Cytokines

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Cytokines are produced throughout the body by cells of diverse embryological origin. Cytokine is a general name; other names are defined based on their presumed function, cell of secretion, or target of action. For example, cytokines made by lymphocytes can also be referred to as lymphokines. 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. Those cytokines secreted by monocytes or macrophages are termed monokines. And chemokines are cytokines with chemotactic activities.

Cytokines/immunocytokines, were initially used to separate the immunomodulatory proteins, also called immunotransmitters, from other growth factors that modulate proliferation and bioactivities of non-immune cells. Some cytokines are produced by a rather limited number of different cell types while others are produced by almost the entire spectrum of known cell types.

Recombinant cytokines are in clinical use, and continues attempts are made to develop hybrid molecules from cytokines. 1 must be aware of the fact that current knowledge is still limited. Cytokines are powerful two-edged weapons that can trigger a cascade of reactions, and may show activities that often go beyond the single highly specific property that it is hoped they possess. New factors are being discovered constantly and they extend our knowledge about the Cytokine network.

The understanding of the biological mechanisms governing cytokine actions are an important contribution to medical knowledge. The biochemistry and molecular biology of cytokine actions explain some well-known and sometimes also some of the more obscure clinical aspects of diseases. Knowledge that cytokines create regulatory hierarchies and provide independent and/or interrelated regulatory mechanisms that can confer distinct and interactive developmental functions lays a solid, albeit rather complicated foundation, for current and future clinical experiences.

The concept of "1 producer cell - 1 cytokine - 1 target cell" has been falsified for practically every cytokine investigated more closely. To classify these factors based on their producer or target cells is therefore also problematic.

Classifications based upon identical or shared biological activities of cytokines especially with broad definitions is also problematic for example: BCDF (B-cell differentiation factors), BCGF (B-cell growth factors), Motogenic cytokines, Chemotactic cytokines (Chemokines), CSF (colony stimulating factors), angiogenesis factors, or TRF (T-cell replacing factors). Designations such as HBGF group (heparin binding growth factors) take into account biochemical shared properties by a variety of cytokines which also problematic.

The term cytokine is used today as a generic name for a diverse group which includes proteins and peptides that act in nano-picomolar concentrations as humoral regulators and modulate the functional activities of individual cells & tissues. Cytokines also mediate interactions between cells & regulate processes taking place in the extracellular environment. Many growth factors and cytokines act as cellular survival factors by preventing programmed cell death.

Cytokines resemble hormones in their biological activity & systemic level, for example, inflammation, systemic inflammatory response syndrome, acute phase reaction, wound healing, and the neuroimmune network.

Cytokines act on a wider spectrum of target cells than hormones. The major feature distinguishing cytokines from hormones is the fact that cytokines are not produced by specialized cells organized in specialized glands. Cytokines are secreted proteins which means that their expression sites does not predict where they exert their biological function.

Several cytokines primary structure was found to be identical with enzymes. Cytokines do not possess enzymatic activities although there is a growing list of exceptions. Other cytokines require proteolytic activation.

Cytokines include Interleukins, Lymphokines, Monokines, Interferons (IFN), colony stimulating factors (CSF), Chemokines and a variety of other proteins.

Type-1 cytokines are cytokines produced by Th1 T-helper cells while Type-2 cytokines are those produced by Th2 T-helper cells. Type-1 cytokines include IL-2 (IL2), IFN-gamma (IFN-G), IL-12 (IL12) & TNF-beta (TNF-b), while Type 2 cytokines include IL-4 (IL4), IL-5 (IL5), IL-6 (IL6), IL-10(IL10), and IL-13 (IL13).

Comparison of cytokine sequences shows that primate cytokines (non-human) are closely related. An example: IL-1 alpha (IL1a), IL-1 beta (IL1b), IL-2 (IL2), IL-4 (IL4), IL-5 (IL5), IL-6 (IL6) , IL8 (IL-8), IL-10 (IL10), IL-12 (IL12), IL-15 (IL15), IFN-alpha (IFNA), IFN-gamma (IFN-G), and TNF-alpha (TNFA) which share 93% to 99 % homology at the protein & nucleic acid level with the human sequences.

