or antagonistically (Figure 3).

Cytokines regulate immune cell activation/inhibition, cell growth, fibrosis and tissue repair, inflammation and morphogenesis. In addition, they regulate the intensity or duration of an immune response by stimulating or inhibiting proliferation of various leukocytes, or by modulating their secretion of antibodies, or other cytokines.

Cytokines are not stored for release as required; rather they must be synthesized 'upon request'. Thus their onset of actions is rather slow, and their production is transient and tightly controlled. The synthesis and action of cytokines is not antigen specific, and cytokines have no enzymatic function.

Cytokines mode of action

Cytokines may act on the secreting cells (ie autocrine action), on nearby cells (ie paracrine action), or on distant cells (ie endocrine action) (Figure 4).

Cytokines produce their effects by binding to high affinity receptors on target cells and then generally function as

local signals. Most cytokines use one of three types of receptors to bind to their target cells:

1. The general cytokine receptor family;
2. The chemokines receptor, and
3. The TNF receptor.

Most cytokines transmit signals via the Jak-STAT pathway; binding of cytokines to their receptors activates the Jak enzyme (a tyrosine kinase enzyme), which consequently phosphorylates and activates a transcription factor known as STAT (signal transducer and activator of transcription). Once STAT molecules become activated, they stimulate transcription of specific genes that induce proliferation or differentiation of target cells, and enhance the expression of new functions (Figure 5). When extracellular levels of cytokine fall toward the end of immune response, they cease binding to receptors, and the events leading to gene transcription will come to an end.

Functional classification of cytokines

Cytokines are classified according to their biological effects, into three main categories (Table 2):

1. Mediators and regulators of innate immunity: produced by activated macrophages and NK cells in response to microbial infection, and act mainly on endothelial cells and leukocytes to stimulate the early inflammatory response to microbes;
2. Mediators and regulators of acquired immunity: produced mainly by T-lymphocytes in response to specific recognition of a foreign antigen;
3. Stimulators of haematopoiesis: produced by bone marrow, stromal cells and leukocytes to stimulate growth and differentiation of immune cells.

Important cytokines

- Interleukins (ILs);
- Interferons (IFNs);
- Chemokines;
- Colony stimulating factors (CSFs);
- Tumour necrosis factors (TNFs);
- Transforming growth factor beta (TGF-β).

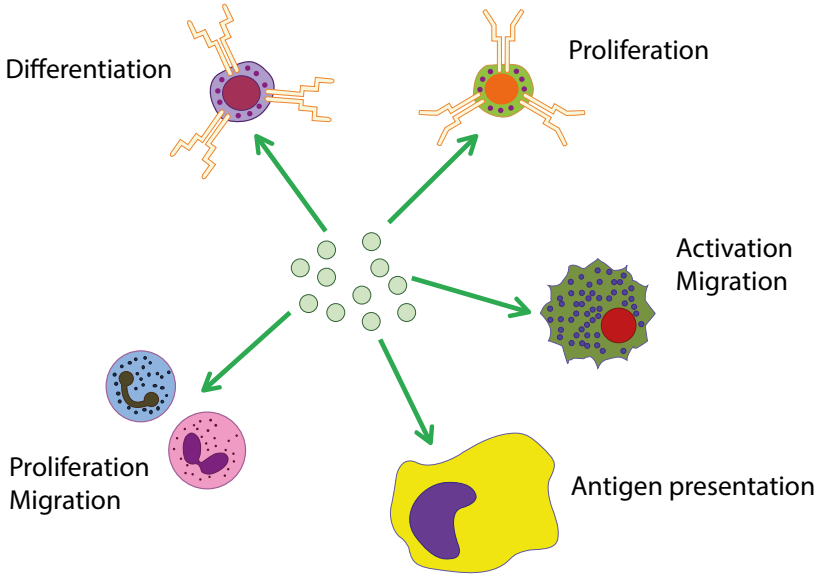


Figure 1. General properties of cytokines: pleiotropy means that a single cytokine can act on several target cells to produce multiple effects.

