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Interaction of interferon with other cytokines

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Summary. Interferons interact with other cytokines to exert their antiviral, cell growth regulatory and immunomodulatory activities. Growth factors, tumor necrosis factors, colony stimulating factors, interleukins and interferons have pleiotropic effects and form a parallel network of intercellular signals. These signals are transduced at the cell surface through specific receptors with intrinsic enzymatic activity or with the capacity to regulate intracellular enzymes through interactive effects with G-proteins. This leads to regulated gene transcription of intracellular and secreted, functional and structural proteins. Although much is known about the interaction of cytokines with their receptors and about the regulation of transcription at the genomic level the various steps linking these two phenomena deserve further research.
Key words. Cytokines; interferons; interleukins; colony stimulating factors; growth factors; inflammation; macrophages; cytokine receptors.

Introduction

Interferon was the term originally given to secreted (glyco) proteins capable of inducing an antiviral state in cells[45, 54]. The purification of interferons and the generation of antibodies directed against interferons made it possible to classify these substances on the basis of their seroreactivity into interferon-α, interferon-β, and interferon-γ[18]. In addition interferon-α and interferon-β, originating mainly from leukocytes and fibroblasts respectively, were clearly distinguished by biochemical and biological characteristics from interferon-γ, which is pro-

duced by stimulated T-cells[92]. With the use of molecular cloning techniques more than 20 subspecies of interferon-α and one type of both interferon-β and interferon-γ were identified[27]. The classification, based on biological and immunological criteria corresponded well with the data of gene structures. The multiple non-allelic variants of interferon-α were classified with subscripts. Expression of the interferon genes led to the production of recombinant products which were used to study the role of interferons in host defense against microbiological and parasitic infections, against cancer and in immune disorders. The availability of purified recombinant and natural interferons as well as monoclonal antibodies to antagonize the interferons have recently been used to resolve several controversies about the other regulatory functions of interferons such as control of cell growth. It is now clear that in addition to their antiviral effects interferons interact with a whole range of other cytokines[9, 24, 29] to concert or counteract their mutual actions.

Cytokines

Cytokines are secreted signalling (glyco)proteins that interact with specific cellular receptors at short range, i.e. in the cellular micro-environment, as well as in distant tissues. The specific activities can be compared to those of the glandulotrophic hormones and are of the order of 10^9 units per mg pure product. This corresponds to biologically active concentrations ranging from 10^{-10} to 10^{-12} molar. Cytokines regulate cell functions such as growth and growth inhibition, cell motility, and secretion. Cytokines are autocrine and paracrine as well as endocrine factors that modulate physiological important functions such as the specific (antibody formation and T-cell receptor function) and aspecific (i.e. immunogen-independent) host defense mechanisms. The interferons and some hormones can thereby be classified as cytokines. Table 1 lists several groups of cytokines as well as their most prominent biological functions.

Among the cytokines that govern the proliferation and development of hemopoietic progenitor cells in vitro, the four colony stimulating factors (CSF)[26, 56] as well as erythropoietin were characterized by molecular cloning[33, 35, 46, 48, 59, 62, 93, 94]. The CSFs were named G-CSF, M-CSF, GM-CSF and multi-CSF (also called interleukin-3) because they directly support in a hierarchic manner the growth of different subsets of progenitor cells directly into granulocytes, macrophages or both, or into all white blood cells. Erythropoietin is a cytokine (hormone) involved in the regulation of the red cell lineages. Other cytokines, called interleukins (IL) are involved in the proliferation and differentiation of T- and B-cells and include IL-1 (lymphocyte activating factor)[89], IL-2 (T-cell growth factor)[75], IL-4 (mast cell growth factor)[97], IL-5 (eosinophil growth factor)[17] and IL-6 (hybridoma/plasmacytoma growth factor)[10, 42, 81]. A compilation of the actions of IL-1 to IL-6 was recently written[66]. The family of interleukins is continuously expanding, and in the meantime interleukin-7[60] and a chemotactic factor, recently designated as interleukin-8[87], have been described.