Cytokines can also be classified into family groups according to the types of secondary and tertiary structure. An example: IL-6 (IL6), IL-11 (IL11), CNTF (C-NTF), LIF, OSM (Oncostatin-M), EPO (Erythropoietin), G-CSF (GCSF), GH (Growth Hormone), PRL (Prolactin), IL-10 (IL10), IFN-alpha (IFN-A), IFN-beta (IFN-B) form long chain 4 helix bundles. IL-2 (IL2), IL-4 (IL4), IL-7 (IL7), IL-9 (IL9), IL-13 (IL13), IL-3 (IL3), IL-5 (IL5), GM-CSF (GMCSF), M-CSF (MCSF), SCF, IFN-gamma (IFNG) form short chain 4 helix bundles. Beta-trefoil structures are formed by IL1-alpha (IL1A), IL1-beta (IL1B), aFGF (FGF-acidic), bFGF (FGF-basic), INT-2 (INT2), KGF (FGF7). EGF, TGF-alpha (TGF-A), Betacellulin (BTC), SCDGF, Amphiregulin, HB-EGF, form EGF-like antiparallel beta-sheets.

Many cytokines are secreted by cells using secretory pathways and therefore are considered glycoproteins. Most genes encoding cytokines give rise to variety of cytokines by means of alternative splicing, yielding molecules with slightly different but biologically significant bioactivities. Usually the expression patterns of different forms of cytokines or of members of a cytokine family are overlapping only partially, suggesting a specific role for each factor.

Membrane-bound cytokines have been are associated with the extracellular matrix. The switching between soluble and membrane forms of cytokines is an important regulatory event. In some cases membrane forms of a cytokine have

been found to be indispensable for normal development, with soluble forms being unable to entirely substitute for them.

Numerous cytokines are not stored inside cells though TGF-beta (TGF-b) and PDGF (P-DGF) are stored in platelets or TNF-alpha (TNF-A) and IL-8 (IL8) are found in human skin mast cells. Most of the cytokine's expression is regulated tightly at practically all levels. The factors are usually produced only by cells after cell activation in response to an induction signal. The production and secretion of cytokines and growth factors frequently is context dependent, i.e., their expression is influenced by individual signals received but also by the balance of signals received through one or more receptors (which themselves may be subject to inducible/repressible expression).

Cytokine's expression is regulated at the transcription level, translation level, and protein synthesis. The expression of cytokines also seems to be regulated differentially, depending on cell type and developmental age. Secretion or release from the producer cells is a regulated process. Once released, their behavior in the circulation may be regulated by soluble receptors and specific or unspecific binding proteins. Regulation also is at work at the receptor level on target cells and at the level of signaling pathways governing alterations in the behavior of responder cells.

Numerous cytokines are pleiotropic effectors showing multiple biological activities. Multiple cytokines have overlapping activities therefore a single cell frequently interacts with multiple cytokines with seemingly identical responses (cross-talk). A possible consequence of this functional overlap is the observation that 1 factor may frequently functionally replace another factor altogether or at least partially compensate for the lack of another factor. Since most cytokines have ubiquitous biological activities, their physiologic significance as normal regulators of physiology is often difficult to assess.

Gene function studies in experimental transgenic knock-out animals in which a cytokine gene has been functionally inactivated by gene targeting are very important in cytokine-research since, unlike in vitro studies, they provide information about the true in vivo functions of a given cytokine by highlighting the effects of their absence. In many instances these studies have shown that null

mutations of particular cytokine genes do not have the effects in vivo expected from their activities in vitro.

Cytokines show stimulating or inhibitory activities and synergize or antagonize the actions of other factors. 1 sole Cytokine elicits reactions under certain circumstances that are the reverse of those shown under other circumstances. The type, the duration, and also the extent of cellular activities induced by a particular cytokine can be influenced considerably by the micro-environment of a cell, depending, for example, on the growth state of the cells (sparse or confluent), the type of neighboring cells, cytokine concentrations, the combination of other cytokines present at the same time, and even on the temporal sequence of several cytokines acting on the same cell. Under such circumstances combinatorial effects thus allow a single cytokine to transmit diverse signals to different subsets of cells.

Although some cytokines are known to share at least some biological effects, the observations that single cells usually show different patterns of gene expression in response to different cytokines can be taken as evidence for the existence of cytokine receptor-specific signal transduction pathways. Shared and different transcriptional activators that transduce a signal from a cytokine receptor to a transcription regulatory element of DNA are involved in these processes such as STAT proteins.

Basic FGF (bFGF) is a strong mitogen for fibroblasts at low concentrations and a chemoattractant at high concentrations. FGFb (FGF-b) has been shown also to be a biphasic regulator of human hepatoblastoma-derived HepG2 cells, depending upon the concentration. Interferon-gamma (IFN-gamma) can stimulate the proliferation of B-cells prestimulated with Anti-IgM, and inhibits the activities of the same cells induced by IL-4 (IL4). On the other hand, IL-4 (Interleukin-4) activates B-cells and promotes their proliferation while inhibiting the effects induced by IL2 in the same cells. The activity of at least two cytokines such as IL1-A (IL1A) & IL1-B (IL1B) is regulated by an endogenous receptor antagonist, the IL1 receptor anagonist (IL1TA). Cytokines, such as TNFA (TNF-A), IFN-gamma (IFN-G), IL-2 (IL2) & IL-4 (IL4), are inhibited by soluble receptors. Cytokines including IL-10 (IL10) and TGF-beta (TGF-B), inhibit other cytokines.