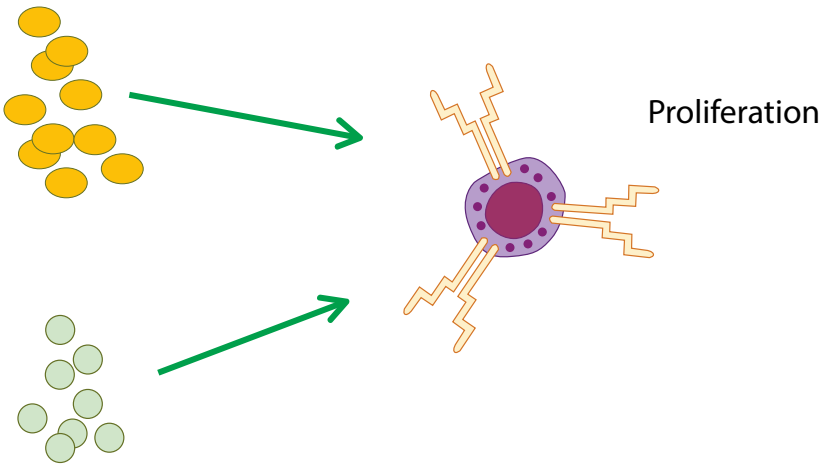
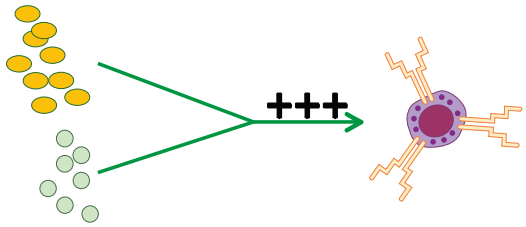


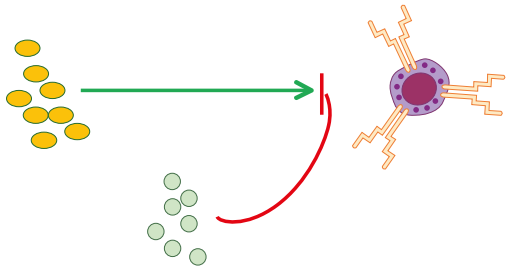
Figure 2. General properties of cytokines: redundancy means that more than one cytokine can act on the same target to produce similar effects.

Term	Definition
Cytokine	A soluble protein secreted primarily by an immunocyte which functions as a signalling molecule to regulate various aspects of immunity
Chemokine	Cytokine that functions primarily to attract immune cells
Monokine	Cytokine produced by macrophages
Interferon	Cytokine active against viral infection
Interleukin	Cytokine acting between leukocytes
Lymphokine	Cytokine produced by lymphocyte

Table 1. Terminology and nomenclatures of cytokines.



Synergism means that more than one cytokine can act together to produce an effect that is more profound than the sum of their individual effects.



Antagonism means that a cytokine can block the effect or reduce the influence of another cytokine on target cells.

Figure 3. General properties of cytokines: synergism and antagonism.