A third group of cytokines which share at least part of their nomenclature is the series of growth factors.

Cytokines	Function(s)	Producer cell	References
Interferons			
IFN-α	Antiviral activity, immunomodulation	B-cells, macrophages	4, 18, 45, 53
IFN-β		Fibroblasts	
IFN-γ		T-cells	
Colony stimulating factors			
G-CSF	Stem cell differentiation and proliferation	Fibroblasts	35,59,62
M-CSF		Stromal cells	48, 93, 94
GM-CSF		Monocytes	33
Multi-CSF (IL-3)			
Interleukins			
IL-1	Immunomodulation	Monocytes	28
IL-2		T-cells	75
IL-3		see CSF	33
IL-4		T-cells	97
IL-5		T-cells	17
IL-6		Many cell types	36, 42, 49, 81, 91
IL-7		Stromal cells	60
IL-8		Monocytes	87
Growth factors			
EGF	Cell growth control	Submaxillary glands	37
PDGF		Platelets	90
FGF		Fibroblasts	50, 51
TGF-α/β		Tumor cells	55
Tumor necrosis factors			
TNF-α/cachectin	Immunomodulation	Macrophages	7
TNF-β/lymphotoxin		T-cells	68

Without providing a complete list, some typical members of this group of cytokines are included in the table (EGF, PDGF, TGF-α and-β, insulin-like growth factor)[37, 50, 51, 55, 90]. That all these factors stand for various biological functions and many have pleiotropic effects is best illustrated with IL-1 and IL-6. IL-1 was also the name given to the substance which was once known as endogenous pyrogen, mediating the general fever response during inflammatory reactions[89]. Now it is generally accepted that the local as well as the general effects of the two species of interleukin-1 (IL-1α and IL-1β), both identified by molecular cloning, are mediated through one type of cellular receptor[74]. Both types of IL-1 can activate lymphocytes, can induce fever and granulopenia[86, 88], and can induce the production of proteases[16], prostaglandins[23] and other cytokines[20, 82, 84, 85]. Among the cytokines induced by IL-1 are IL-2, G-CSF, GM-CSF, IL-6 and IL-8. This already illustrates a point that will become more apparent in other examples, that in cellular crosstalk, cytokines interact so as to form a sort of network. The interactions within this network are not in a linear arrangement, (such as a sentence, which is built by a linearly consecutive array of words) but rather take place in a branched hierarchical organization. The record holder in nomenclature up to now is IL-6: first named IFN-β_2[72, 91] and 26 K molecule[19, 38], coinduced with interferon-β_1, this substance has also been called hybridoma/plasmacytoma growth factor[81], B-cell stimulatory factor 2[42, 49], and hepatocyte-stimulating factor[36], and also named hippocratin and inflammatin, to be rebaptized finally as IL-6[69, 81]. The cytokine has several additional biological effects including the promotion of growth of T-cells and stem cells[95]. It is an autocrine factor for certain plasmacytomas and stimulates the proliferation of hybridomas and other B-cells[47, 49].

Cytokine receptors

If the cytokines are the words of the intercellular communication, the cytokine receptors recognize and understand this language. For many polypeptide hormones and several growth factors receptors have been isolated and characterized. The autocrine stimulation of cell growth as a basic mechanism of oncogenesis has been well documented[76, 77]. It is now generally accepted that oncogenes can in one or another way mimic or short-circuit the action of cytokines; by structural analogy to the growth factor itself[90], to the growth factor receptor[80], to a part of the growth factor receptor (noticeably the kinase domain)[5, 30] or by activation of the corresponding second messenger that is activated by the post-receptor mechanisms. The receptor for EGF has become a prototype[44] in the sense that it clearly shows four functional domain structures: 1) the extracellular part which binds the ligand, 2) the transmembrane domain of hydrophobic amino acids that is embedded in the cell membrane, 3) the intracellular enzymatic domain in the form of a (protein)kinase, sulphatase or other enzyme, and 4) an autophosphorylation part (that might change conformation after stimulation). At present only simplified models exist describing the fate of signal transductions after the presence of the cytokine is perceived by the cell. Ion fluxes, generation of second messenger molecules and phosphorylation of proteins have been implicated in the transmission of cytokine signals. Recently a whole series of G-proteins have been implicated in signal transduction[34, 39, 61]. To exert their function, these proteins are translocated from a cytoplasmic pool to cell membranes.

