Occasional articles

Cytokines as biological response modifiers

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Introduction

The immune system has evolved into a complex series of cell types, and the division of labour within this system falls essentially between those cells which are involved in antigen specific recognition and those which have an all-purpose defensive role, thereby providing an antigen nonspecific response. The development of antigen specific immunity and the maintenance of innate resistance is finely controlled by molecular signals mediated through the release of cytokines. Mature immunocytes develop from bone marrow precursors along defined lineages, and the processes of differentiation and expansion (proliferation) are controlled through the local production of cytokines with specialised functions. Elsewhere in the body, usually in lymphoid tissue, further maturation and proliferative signals allow immunocompetent cells to assume a specific function in defence against foreign or abnormal cells and invading organisms. We now recognise that cytokine production by lymphoid cells is essential for the development and maintenance of immunity, and it has become clear that many cell types, other than those of the immune system, produce and respond to these molecules. In this review some of the main features of the cytokine network will be considered, although it will not be possible to cover in detail all the communication pathways that are now recognised.

Biological properties of cytokines

The main groups of molecules classified as cytokines include: all the interleukins (1-12); the interferons (α , β , and γ); colony stimulating factors (G-CSF, M-CSF and GM-CSF); tumour necrosis factors- α (cachectin) and β (lymphotoxin); the transforming growth factor β family; and additional growth factors which include erythropoietin, nerve growth factor, epidermal growth factor, fibroblast growth factors, insulin-like growth factors and platelet derived growth factor (table 1). Genes known as "proto-oncogenes" encode for many of these or their cell surface receptor, and their enhanced expression results in an increase in cell proliferation, or causes the cell to differentiate.¹⁻³ When gene expression is unregulated, uncontrolled proliferation can occur, and cell transformation may result.

Most cytokines are proteins or glycoproteins of a molecular weight of less than 80 kilodal-

tons, and act in either an autocrine or paracrine manner—that is, they influence the biological behaviour either of the cell producing the cytokine or cell types of a different lineage (fig 1). Cytokines have a role in the development and maintenance of immunity and inflammatory processes, regulating the amplitude and duration of the response, and unlike the endocrine system, these molecules act over comparatively short distances, as potent modulators of cell behaviour. The cellular response occurs as a result of cytokine interaction with specific high affinity cell surface receptors. Although certain cytokines are preformed—for example, IL-1 and tumour necrosis factor α (TNF α) may be held within the membrane of cells bound to precursor molecules—the production of most cytokines requires the depression of cytokine genes and the subsequent translation of mRNA into protein. The response of a given cell type is dependent on that cell expressing the appropriate receptor molecules and the interaction of the receptor with specific regions of the cytokine (epitope, defined by a specific amino acid sequence). Accessory molecules, which themselves have no cytokine binding ability, may associate with the receptor to increase the affinity of binding of that particular cytokine. For certain cytokines, such as IL-1, different binding proteins (receptors) are present on different cell types, and the number of cytokine molecules required to initiate a biological response can be extremely low; for IL-1 it is thought that a single molecule interacting with its receptor is sufficient to cause cell activation. An important point to make here is that receptor occupancy alone is insufficient to induce cell activation. As will be discussed later, the blockage of receptor sites by small antigenic receptor-binding peptides can occur, and this may have some clinical use in regulating adverse cytokine effects.

The consequence of cytokine binding to its receptor is the transduction of a signal across the cell membrane and the activation of intracellular biochemical pathways. One known pathway involves G-proteins and adenylate cyclase and protein kinase C activation. Common and unique factors regulate the transcription of cytokine and cytokine receptor genes, and the second and third messenger pathways involved are the subject of intensive research.⁴ Internalisation of the cytokine receptor complex then occurs, but this event is

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Table 1 Recognised cytokines

Interleukins	1-12
Interferons	α, β, γ
Tumour necrosis factor	α, β
Colony stimulating factors	
Transforming growth factor family	
Other growth factors	

Figure 1 Autocrine and paracrine action of secreted cytokines.

unlikely to provide additional activation signals which influence cell behaviour. Many of the cytokine receptors are heterodimeric (fig 2).

