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Note added in proof—Since this article was written a further gene in the chromosome 5q21 region has been cloned. This gene, named APC (for adenomatous polyposis coli) is situated in the same region as MCC. Individuals with germ-line mutations of APC develop colonic polyposis: in contrast no germ-line mutations of MCC have been found.

For review see Bourne HP, Suppression with a difference. *Nature* 1991, **353**, 696–697.

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Cytokine Modulation of Cell Growth and Role in Tumour Therapy

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Cytokines are a group of secreted proteins which act as intracellular signals co-ordinating the growth and function of cells in the haematopoietic systems. Despite often overlapping functions they appear to have evolved separately but their receptors do share several features suggesting a common ancestor. Taking interleukin 2 (IL2) as an example we discuss the mechanisms involved with the regulation of IL2, the interleukin 2 receptor (IL2R) and their modes of action. Finally we discuss the various aspects of cytokines which allow their use as antitumour agents.

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INTRODUCTION

THE CYTOKINES are a group of secreted proteins which act as inter-cellular regulatory factors. Their major role is to coordinate the growth and function of cells in the haematopoietic system. Thus they exert effects on cells ranging from precursors to mature effector cells. The nomenclature of the cytokines is fragmented reflecting the historical context in which they were discovered. It is now apparent that the categories are rather artificial and that there is much functional crossover between the various groups, which include the interleukins (ILs), the interferons (IFNs), tumour necrosis factor (TNF) and lymphotoxin, the colony-stimulating factors (CSFs) and erythropoietin.

The cytokines share the general characteristics that they are all relatively low molecular weight (less than 80 kD) proteins and act in a paracrine or autocrine manner. Certain cytokines have overlapping sets of functions, for example the colony stimulating factors (CSF), granulocyte macrophage CSF (GM-CSF), granulocyte CSF (G-CSF), macrophage CSF (M-CSF) and IL3 can exert identical effects on some bone marrow progenitor cells.

Despite overlapping functional activities of cytokines, they share surprisingly little amino acid sequence homology. There is some organisational similarity between the IL6 and GCSF genes in terms of intron/exon structure suggesting a possible ancient relationship [1], but it appears that in general the cytokine genes are unrelated and have evolved separately.

There is, however, an interesting cluster of the genes for IL3, IL4, IL5, GM-CSF, M-CSF and the M-CSF receptor [2, 3], on the distal portion of the long arm of chromosome 5. Loss of either the whole, or the long arm, of chromosome 5 has been observed in the myeloid cells of patients with some myeloid leukaemias and myelodysplastic syndromes [4, 5]. Several of the cytokine genes, GMCSF, G-CSF, IL3, IL2, IL4 and IL5, have a 10 bp concensus sequences in the 5′ flanking region [6, 7]. This is a transcription factor binding site for NF-GM (nuclear factor for GMCSF) which probably plays a regulatory role in cytokine gene expression.

Although the cytokines are structurally unrelated, several components of their receptors have marked amino acid sequence homologies. The receptors for which the signalling complex structures have been best defined appear to be heterodimers. The interleukin-2 receptor (IL2R) has two membrane spanning chains of 55 and 75 kD, both of which have ligand binding sites and form a dimer to give a high affinity receptor [8]. Similarly the IL3R and GM-CSFR are also heterodimers. In this case the two receptors share a common chain which may explain some of their overlapping biological functions [9]. Components of the IL2 receptor, IL3 receptor, IL4 receptor, IL5 receptor, IL6 receptor, IL7 receptor, the erythropoietin receptor, G-CSF

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receptor, and the GMCSF receptor have areas of common structure, which they share with the prolactin and growth hormone receptors (for review see Ref. 10). The main region of homology is in the extracellular domain which contains a highly conserved region of four cysteine residues at the *N*-terminus and a Tryptophan, Serine, X, Typtophan, motif at the plasma membrane. Furthermore, IL2R and erythroprotein R share sequence similarities in their cytoplasmic domains [11]. These homologies suggest that these cytokine receptor genes belong to a superfamily with a common ancestor. In addition the genes for the IL1 receptor, the IL6 receptor and the IFN-γ receptor have a domain structure characteristic of the immunoglobulin superfamily [12–14].

HOW DO CYTOKINES WORK?

The cytokines behave as a signalling network coordinating the behaviour of a variety of cells. They can have overlapping effects, antagonistic effects and can influence each others secretion and action. Although cytokines can have very different effects, they follow similar patterns of behaviour. They are produced by particular cells in response to appropriate stimuli. Once secreted they bind to specific cell surface receptors present on effector cells. These receptors then mediate intracellular signals to effect various changes in cell behaviour. To consider each cytokine in detail is beyond the scope of this contribution, but we shall consider IL2 as an example.

