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REVIEW

The interleukins in acquired disease

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INTRODUCTION

The 'interleukins' are a group of polypeptides belonging to the family of 'cytokines', i.e. hormone-like molecules which can affect various cell functions thereby enabling communication between different cell types. The interleukins can be released by lymphoid cells in response to antigen but in contrast to the chemical composition of antibodies their chemical composition is not determined by that of the stimulating antigen. However, it is now clear that non-antigenic stimuli also induce synthesis of interleukins and that many non-lymphoid nucleated cells can be producers of interleukins and/or express functional interleukin receptors. At the present time (June 1988), the interleukin family comprises six well-characterized members, a number which will certainly increase in the near future. Generally, interleukins 1–6 (IL-1–IL-6) modulate both localized and systemic host defence mechanisms (inflammation and immunity) by regulating the growth, mobility and differentiation of lymphoid as well as non-lymphoid cells. They are synthesized by the host in response to injury, infection and various immunological reactions and their effects are mediated through at least six distinct cell surface receptors. Interestingly, some interleukins can interact specifically with more than one cell surface receptor molecule (Smith, 1987). An assessment of the function of interleukins coupled with their availability as cloned purified entities suggests that they may have an important therapeutic role in human disease.

INTERLEUKIN 1

Two distinct human IL-1 genes (IL-1α and IL-1β) have been identified (Auron *et al.*, 1984; March *et al.*, 1985) and their expression can be induced by a number of stimuli (Table 1). IL-1 promotes the T lymphocyte differentiation (Fig. 1) and augments the in-vitro proliferation, differentiation and antibody-producing functions of B lymphocytes. Recent studies have shown that IL-1 activities can be produced by virtually every nucleated cell, the growth and differentiation of numerous cell types are stimulated by IL-1 and that some of the IL-1 activities can also be induced by tumour necrosis factor (Table 2) (for a comprehensive review see Dinarello, 1986; Oppenheim *et al.*, 1986).

IL-1 increases the expression of IL-2 receptors (Fig. 1), thereby acting synergistically with IL-2. As such, IL-1 is being investigated in clinical trials combining it with IL-2 in attempts to activate anti-tumour immune response (Ochoa *et al.*, 1987). Such trials are based primarily on the immunologic effects of IL-2 and are described in further detail in the IL-2 section (below). IL-1 is a potent inducer of the production of lymphokines and cytokines by other cells (Billiau *et al.*, 1986) and therefore, in theory, the specific inability to produce IL-1 (or a molecular defect in the response to IL-1) could result in multiple physiological imbalances. However, to date, no specific disease states have been attributed to either a specific or non-specific deficit in IL-1 production or response. It is of interest that the urine of febrile patients and pregnant women contains IL-1 inhibitors (Oppenheim *et al.*, 1986), however, their pathophysiological significance remains to be elucidated.

The current considerable interest in IL-1 is largely motivated by the accumulating evidence for the involvement of this molecule in the pathogenesis of arthritis (Oppenheim *et al.*, 1986). IL-1 mediates cartilage matrix degradation (probably by stimulating chondrocytes to synthesize and secrete collagenase and other neutral metalloproteases), inhibits the synthesis of proteoglycans by chondrocytes and induces the breakdown of bone matrix by a PGE_2-independent mechanism. Not only does synovial fluid from patients with rheumatoid arthritis and osteoarthritis contain raised levels of IL-1 but intra-articular administration of purified IL-1 produces inflammatory changes identical to those seen in an animal model of chronic arthritis. Therefore, the application of various IL-1 inhibitors in arthritis may prove to be a useful therapeutic intervention.

INTERLEUKIN 2

The expression of the IL-2 gene is a pivotal event in T cell activation (Malkovský & Sondel, 1987). IL-2 is synthesized by activated lymphocytes and a subset of large granular lymphocytes and its synthesis is stimulated by tumour-promoting

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Table 1. Inducers of IL-1 Production

Foreign proteins (via antibody or lymphokine production)

Inflammatory agents
- Bile salts
- C5A
- Urate crystals

Immune complexes

Lymphokines
- Interferons
- Colony stimulating factor
- Macrophage-activating factor

Microorganisms
- Viruses
- Bacteria (e.g. *Staphylococcus albus* and *aureus*)
- Spirochetes
- Yeasts

Microbial products
- Endotoxins from Gram-negative bacteria
- Peptidoglycans from all bacteria
- Exotoxins from staphylococcal and streptococcal pathogenic strains
- Yeast polysaccharides

Plant lectins
- Phytohaemagglutinin
- Concanavalin A

Others
- Antigen plus Ia
- Muramyl dipeptide
- Poly I:C
- Bleomycin
- Phorbol esters
- Cell injury
- Anti-IgM
- Aluminium hydroxide
- Silica
- UV irradiation
- No detectable stimulant (cell cycle-dependent IL-1 production)
- A23187
- Hydroxyurea
- Carrageenan