Synergistic and multifunctional properties of cytokines

One of the main features of cytokines is their ability to act in concert to bring about cell activation. This is exemplified during haemopoiesis, where cells mature from multipotential bone marrow stem cells into progenitor cells for various blood cell types. This maturation process involves the exposure of bone marrow cells, at different stages of their development, to combinations of cytokines which will determine the fate of that particular

cell. Multipotential stem cells express receptors for a range of cytokines and undergo self renewal or differentiation along lymphocyte or myeloid pathways, which is a consequence of the cytokines they encounter and their relative concentrations. Activation and cytokine secretion is also governed by cell to cell contact (fig 3) when stem cell-bone marrow stromal cell adhesion results in the controlled release of cytokines. Certain cytokines, including IL-1, IL-6, and GM-CSF, have a broad target specificity, whereas others for example, G-CSF, M-CSF, IL-5 and erythropoietin, have more limited target specificities. The mature cells which result from these proliferative and differentiation events include erythrocytes, granulocytes, lymphocytes, monocytes, macrophages, mast cells and platelets.

There are numerous examples of cytokines acting in a multifunctional manner, but this review can only consider some of these. IL-1, IL-6, and TNF- α are classic examples of cytokines with multifunctional activity, which are produced mainly, but not exclusively, by monocytes and are involved in the induction of immunity, haemopoiesis, and inflammation.⁵ IL-1 and IL-6 stimulate acute phase protein production by hepatocytes, and IL-1 shows the diverse effects of basophil and eosinophil activation, fibroblast proliferation and collagen production, the release of hypothalamic and pituitary peptides including adrenocorticotrophic hormone (ACTH), antiproliferative effects on some tumour cell lines and an increase in the resistance of mice to Gram negative bacterial infection.⁶ Table 2 shows some of the major effects of this cytokine. IL-6 is a growth factor for hybridomas and plasmacytomas, but can also mediate antiviral activity, and was originally referred to as interferon- β -2. IL-6 also acts synergistically with other cytokines to induce T cell activation, thymocyte proliferation, and B cell differentiation.

TNF- α , as its name implies, can cause the necrosis of some experimental tumours, but this molecule also has other wide-ranging biological effects: both TNF- α and IL-1 can protect cells of the immune system against lethal doses of irradiation (radioprotective), which may allow them to be used as protective agents during radiotherapy. TNF- α has also been shown to be a mediator of Gram negative bacterial endotoxic shock, and seems to be responsible for causing fever, metabolic acidosis, diarrhoea, hypertension, disseminated vascular coagulation and even death. Furthermore, TNF- α activates neutrophils, induces IL-1 gene expression, enhances the expression of class I major histocompatibility complex (MHC) antigens and adhesion molecules on endothelial cells, and is involved in bone marrow resorption and the production of prostaglandin E₂ and collagenase from human synovial cells and fibroblasts. A given cell may therefore receive an extensive series of concurrent messages transmitted by cytokines, which results in a multiplicity of checks and balances that serve to govern the intensity and duration of the response.

Figure 2 Examples of growth factor receptors known to be composed of two or more subunits, which, together, mediated high affinity binding and signal transduction.

Figure 3 Bone marrow stem cell-stromal cell adhesion, causing the release of cytokines which promote (i) self renewal; (ii) differentiation.

Cytokines and the immune response

Cytokines have a decisive role in determining the immune status, and the integrity of the immune system is controlled by efficient cellular responses to cytokine stimulation. As a consequence of cytokine activation, the natural defence system of the body is maintained on heightened alert and the specific immune response to foreign antigens can be efficiently mobilised. Communication between different populations of cells occurs in lymphoid organs when cells cluster and respond to foreign antigens simultaneously with cytokine activation; interaction between cells takes place as a result of surface molecules which mediate cell adhesion.⁷