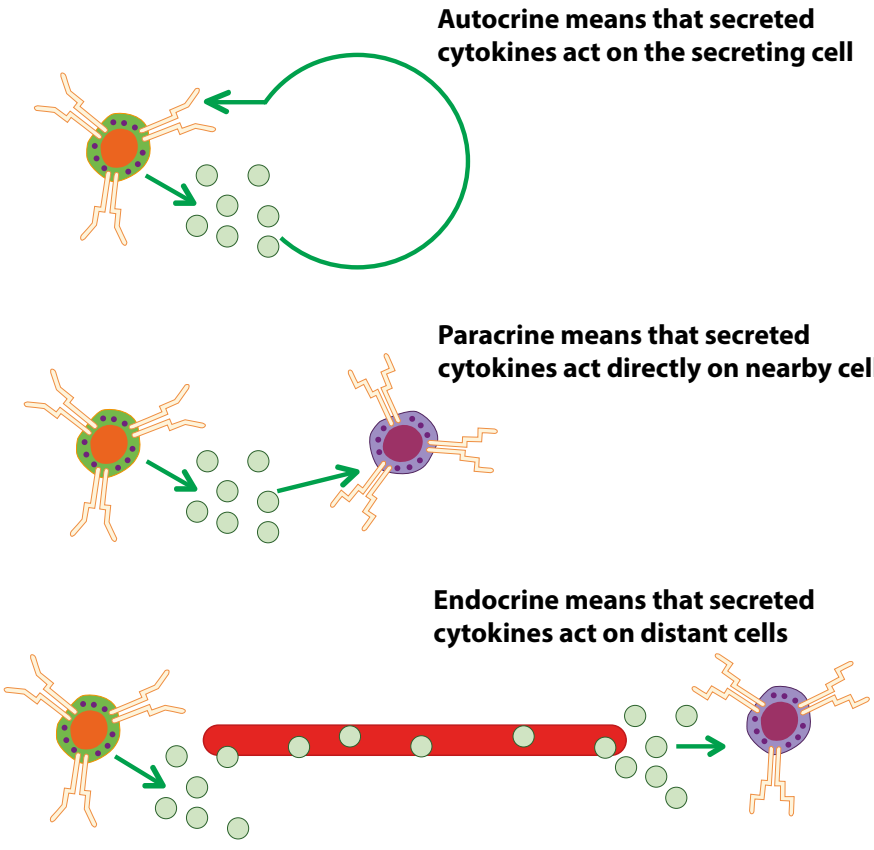


Figure 4. Cytokines mode of action.

The cytokine super-family contains numerous molecules that exert diverse functions (Table 3).

Interleukins (ILs)

The largest group of the cytokine family, they were so named because they were initially thought to act between leukocytes, but have much wider effects on different types of cells. The interleukins (IL-1, IL-2, IL-3... etc) were named in the order they were discovered, and currently there are 36 known. Functions of interleukins are diverse and include activation of immune cells (B-cells, T-cells, eosinophils and mast cells), modulation of inflammatory responses, and chemo-attraction.

Interferons (IFNs)

Interferons are so called because they 'interfere' with viral replication. The main function of interferons is to protect cells from viral infections. Interferons can also activate immune cells such as macrophages and natural killers (NKs), and increase host defences by up-regulating the antigen presentation capacity of antigen presenting cells (APCs). Interferons are increasingly manufactured as biological medications to treat various autoimmune, infectious and malignant diseases. There are three main types of interferons: IFN-α, IFN-β and IFN-γ (Table 4).

Chemokines

Chemokines are so called because of their ability to induce chemotaxis of nearby cells. Historically, chemokines were known under other names, such as the SIS family of cytokines, SIG family of cytokines, SCY family of cytokines, platelet factor-4 super-family or intercrines. The major function of chemokines is to act as chemo-attractant to guide migration of immune cells to the site of inflammation. Chemokines are classified according to their structure into four main groups: the CC chemokines, the C chemokines, the CXC chemokines and the CX3C chemokines (Table 5).

Category	Function	Examples
Mediators and regulators of innate immunity	Act mainly on endothelial cells and leukocytes to stimulate the early inflammatory response to microbes	IL-1, IL-10, IL-12, TNF-α, IFNs, chemokines
Mediators and regulators of adaptive immunity	Produced mainly by T-lymphocytes in response to specific recognition of foreign antigens	IL-2, IL-4, IL-5, IL-13, IFNs, TGF-β, TNF- β
Stimulators of haematopoiesis	Produced by bone marrow, stromal cells and leukocytes to stimulate growth and differentiation of immune cells	IL-3, IL-7, GM-CSF, G-CSF, M-CSF

Table 2. Functional classification of cytokines.

Cytokines	Abbreviation	Activities	Examples
Colony stimulating factors	CSFs	Promote leukocyte maturation/ differentiation	GCSF
Interferons	IFN	Macrophage-activating	IFN-γ
Interleukins	IL	Anti-inflammatory	IL-10, IL-13, IL-1ra
		T-cell-activating	IL-2, IL-4. IL-12
		B-cell-activating	IL-4, IL-5, IL-6, IL-21
		Eosinophil/mast cell-activating	IL-3, IL-4, IL-5, IL-13
		Pro-inflammatory	IL-1, IL-6, IL-8 and IL-17
Transforming growth factor	TGF	Cell cycle regulation, apoptosis	TGFβ
Tumour necrosis factors	TNF	Pro-inflammatory	TNF-alpha, TNF-beta

Table 3. Important cytokines.

Colony stimulating factors (CSFs)

Colony stimulating factors are so called because of their ability to stimulate proliferation and differentiation of haematopoietic cells. Colony stimulating factors bind to specific receptors on bone marrow haematopoietic cells to stimulate their differentiation into different types of blood cells, including immune cells. CSFs are produced by a number of different cells including fibroblasts, endothelial cells, macrophages and other immune cells. There are three main types of colony stimulating factors: Granulocyte colony stimulating factor (G-CSF), Granulocyte-macrophage colony stimulating factor (GM-CSF), and Monocyte-macrophage colony stimulating factor (MM-CSF). CSFs are also manufactured as medications,