IL2

IL2 is a cytokine secreted by activated T lymphocytes which binds to the IL2R on effector cells and causes proliferation and differentiation of T and B lymphocytes, natural killer (NK) and lymphokine activated killer (LAK) cells, and enhances the cytotoxic of NK cells, LAK cells and macrophages (Table 1).

In common with other cytokines, IL2 is encoded by a single gene. The human IL2 gene spans 8 kilobases and is divided into four exons and three introns [15, 16]. Upstream of the IL2 gene, between −52 bp and −329 bp (relative to the start codon for IL2 gene) there is a promoter region which regulates IL2 gene expression [17, 18].

IL2 gene expression

IL2 is produced almost exclusively by activated mature T lymphocytes of the T helper subset. Resting lymphocytes are activated by binding of their T cell receptor to antigen in association with MHC class II expressed on antigen presenting cells. A second signal, e.g. IL1 secreted by macrophages, is also required (Fig. 1).

The receptor/antigen binding leads to triggering of the CD3 molecule complex which in turn activates phospholipase C (PLC). This hydrolyses membrane phosphotadyl inositol 4,5 diphosphonate (PIP_2) to generate inositol 1,4,5 triphosphate

Table 1. *Cellular effects of interleukin* 2

T cell proliferation and differentiation
B cell proliferation and differentiation
Increased macrophage cytotoxicity
NK proliferation and increased toxicity
Generation of lymphokine-activated killer (LAK) cells
Stimulation of production of IFN, TNF and lymphotoxin

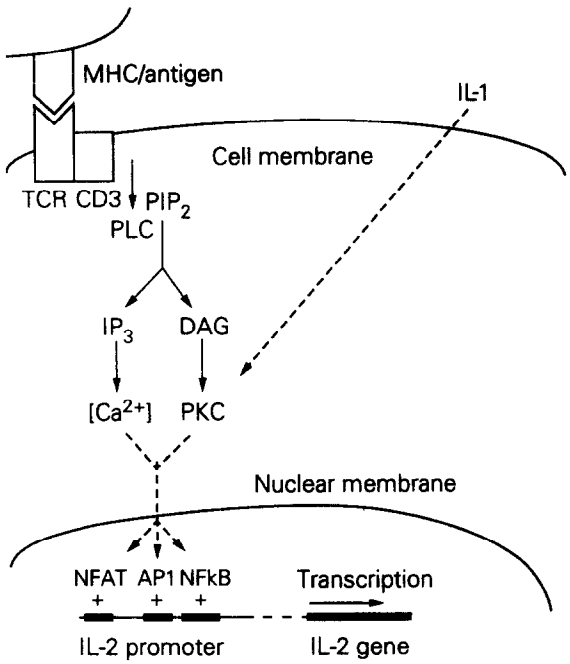

Fig. 1. Regulation of IL2 gene expression.

(IP_3) and diacyl glycerol (DAG). These intracellular signalling molecules act in concert to increase intracellular Ca^{2+} concentrations and activate protein kinase C (PKC), respectively [19]. The pathways involved in the IL1 signal remain controversial, with PKC and cyclic AMP proposed as intermediary messengers [20, 21]. The next step in the intracellular message is undefined but is followed by the activation of several transcription factors: NFAT (nuclear factor of activated T cells) which is present only in activated T lymphocytes [22]; NFkB which was originally discovered as a regulator of lgK light chain expression [23], AP1 which is a complex product of c-fos and c-jun proteins and is involved in many cell signals involving proliferation. These transcription factors bind to specific sequences in the promoter region of the IL2 gene and enhance its transcription [22, 24].

Cyclosporin A, a cyclic undecapeptide with immunosuppressive effects specifically inhibits the function of several of these nuclear transcription factors [25].

IL2 receptor

Secreted IL2 binds to a specific surface receptor. The receptor is currently thought to consist of two chains, the 55 kD α chain and 75 kD β chain [26, 27]. IL2 binds to the α chain alone with low affinity and the β chain with intermediate affinity [8, 28]. However, if both chains are present they form a dimer and bind IL2 with high affinity [8].

Resting T cells express little IL2β and IL2α receptor chains and therefore little high affinity receptors [28, 29]. These cells are relatively unresponsive to IL2. NK cells, which also have very little IL2Rα chain, have more β chain (and therefore intermediate affinity receptors) and can respond to high concentrations of IL2 [26]. Upon activation by antigen, T lymphocytes show a large increase in IL2Rα and IL2Rβ chains and this results in an increase of high affinity receptors and so these activated lymphocytes respond to low concentrations of IL2 [8, 28].