B lymphocyte development is influenced by cytokines in the bone marrow, and apart from those already mentioned which have a role in haemopoiesis, a recently discovered cytokine, IL-7, produced from the stromal cells within the bone marrow has been shown to be influential in inducing proliferation and differentiation of pro- and pre-B cell precursors.⁸ The mature B cell response to a specific antigen can be initiated following the binding of that antigen to surface immunoglobulin. This complex is then taken up by the B lymphocyte, processed within the cell, and a proteolytically cleaved peptide is expressed at the cell surface bound to class II major histocompatibility complex (MHC-II) antigen. During this process the B cell is primed to respond to a variety of cytokines produced by T helper cells. The cytokines released include IL-2, IL-4, IL-6 and interferon γ . These cytokines have decisive roles: IL-2 acts together with IL-5 to induce B cell proliferation, while IL-6 determines the maturation status of the cell. Other cytokines are known to inhibit these events and so prevent uncontrolled B cell activation from taking place. This brief summary of the induction phase of specific antibody producing B

cells serves to illustrate two important requirements for cell activation: first, interaction between surface receptor molecules and antigen is necessary to prime cells to respond to cytokines, and second, the release of cytokines is determined by local cell-cell interactions. The development of cell mediated immunity, involving the production of cytotoxic T lymphocytes which are essential for full immunocompetence to invading organisms, particularly viruses, is dependent on the production of cytokines, especially IL-2 and IL-4. These are the principal T cell growth factors, although the synergistic effects of other cytokines are also necessary for T cell activation. The cytotoxic T cell response is initiated by antigen presenting cells (APC), aided by helper T lymphocytes. Here, antigen taken up and processed by APC is presented at the cell surface as peptide fragments associated with MHC class II antigens. T cells interact with the presented peptide and respond to IL-1 and IL-6 which are secreted from the APC; IL-2 is subsequently released by T helper cells and causes the proliferation of antigen specific T cell clones.⁹ In the effector phase cytotoxic T cells will recognise a single specific antigen (epitope or amino acid sequence) on the appropriate target only when it is expressed in association with MHC class I molecules.⁹ This phenomenon is known as genetic restriction and is a consistent feature of the cellular response of higher mammals. IL-4 is likely to represent the major influence for the clonal growth of antigen specific T cells, while IL-2 can also act as a polyclonal activator of T cells and natural killer cells (large granular lymphocytes), and can also cause cells to develop potent antigen non-specific cytotoxic responses.

The most potent macrophage activating factor known is interferon- γ (IFN- γ), a 55 kilodalton protein produced mainly by T cells and possessing, as its name suggests, antiviral activity. The many effects of IFN- γ include the ability: to induce MHC class II antigens, and thereby influence antigen presentation to lymphocytes; to stimulate production of reactive oxygen radicals, which mediate cell toxicity^{10 11}; and to initiate the production of other cytokines, such as IL-1, CSF-1, and G-CSF. IL-1 and IL-2 can also activate monocytes, due in part to the production of TNF- α .¹² Cytokines produced by monocytes also contribute to the recruitment of host defence cells into a site of inflammation, although the overproduction of these cytokines is harmful to the host, as shown by the involvement of IL-1 and TNF- α in septic shock in patients with meningococcal septicaemia.¹³

Interleukin-2: an essential cytokine for immunocompetence
IL-2 is central to processes involved in the development of antigen specific and antigen non-specific immune responses. This cytokine is produced in the main by CD4 positive helper T lymphocytes, and interacts with those cells expressing IL-2 receptors. IL-2 governs the behaviour of T and B lymphocytes, natural

Table 2 Interleukin 1 α , 1 β

Synthesised as precursors cleaved to 159 (α), 153 (β) aa (17 kilodaltons) not glycosylated	
Paracrine action induces IL-2, IL-6, PDGF	
Target	Response
T	Activation—cytokine release
B	Proliferation, differentiation
Fibroblasts	Proliferation, PG/collagenase secretion
Synovium	Collagenase secretion
Hepatocytes	Acute phase protein release
Muscle	Proteolysis
Osteoclasts	Bone resorption
Chondrocytes	Cartilage breakdown
CNS	Fever, sleep
Bone marrow	Induces GM-CSF, G-CSF, IL-6 resulting in haemopoiesis

Table 3 Responses induced by interleukin-2

Growth of activated T-cells and thymocytes
Stimulates cytokine production, such as IFN γ , TNF α
Causes B cell proliferation, and growth of CLL B cells
Augments natural killer (NK) cell cytotoxicity
Enhances monocyte killing
Promotes the development of lymphokine activated killer (LAK) activity in vitro and in vivo

killer cells, and mononuclear phagocytes, and we are aware of many of the events involving IL-2 interaction with its receptor.