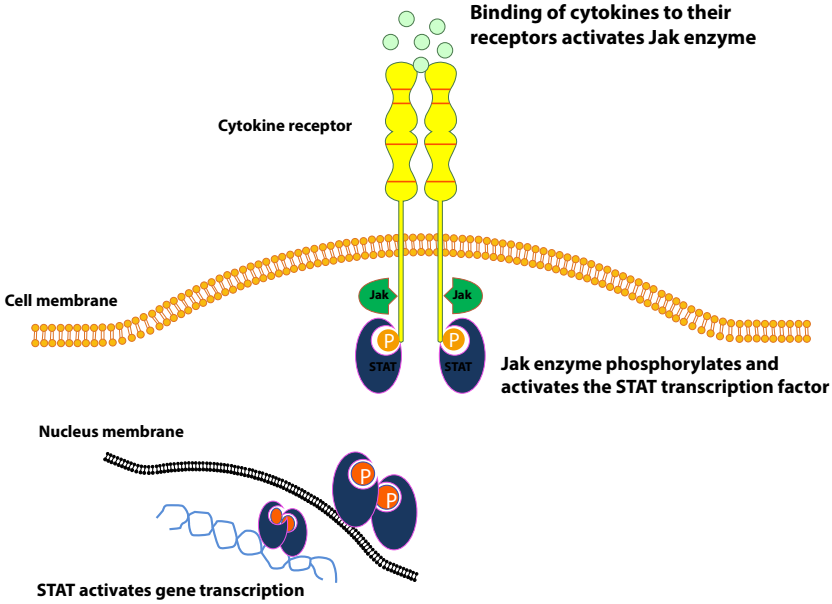


Figure 5. The Jak-STAT pathway.

Type	Origin	Functions
IFN-α	Leukocytes	Anti-proliferative for several cell types including virally-infected cells
IFN-β	Virus-infected cells	Anti-proliferative for several cell types including virally-infected cells
IFN-γ	Activated T-cells	Activates macrophages and T-helper cells, antagonizes IL-4, induces the expression of Class II MHC antigens

Table 4. Types and functions of interferons.

Chemokine	Examples of Activities
C	Attract T-cell precursors to the thymus
CC	Induce monocyte, dendritic cell and NK cell migration
CXC	Induce neutrophil migration
CX3C	Chemo-attractant and act as adhesion molecules

Table 5. Types and functional activities of chemokines.

Type	Origin	Functions
TNF-α	T- and B-cells, macrophages, NK cells, endothelial cells and keratinocytes	Pro-inflammatory cytokine, up-regulates adhesion molecules on vascular endothelial cells and enhances expression of MHC Class I and II antigens, primes neutrophils for adhesion. Chemotactic for inflammatory cells. Initiates apoptosis (programmed cell death). Induces production of matrix-metalloproteases (MMPs) by stromal cells which may lead to tissue remodelling and enhances secretion of keratinocyte growth factor (KGF). Stimulates the production of collagenase and PGE2. Induces liver production of acute phase proteins. Induces fever
TNF-β	T- and B-cells, NK cells, and astrocytes	Mediates proliferation of fibroblasts and endothelial cells and is important in wound healing

Table 6. Types and functions of TNFs.

for example G-CSF has been approved for the treatment of neutropenia caused by chemotherapy and acute leukemia.

Tumour necrosis factors (TNFs)

Tumour necrosis factors are so called because of their ability to induce necrosis in cancer when injected into animals at high concentrations. TNFs are produced by various cells including activated macrophages, B- and T-lymphocytes, natural killers, keratinocytes, fibroblasts and astrocytes (neural cells). TNFs are important mediators of immune responses, can induce acute phase proteins, and are necessary for wound healing. There are two types of TNFs: TNF-α and TNF-β (Table 6).

Transforming growth factor beta (TGF-β)

TGF-β is a multi-function cytokine involved in development, haematopoiesis, wound healing and tissue repair. TGF-β has a crucial role in regulation of the cell cycle and apoptosis. It exists in three different isoforms (TGF-β 1–3).

Conclusion

Cytokines are low molecular weight secreted proteins that facilitate communication and interaction between immune cells.

Cytokines are produced predominantly by helper T-cells and macrophages.

The main cytokines are interleukins, interferons, tumour necrosis factors, colony stimulating factors, and transforming growth factors.

Their effects are largely mediated by the Jak-STAT signalling pathway.

CPD ANSWERS
JUNE 2017

1. D
2. C
3. D
4. A
5. C
6. D
7. B
8. D
9. C
10. D