Like the IL2 gene, the IL2R gene has an upstream promoter region (spanning −476 to −225 bp relative to the start codon)

with multiple transcription factor binding sites, some of which it shares with the IL2 promoter (e.g. NFkB) [30]. There are, however, differences in the regulation of IL2 and IL2Rα expression, IL2 gene expression requires two different signals but IL2α expression can be induced by various single signals.

IL2 signal transduction

Following the binding of IL2 to the IL2R complex, there is a series of intracellular signalling events. The signal transducing component is the IL2Rβ chain [31]; a region within its cytoplasmic domain of 286 residues has been shown to be essential for IL2R function. Several studies have demonstrated that IL2 causes a rapid increase in tyrosine phosphorylation of cellular substrates [33, 33] and that there is interaction of the IL2Rβ chain with the tyrosine kinase $p56^{lck}$ [34].

Subsequent signals result in different effects in different cells. IL2 causes proliferation of activated T and B lymphocytes, NK cells and LAK cells. LAK cells are IL2 responsive cytotoxic large granulocytes which can be grown out *in vitro* from peripheral blood lymphocytes. Their origins are unknown; they appear to be related to NK cells but are cytotoxic to cell lines traditionally thought to be NK resistant.

IL2 also increases the cytotoxicity of NK and cytotoxic T cells. One of the mechanisms involved is an increase in the production of a pore forming protein, perforin [35]. This protein, which is related to the $C_6C_7C_8C_9$ complement complex [36], incorporates into the target cell membrane and forms a pore allowing small ions to pass through. This increases the internal osmotic pressure drawing in water and the target cell swells and ultimately bursts. IL2 also increases the cytotoxicity of macrophages [37] but this is not mediated by perforin.

IL2 induces the production of further cytokines, IFN-γ, TNF and lymphotoxin.

Control of the IL2 response

Thus, following activation by antigen of T cells, there is an upregulation of IL2 gene expression (in T helper cells) and IL2R gene expression (in effector immune cells). In the case of T helper cells, an autocrine loop is formed [38, 39] where upregulated IL2 binds to upregulated IL2R, which allows a proliferative signal and increases the number of antigen activated T cells. On removal of antigen there is a downregulation of IL2Rα leading to unresponsiveness, interruption of the positive feedback loop, and a return to the resting state. Similarly there is a paracrine loop stimulation of cytoxic T cells and other effectors (Fig. 2).

In HTLV-1 mediated adult T-cell leukaemia this control is disrupted. The HTLV-1 genome encodes a protein, Tax, which induces IL2Rα chain and IL2 gene expression possibly via NFkβ. This disturbs the normal control mechanisms in T cell proliferation and is thought to play a part in the early leukamogenic processes [40].

CYTOKINES IN CANCER THERAPY

Cytokines modulate cell behaviour and aspects of normal cytokine effects on target cells have been exploited in cancer treatment and may therefore have a therapeutic potential in cancer treatment.

Direct cytotoxic effects

Some cytokines have a direct cytotoxic effect on tumour cells, e.g. TNF and lymphotoxin. TNF activates phospholipases which generate arachadonic acid and this leads to generation of prostaglandins, leukotreins, and free oxygen radicals which are toxic to cells. TNF can also cause death by apoptosis, a process in which there is activation of endogenous nucleases which lead to a fragmentation of the DNA followed by membrane disruption [41, 42].

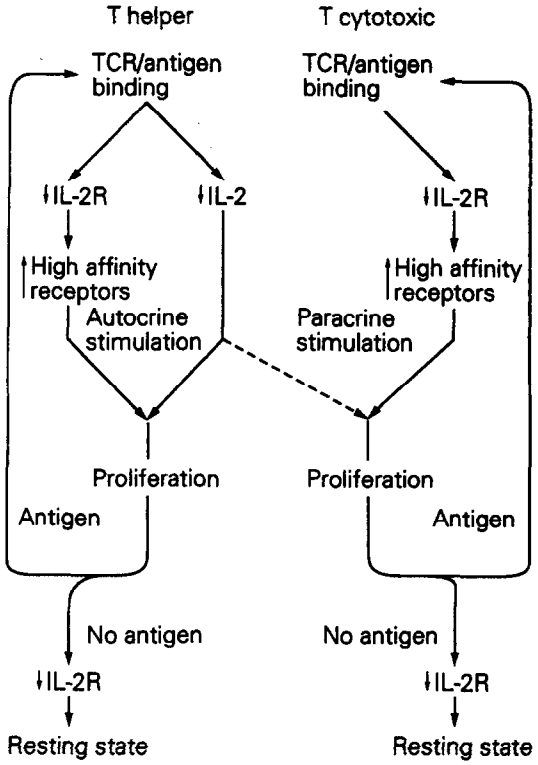

Fig. 2. Control of IL2 mediated cell proliferation.