Naturally produced IL-2 has been characterised as a glycoprotein of molecular mass between 15 000 and 18 000,¹⁴ although the recombinant protein produced from the cDNA is non-glycosylated and essentially has the same biological activity as the native molecule.¹⁵ Discrete regions of the IL-2 molecule are responsible for binding to specific epitopes on the high affinity IL-2 receptor complex, which consists of a p55 α chain and a p70-75 β chain. Depending on the relative expression of the α and β subunits at the cell surface, they constitute low (p55 alone), intermediate (p70-75 alone), or high affinity (p55 and p70-75) receptors for IL-2¹⁶; the p70-75 subunit is responsible for signal transduction. The p55 protein, although incapable itself of transducing the IL-2 signal, is essential for the high affinity binding characteristics of the IL-2 receptor complex. Thus the α and β chains associate with different epitopes of the IL-2 molecule.¹⁷ Recently a third component of the IL-2 receptor complex has been discovered (the γ subunit or p95-110), which seems to be associated with the p70-75 β subunit and is involved in determining the affinity with which the β chain binds IL.¹⁸ There also seems to be a relation between the p55 component (*Tac* antigen) of the IL-2 receptor and a protein (p95) which is identical with intracellular adhesion molecule 1 (ICAM-1) on activated T cells.¹⁹ IL-2 receptor/ICAM-1 complex may interact with lymphocyte function-associated antigen-1 (LFA-1), thereby enhancing cell-cell contact and adhesion. The consequence of this interaction would be a prolonged clustering of different cell types which would allow an enhanced immune response to develop.

The T cell response to IL-2 is perhaps the best known and characterised of all cytokine activation events, and is an essential step in the development of antigen specific and non-specific immune activation (table 3). Comparatively little is known about the multiplicity of genes (probably in excess of 8,000) which are activated through IL-2 signalling, and we are able to glean only a narrow perspective of the molecular process involved in the response to IL-2. Antigen can activate T cells via the T cell receptor-CD3 (TiCD3) complex, committing the cells to progress from G0 to G1 of the cell cycle, making them responsive to IL-1 (released from APC) and causing helper T cells to produce IL-2 and express *Tac* antigen. The autocrine action of IL-2 promotes further cell division,²⁰ and immunological communication takes place usually within small cell clusters where the interaction between APC, and T cell subsets allows antigen specific responses to

develop. Alternative pathways of IL-2 activation cause either natural killer cells and certain T cell subsets to respond and mediate a cytotoxic response in a non-MHC restricted manner. When lymphocytes are activated in vitro by culturing the cells in the presence of IL-2 for three to five days, a potent killer cell activity is generated, which has been referred to as lymphokine activated killing, or LAK activity.^{17 21 22} These cells have been shown to mediate potent antitumour cytotoxicity in vitro against target tumour cells freshly derived from "solid" tumour tissue. Cells mediating LAK activity release a variety of cytokines including IL-1, IL-2, TNF- α and IFN- γ , all of which can influence the development of antigen specific and innate immunity, as well as acting as chemotactic molecules for determining the trafficking pattern of immunocytes. Their direct or indirect action results in tumour regression, and they are likely to be of considerable importance in cancer immunotherapy.

IL-2 also influences the behaviour of other cell types, and several reports have shown that IL-2 is an essential growth factor for the function of B cells, eosinophils, monocytes and macrophages. In vitro activation of human blood lymphocytes, or in vivo administration of IL-2 induces the sequential expression of cytokine genes, including IL-1 α and β , IFN- γ and TNF- α and β . IL-1 gene transcription occurs within two hours of activation and is recognised as an early event in the cell activation process.²³ Another important aspect of the IL-2 response is the ability of other cytokines to act synergistically with IL-2 to increase the degree of activation. IL-1, TNF- α , and IFN- γ are examples of cytokines which are known to synergise with IL-2.^{3 7 12} Several other factors regulate lymphocyte activation, as shown by IL-4 and members of the TGF- β family, which are capable of suppressing the immune response induced by IL-2.^{24 25}

Cytokine modulation of tumour cell behaviour

As previously stated, cytokines are produced by, and interact with, cells other than those belonging to the immune system. TNF- α , for example, can cause necrosis of certain experimental tumours, but its effect on cancer cells can be wide-ranging. Recently it was shown that TNF- α can induce the expression and release of enzymes from cancer cells, a step which is important in basement membrane degradation during tumour metastases. In particular, TNF- α induces a 92 kilodalton gelatinase enzyme, also known as a type IV collagenase, from human sarcoma cell lines and melanoma cells lines (unpublished observations).²⁶ This molecular weight species of enzyme has been linked with metastatic cell types and its expression can be upregulated by the presence of TGF- β . Our studies suggest that other cytokines such as IL-1 and IL-6 may also regulate degradative enzyme secretion patterns.