Figure 1 illustrates how cytokine receptors interact and how the intracellular signals are transmitted finally into changes in the molecules that regulate gene transcription. It is surprising that, in spite of the fact that interferons were amongst the first cytokines to be studied by molecular cloning of their cDNAs, it is only recently that the primary structure of the interferon receptors has been deduced from cloning experiments[2, 73]. One could however foresee that with the recent description of the purification of the IFN-γ receptor, the availability of monoclonal antibodies against them[1] and the pure recombinant ligands for the affinity purification of the receptor, the complete amino acid sequences of the receptors could soon be known. On the other hand, cytokines that have only recently been brought into focus by the molecular biologists, such as IL-1 and IL-6 have already been used to disclose the primary structure of their receptors[74, 96].Both the IL-1 and the IL-6 receptors belong to a superfamily of immunoglobulins, whose number of characterized members is constantly growing.

In analogy with the cytokine network one can presume that the cytokine-receptors on a certain cell will also interact with each other. At least two different types of receptor-interactions are well known: down-regulation and transmodulation[76]. The first can be defined as a reduction of receptor-number by a structurally homologous ligand, resulting in a diminished responsiveness of the treated cells to the natural ligand. An illustrative example of this type of receptor interaction is the downregulation of protein kinase C (the receptor for diacylglycerols) by the structurally homologous phorboid tumor promoters[22, 63 - 65]. The phenomenon of receptor downregulation is widely applied in human therapy for the design of pharmacological substances to antagonize the action of all kinds of ligands e.g. neurotransmitters. Transmodulation is conceived as a conformational change in the receptor or an alteration in its cellular distribution, resulting in an affinity for a different second ligand, without the requirement of any structural cross-reactivity of the two different ligands. For instance EGF shows a lower affinity for its receptor in the presence of PDGF[76]. Whether a third, different mechanism is involved in receptor cross-talk, namely multifunctionality of receptors, remains an open ques-

tion. An example of such a mechanism might be the recent discovery that the mannose-6-phosphate receptor is identical to the receptor for insulin-like growth factor II[57].

The possibility that IL-6 (previously also called IFN-β_2) might interact with a multifunctional IFN-β_1 receptor seems not to be the case. Since the primary structure of the IL-6 receptor is known, we only have to await for the comparison with the amino acid sequence of the IFN-β_1 receptor to answer this question. Previous studies[21], however, seem to indicate that receptor transmodulation or induction of IFN-β_1 by IL-6 might be the only explanations for the so-called antiviral activity of the latter.