Early Cytokines preactivate cells so that they then can respond to late-acting cytokines. Cytokines induce the synthesis of novel gene products once they have bound to their corresponding. Several of the novel products are themselves cytokines. In addition, there are a variety of biological response modifiers that function as Anti-cytokines.

Cytokine mediators swiftly remote areas of a multicellular organism & multiple target cells can be degraded quickly, One can assume that cytokines play a pivotal role in all sorts of cell-to-cell communication processes although many of the

Thorough examination of the physiological effects of the expression of cytokines in complex organisms has shown that these mediators are involved in all systemic reactions of an organism, including the important processes as regulation of immune responses, for example: BCDF(B-cell growth and differentiation factors), BCGF (B-cell growth factors) TRF (T-cell replacing factors), Isotype switching, inflammatory processes, hematopoiesis, and wound healing.

Embryogenesis and organ development inlvolves important mediators called Cytokines. Their activities in these processes may differ from those observed postnatally. Cytokines play a key role in neuroimmunological, neuroendocrinological, and neuroregulatory processes. Cytokines also regulate cell cycle, differentiation, migration, cell survival & cell death, and cell transformation. Viral infectious agents exploit the cytokine repertoire of organisms to evade immune responses of the host. Virus-encoded factors affect the activities of cytokines in at least four different ways: by inhibiting the synthesis and release of cytokines from infected cells; by interfering with the interaction between cytokines and their receptors; by inhibiting signal transmission pathways of cytokines; and by synthesizing virus-encoded cytokines that antagonize the effects of host cytokines mediating antiviral processes. Bacteria and micro-organisms also appear to produce substances with activities resembling those of cytokines and which they utilize to subvert host responses.

Cytokines are rarely related among eachother in their primary sequences. Some appear to have common 3 dimensional features and some of them can be grouped into families. An example is the TNF ligand superfamily members (with the exception of LT-alpha) are type 2 membrane glycoproteins (N-terminus inside) with homology to TNF in the extracellular domain (overall homologies, 20 %).

The HBNF family includes members of the group of fibroblast growth factors. The chemokine group which contain diverse factors also have conserved sequence features. Analysis of crystal structures of several cytokines with very little sequence homology has revealed a common overall topology that is not deducible from sequence comparisons.

Cytokine biological activity of is mediated by specific membrane receptors, which are expressed on all cell types known. Cytokine expression is also subject to several regulatory although some receptors are expressed also constitutively.

Cytokine receptor proteins are multi-subunit structures that bind ligands and at the same time possess functions as signal transducers due to their intrinsic tyrosine kinase. Many receptors often share common signal transducing receptor components in the same family, which explains, at least in part, the functional redundancy of cytokines. Cross-communication between different signaling systems allows integration diversity of stimuli, which a cell can be subjected to under varying physiological situations. This and the ubiquitous cellular distribution of certain cytokine receptors have hampered attempts to define critical responsive cell populations and the physiologically important cell-specific functions of cytokines in vivo. Numerous receptors are associated with special signal transducing proteins in the interior of the cell. Receptors bind more than 1 cytokine. Cytokine receptors shown to be converted into soluble binding proteins that regulate ligand access to the cell by specific proteolytic cleavage of receptor ectodomains.

Specific activities of cytokines have been the basis for current concepts of therapeutical intervention, in particular of the treatment of hematopoietic malfunctions and tumor therapy. Applications involve the support of chemo- and radiotherapy, bone marrow transplantation, and general immunostimulation.

Cytokines and their receptors exhibit very high affinity for each other. Because of this high affinity, picomolar concentrations of cytokines can mediate a biological effect. Following are the different types of secretory actions : **Autocrine action** by binding to receptor on the membrane of the same cell that secretedit.

Paracrine action binding to receptors on a target cell in close proximity to the producercell.

Endocrine activity by traveling through circulation and acting on target cells in distant parts of the bod

Cytokines can regulate cellular activity in a coordinated interactive way due to the following attributes:

Pleiotrophy

one cytokine has many different functions.

Redundancy

several different cytokines can mediate the same or similar functions.

Synergism

- occurs when the combined effect of two cytokines on cellular activity is greater than the additive effects of individual cytokines.

Antagonism

the effects of one cytokine inhibits or offsets the effects of another cytokine.