Many of the cytokines—for example, IL-1, TNF- α and the interferons—are anti-

proliferative and known to decrease the growth of cancer cells in culture. In some instances this may be due to a reduced rate of proliferation rather than a direct toxic effect, although the detailed characterisation of this effect on tumour cells is not fully understood. The interferons and TNF- α can induce or increase the expression of class I and II MHC antigens, and it has been shown that IL-1, TNF- α , and IFN- γ can increase the expression of ICAM-1. Although cytokines have a profound influence on the immune system, they can clearly influence the behaviour of non-lymphoid cells, including tumour cells.

Cytokines and the inflammatory response

Inflammation has a central role in the host defence and wound healing processes, and contributes to the pathogenesis of many diseases. A variety of agents elicit a non-specific response to tissue injury, and these include bacteria, viruses, parasites and chemical or physical agents. The inflammatory process is complex, consisting of vasodilatation and increased vascular mobility, the adhesion of leucocytes to the blood vessel walls and their migration into the inflammatory focus, together with the exudation of fluids and plasma proteins. These events can lead to pain, fever, leucocytosis and the appearance of acute phase proteins in the serum. Inflammatory responses are in general beneficial reactions which eliminate the invading organism and initiate tissue repair to injury, although persistent inflammatory responses can prove harmful. The process is dependent on the production of corticoids, prostaglandins, leucotrienes and histamine-like molecules. Cytokines have been implicated as humoral factors which regulate inflammatory events, the important signals being mediated through IL-1, IL-6, TNF- α and β , platelet activating factors and the interferons. Tissue macrophages and monocytes produce IL-1 and TNF- α and these act as early "alarm" cytokines; subsequently the release of other peptides, including transforming growth factor β , occurs.

The expression of adhesion molecules on blood vessel capillary endothelial cells is an important aspect of leucocyte migration into a site of inflammation, and the expression of the adhesion molecule ELAM-1 (which increases the neutrophil binding), is enhanced by IFN- γ . IFN- γ also enhances IL-6 production by endothelial cells.²⁷ TNF- α , IFN- γ , and IL-4 increase endothelial cell adhesiveness for T lymphocytes and can act in combination at a site of inflammation to promote lymphocyte extravasation.²⁸ Similarly, cytokines can enhance the adhesion of eosinophils to endothelial cells, although the mechanism for eosinophil recruitment at sites of allergic inflammation may be distinct from that of neutrophils.²⁹ The production of IL-1 and IL-6 may also affect cells of the central nervous system and increase the production of ACTH and cortisol. An increase in metabolism of the bone marrow also occurs and maturation of inflammatory cells results from colony

stimulating factors produced at the site of inflammation. Acute phase proteins are induced by cytokines from hepatocytes and act as early protective mechanisms, although the role of many of the acute phase proteins are not known. IL-6, which has also been termed "hepatocyte stimulating factor", activates the greatest number of acute phase protein genes in vitro and in vivo, and this cytokine, together with IL-1 and TNF- α are involved in the induction and regulation of these liver proteins. The interferons seem to be important in regulating acute as well as chronic inflammatory responses, and their role as molecular signals for increasing or inhibiting inflammation is suggested from available experimental results. Their effect largely depends on the time at which the interferon is produced, the type of interferon, its dose and the presence of other inflammatory cytokines.

Because many of the symptoms of infection with gram negative bacteria or malaria seem to be due to the release of cytokines, one current approach to the treatment is to use antagonistic peptides or antibodies which block cytokine-cytokine receptor interaction. This has been shown to be valid experimentally³⁰ where administration of a receptor antagonist to IL-1 (raIL-1) can reduce the symptoms and mortality rate in shock induced by endotoxins. This form of treatment may prove clinically appropriate in the future, and it offers an additional approach to current treatments.

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