Post receptor mechanisms

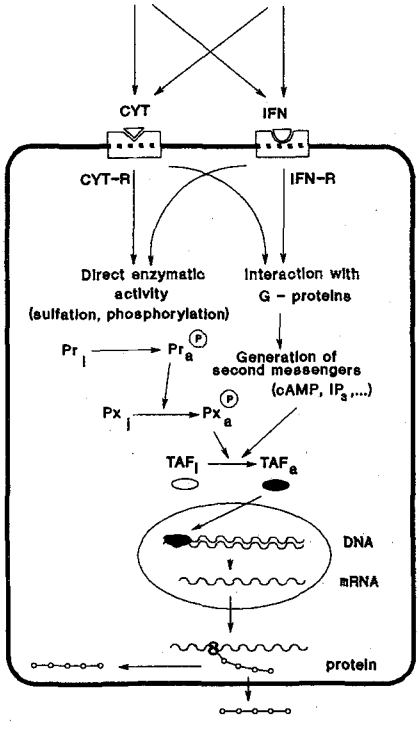
As briefly outlined in figure 1, general concepts exist for the generation of intracellular second messenger molecules after stimulation by hormones, neurotransmitters and cytokines[6, 64]. Stimulatory (Gs), inhibitory (Gi) and other (Go) GTP-binding proteins were shown to play a role in signal transduction[34]. Other GTP-binding proteins (initiation factors, elongation factors of protein synthesis) mediate the intracellular response to interferons[53]. The ras-oncogene belongs to the same superfamily of G-proteins and, like interferon and growth factors, it seems to modulate cell division[3]. Studies in our laboratory indicate that cytokines (e.g. IFN-γ) use the G-protein signalling pathways. Another aspect of the intracellular signal is the activation of protein kinases with the phosphorylation of regulatory proteins as an end-result. Among these are not only transcription factors that directly regulate gene-transcription, but also factors that influence the intracellular compartmentalization and transport as well as the secretion of bioactive molecules.

Interactions between different cytokines

The cellular effects of different cytokines on one particular cell are attained through different or interacting receptor mechanisms and convergent intracellular post receptor mechanisms. However, this section will deal mainly with the extracellular events of cytokine interaction: i.e. the cytokine network. Figure 2 summarizes the known interactions between the interleukins and colony stimulating factors (center of the figure) with the three types of interferon (at the borders of the figure).

Interferons

Interferon-γ is produced by stimulated lymphocytes and it is one of the major macrophage activating factors (MAF). The macrophage/monocyte plays a crucial role



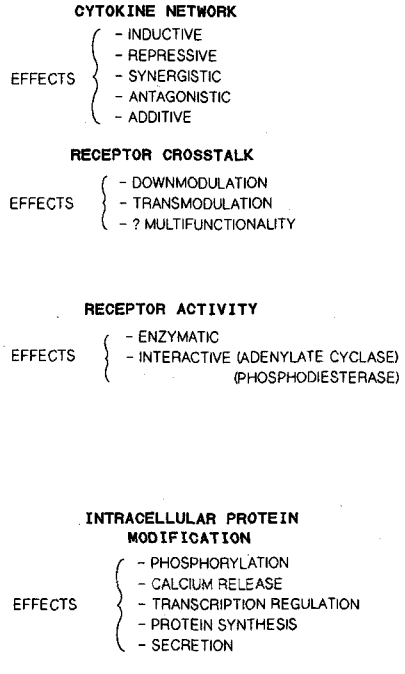


Figure 1. Levels of interaction between interferons and other cytokines. The coordinated secretion in the extracellular environment of signal molecules such as the interferons (IFN) and other cytokines (CYT) and the concerted action of these in the cytokine network leads to the generation of signals that are transduced to the intracellular compartment through specific receptors (CYT-R and IFN-R). Signal transduction is effected through direct enzymatic activity of the receptor or by interaction with regulatory G-proteins. Inactive protein substrates (Pr_i, Px_i, e.g. transacting factors (TAF_i) are thus activated (Pr_a, Px_a, TAF_a) by phosphorylation, sulfation, glycosylation, etc. The generation of second messenger molecules such as cyclic adenosine monophosphate (cAMP), diacylglycerol and inositoltriphosphate (IP_3) also occurs through enzymatic activity (adenylate cyclase, phosphodiesterase). These second messengers cause the activation of regulatory proteins (e.g. protein kinases) and intracellular ion fluxes. This leads to regulated transcription of genes coding for intracellular and secreted, structural and functional proteins.