Several clinical trials with TNF for the treatment of cancer have been performed [43–45] but so far there have been no significant antitumour responses. Manipulations of dose, route and site of delivery and combinations with other agents are presently being investigated.

Direct cytostatic effects

The interferons have a direct cytostatic effect which inhibits growth of normal and transformed cells. *In vitro* many tumour cell lines are sensitive to the growth inhibitory effects of interferon [46]. Clinically interferons have been used for several malignancies with very good effect. In hairy cell leukaemia response rates (CR and PR) of 70–90% are achieved with αIFN [47, 48]. There is evidence to suggest that IFNα can exert its cytostatic effects on hairy cells directly [49, 50]. Other possible mechanisms include upregulation of TNFα receptors and inhibition of IL6 mediated hairy cell proliferation [51]. IFNα has also been shown to have useful antitumour effects in B cell lymphomas, chronic myeloid leukaemias, myeloma, APUD tumours, bladder and renal cell carcinomas.

Immunomodulation

IFNs can also exert an antitumour response by modifying the immune response; IFNγ causes an upregulation of MHC surface antigens thereby increasing the amount of appropriately presented tumour antigen available to immune effector cells.

As we have seen IL2 has a pivotal role in the modulation of the immune response, and by causing T and B cell proliferation and differentiation and increasing the toxicity of cytotoxic T

cells, NK cells, LAK cells and macrophages, can enhance the antitumour immune response. Clinical trials with IL2 have shown significant response for several tumours including melanoma, renal cell carcinomas, and lymphomas [52]. Systemic IL2 has significant toxicity and several approaches to reduce this have been investigated. The ability to grow LAK cells and now TIL cells (tumour infiltrating lymphocytes) *in vitro* with IL2 and then administering them with IL2 can increase the efficacy without increasing toxicity [53–55]. Variations in dose, route of delivery and combinations with other treatments is being investigated.

Induction of differentiation

The effect of cytokines on maturation suggested that cytokines might be used in cancer treatment to induce differentiation of malignant myeloid precursors to more chemoresponsive or non-proliferating mature cells. *In vitro* treatment of myeloid leukaemia cells with GM-CSF can increase the fraction of leukaemic blasts in S phase and thereby enhance cytoarabine mediated cytotoxicity [56]. *In vitro* differentiation of leukaemic cells in AML to eosinophils with IL5 has been shown [57].

Marrow regeneration

As growth and differentiation factors for haematopoietic progenitor cells, cytokines have proved very useful in enhancing marrow regeneration following marrow toxic chemo and radiotherapy. Clinical trials have already shown rapid recovery of leukocyte counts in patients treated with myelosuppressive agents followed by administration of recombinant GM-CSF and GCSF [58, 59].

Thus cytokines already have several uses in cancer therapy and as our understanding of the cytokine network improves it should be possible to manipulate the haematopoietic and immune systems with finer precision.

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Glossary

An asterisk indicates a related entry.

Active genes. Genes transcribed in the cell type in question. Some genes are active in all cells (housekeeping genes) whilst others are specific to one cell type (e.g. haemoglobin gene in erythrocytes). Associated conformational features include looser duplex winding around nucleosomes*, less histone* H1 binding and situation in euchromatin.

Adduct. (see drug adduct).

Alkylation. Process of covalent binding of reactive alkyl group of drug (e.g. CH_2Cl) to biological molecules (DNA bases or proteins) which have an excess of electrons.

Alleles. Alternative DNA sequences at a locus, can be coding or non-coding.

Amplification. Increase in copy number of a chromosomal region, typically by tandem* duplication.

Anchorage dependence. The dependence of normal cells on an appropriate surface/substrate on which to grow in culture.

Annealing. Complementary base pairing of homologous single strands of nucleic acids, e.g. attachment of primers* to denatured target DNA in PCR.

Antisense. A nucleotide sequence (RNA or DNA) complementary* to the coding (sense*) sequence.

Apoptosis. An active mechanism of cell death in which DNA degradation and nuclear destruction precede loss of plasma membrane integrity and cell necrosis.

Autocrine. A mechanism of growth stimulation involving the binding of a growth factor* secreted by a cell to its own plasma membrane receptors, cf. paracrine*.

Bacterial transformation. The uptake of foreign DNA by a bacterium which may result in, e.g. antibiotic resistance or some other phenotype.

BSO. Buthionine sulphoximine, an inhibitor of γ-glutamyl cysteine synthetase, leads to depletion of GSH*.

Carcinogen. A physical or chemical agent which has a causal role in the development of cancer (these are often, but not always mutagens*).