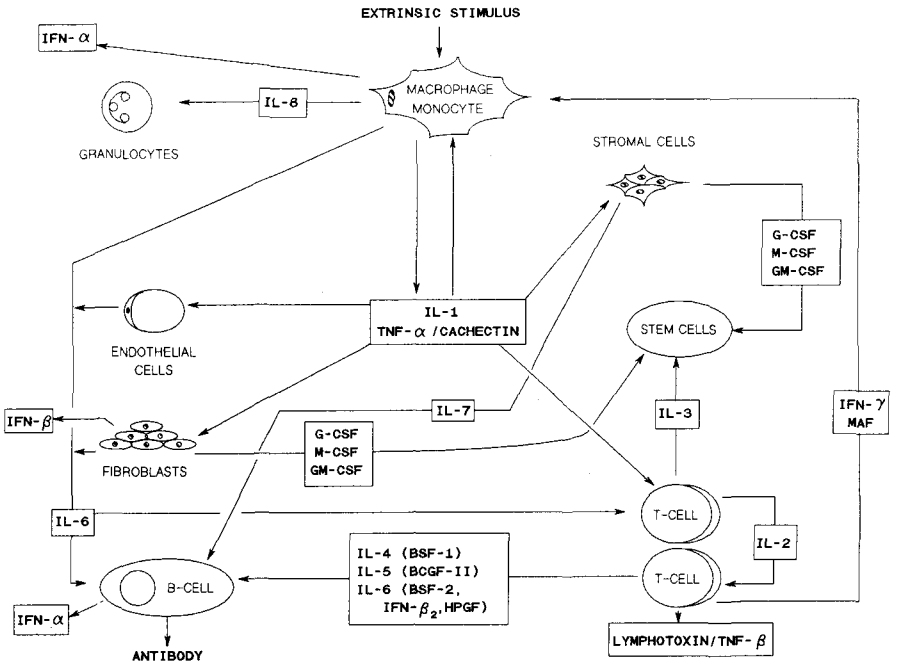


Figure 2. The cytokine network. Extrinsic stimulation of macrophages (by e.g. lipopolysaccarides, infectious agents, altered immunoglobulins) leads to the secretion of interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α). These central control mediators activate several cell types (fibroblasts, endothelial cells, lymphocytes, monocytes, stromal cells, chondrocytes, synovial cells,...) to produce other cytokines. Thus a whole repertoire of signal molecules is generated. These are active in unspecific and immunogen-dependent host defense. The different types of interferons produced are indicated at the sides of the figure. The several arrows point from the producer cell towards the effector cells.

in several host defense mechanisms (e.g. antigen presentation, production of complement factors, lysozyme, elastase,...) and fulfills a key function in the production of cytokines (IL-1, TNF-α, IL-6) (fig. 2). IFN-γ-stimulated production of IL-1/TNF-α, resulting in subsequent production of IL-2 and IFN-γ by the T-cells, forms a positive feed-back loop yielding a full-blown inflammatory response. Homeostatic mechanisms must exist to certify that this short-circuit does not lead to undesirable side effects[79]. One can anticipate that further research will lead to the identification of natural anti-cytokines. Another implication of the IFN-γ/IL-1/TNF-α/IL-2 loop is that the antagonization of one or several cytokines can be used therapeutically to prevent the detrimental side effects of inflammatory reactions in e.g. experimental allergic encephalitis, generalized Shwartzman reaction, or severe cerebral malaria[11,12,40,41]. The use of monoclonal antibodies, directed against the cytokines or modified synthetic peptides to compete with the active center(s) of the cytokines, are here defined as cytokine-antagonization. In contrast to the naturally occurring inhibitors or anti-cytokines (these might be natural variants of the cytokines, e.g. glycosylation variants, (glyco)peptides originating from aminoterminal, carboxyterminal or internal clipping), the cytokine-antagonists are artificially-made switches for the positive feed-back loops. Finally recent studies seem to indicate that the antiviral activity of IFN-γ seems to be indirect i.e. through the production of IFN-α/β[43]. Fibroblast interferon (IFN-β) is produced by 'stimulated' fibroblasts in response to viral infection and also after stimulation with cytokines. IL-1 and TNF-α have been reported to exert an indirect antiviral effect which is mediated by IFN-β and not by IFN-β_2[83]. IFN-β (sometimes referred to as IFN-β_1) is the product of a human gene located on chromosome 9, clustered with the IFN-α genes. The so-called IFN-β_2 gene, located on human chromosome 7[71] will be henceforth referred to as the IL-6 gene[69]. It is still a point of discussion whether IL-6 has direct, if any, antiviral activity. It is certainly coinduced with IFN-β and it also is an interactive factor in the cytokine-network[52,82]. There exist many subtypes of IFN-α. These interferons are produced by macrophages but also by lymphoblastoid cells and other white blood cells[4]. Whether the structural differences between these subtypes of IFN-α reflect different functions (e.g. targetting to different cells, control by competitive antagonization,...) is not yet clear.

Interleukins

The definition of the various interleukins, at least to replace the many functional names for different cytokine activities, has helped to clarify to a great extent the complexity of the cytokine network. IL-1 is produced by macrophages (Kupffer cells in the liver, Langerhans cells in the skin, histiocytes or tissue-macrophages, peritoneal, pleural, and synovial macrophages, monocytes,...) and plays, together with tumor necrosis factor-α, a central role in the activation of the cytokine-network after the macrophages have been stimulated by all kinds of stim-

uli[28] (lipopolysaccharides[8], agalactosyl immunoglobulins[67], denatured antibodies, viruses, chemical substances,...). IL-1 can induce the production of many, if not all other interleukins (fig. 2)[14]. In T-lymphocytes it can stimulate the synthesis of IL-2, IL-3, IL-4, IL-5. In almost all cell types it induces the formation of IL-6. Although it has not yet been shown that IL-1 can stimulate bone marrow stromal cells to synthesize IL-7, it is already established that these cells can produce colony stimulating factors in response to IL-1[31]. Finally macrophages (and also other cells) secrete a chemotactic factor (interleukin-8) after stimulation with IL-1[87].

Colony stimulating factors, other growth factors and TNF

Colony stimulating factors are secreted by the stromal cells in the bone marrow.This cell-rich stroma contains a mixture of endothelial cells, fibroblasts, adipocytes and macrophages. It is not surprising that similar cells at other localizations (e.g. dermal fibroblasts) can also synthesize the CSFs[31,32,98]. Although IL-1 appears to play a crucial role in the induction of CSFs in fibroblasts and stromal cells, other cytokines such as TNF-α and PDGF can also exert similar effects on CSF production[15,25,58]. Growth factors, other than CSFs and interleukins, although their names perhaps do not suggest immunomodulatory functions, interact in the cytokine network. Particularly interesting is PDGF. It has been shown that PDGF mimics IL-1 and TNF-α in the induction of IL-6[52]. On the other hand, PDGF has also been found to antagonize the action of IFN-β with respect to induction of specific proteins[78]. Tumor necrosis factor-α (and IL-1) mimic IFN-β by their indirect antiviral effect[13,84,85,89].

Perspectives

The availability of DNA or RNA-probes of the cytokine genes and of other genes induced or repressed by cytokines will undoubtedly contribute to our understanding of the cytokine network. It is not difficult to envisage that one will be able to study the regulatory pathways with accuracy by using pure cytokines to induce (or repress) other cytokines which could be traced with the use of monoclonal antibodies, or whose gene expression can be probed with cloned sequences. On the other hand, there exist whole batteries of cloned gene-sets induced e.g. by interferon[70] or by PDGF. With the use of these genes it will be possible to unravel the complexity of interactions (inductive, repressive, synergistic, antagonistic, additive) between cells and cytokines and interferons individually and in combination. Because these interactions are present in all physiopathological processes, a better understanding of them will point to novel strategies for the treatment of immune diseases, inflammatory processes and probably cancer.

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