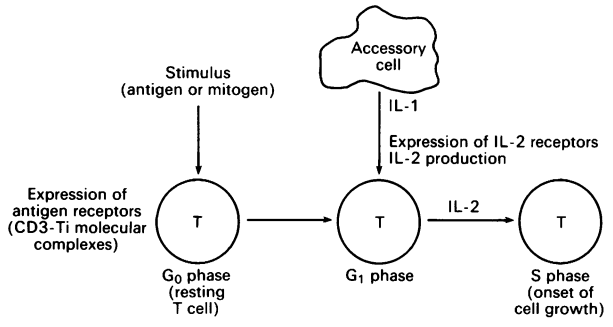

Fig. 1. Immunological events following T cell stimulation. Stage 1: A resting T cell (in G_0 phase) expresses few IL-2 receptors, but displays numerous antigen receptors (CD3-Ti molecular complexes—see Weiss *et al.*, 1986; Reinherz, 1987; Toyonaga & Mak, 1987). Stage 2: The T cell acquires the growth competence (G_1 phase) through CD3-Ti triggering by antigen and major histocompatability complex (MHC)-restricting element. This results in CD3-Ti modulation (thus reducing the number of surface antigen receptors) and a rapid induction of surface IL-2 receptor expression. The antigen-specific signal transduction via CD3-Ti also leads to production and secretion of endogenous IL-2, the synthesis of which is potentiated by IL-1. IL-2 subsequently binds to the surface IL-2 receptors. Stage 3: Once a critical density of occupied IL-2 receptors is achieved, the T cell progresses through the proliferation phases (G_1, G_2 and M).

phorbol esters, lectins (e.g. phytohaemagglutinin of concanavalin A), certain mitogenic antibodies (e.g. directed against the CD2 determinant), and antigens. Maximal IL-2 synthesis and secretion requires both antigen (or mitogen) and IL 1 and the scenario of immunological events leading to and following the IL-2 secretion is illustrated in Fig 1.

IL-2 interacts with p55 (Tac antigen) and p75 IL-2 receptor molecules which are displayed by many lymphoid cells including T and B lymphocytes, natural killer cells, thymocytes and monoctyes (Malkovský & Sondel, 1987). However, the cellular internalization of IL-2 is mediated only by p75 (Robb & Greene, 1987) which alone is responsible for IL-2 signalling in large granular lymphocytes (Siegel *et al.*, 1987; Tsudo *et al.*, 1987). Since IL-2 deficit appears to promote unresponsiveness (Malkovský & Medawar, 1984; Malkovský, 1987), it is not surprising that inhibitors of IL-2 production such as glucocorticoids (Gillis *et al.*, 1979), cyclosporin A (Wagner, 1983) or PGE_1 and PGE_2 (Rappaport & Dodge, 1982) can display potent immunosuppressive effects. Interestingly, retinoids potentiate both the IL-2 production (Colizzi & Malkovský, 1985) and the immune reactivity (Malkovský *et al.*, 1983).

There are several immune reactions where control of the IL-2 related response could have a significant clinical effect. These include the immune responses to infectious organisms, to normal tissues in autoimmune diseases, to allogeneic transplanted tissues as well as to neoplastic tissues. Indeed, defective IL-2 production has been reported in patients with severe combined immunodeficiency (SCID) or Nezelof's syndrome (Flomenberg *et al.*, 1983), acquired immunodeficiency syndrome (AIDS) (Murray *et al.*, 1985; Borzy, 1987), type I diabetes mellitus (Kaye *et al.*, 1986), systemic lupus erythematosus (Linker-Israeli *et al.*, 1983) and could be one possible mechanism for the abnormal immune function in patients after bone marrow transplantation (Welte *et al.*, 1984). Defective induction of lymphokine-activated killer (LAK) cells by IL-2 has been demonstrated in patients with hypogammaglobulinaemia (Gao *et al.*, 1985), or sarcoidosis (Jira *et al.*, 1987). Disorders of IL-2 receptor expression have been described in patients with AIDS (Tsang *et al.*, 1985), hypogammaglobulinae-

Table 2. Target Cells and IL-1 Activities

Target cells	IL-1 induces
Basophils	Degranulation Histamine release
Beta-islet cells of Langerhans	Direct cytotoxic damage
B lymphocytes	Augmented antibody secretion Enhanced proliferation Membrane immunoglobulin receptor expression Chemotaxis Maturation of pre-B cells
Chondrocytes	Cartilage matrix breakdown Prostaglandin, collagenase, proteoglycanase and plasminogen activator production Inhibition of proteoglycan synthesis
Endothelial cells	Proliferation Production of prostaglandins, thromboxane and GM-CSF activity Production of pro-coagulant activity* Synthesis of leucocyte adhesion molecules Increased neutrophil adherence*
Epithelial cells	Proliferation Secretion of collagen type IV
Fibroblasts	Proliferation Production of PGE_2 and collagenase* Production of GM-CSF activity
Hepatocytes	Elevation of acute-phase proteins* Increased plasma copper Decreased albumin synthesis* Decreased plasma iron and zinc
Hypothalamus (Central nervous system)	Prostaglandin-induced fever* Anorexia Somnolence Production of PGE_2
Large granular lymphocytes (OKM 1-positive NK cells)	Augmented NK activity
Leucocytes	Enhanced adherence to endothelial cells*
Melanoma cells	Direct cytotoxic damage*
Mesangial cells	Proliferation
Monocytes	Chemotactic mobilization Increased thromboxane synthesis Prostaglandin-mediated cytocidal activation Production of PGE_2 Increased transcription of complement components*
Muscle cells	Production of PGE_2 Prostaglandin-mediated proteolysis
Neutrophils	Chemotactic mobilization Release from bone marrow Metabolic activation* Increased thromboxane synthesis* Release of lysozyme, lactoferrin and specific granules
Osteoblasts	Proliferation Production of collagen and prostaglandins
Osteoclasts	Resorption of bone Production of prostaglandins and collagenase
Synovial cells	Proliferation Production of collagenase and PGE_2* Production of plasminogen activator
Thymocytes	Enhanced proliferation
T lymphocytes	Enhanced proliferation (IL-2-medicated) Cytotoxic activity (may be IL-2-mediated) Increased lymphokine production (IL-2, IFN, BCGF, CSF, etc.) Expression of IL-2 receptors Chemotaxis Radioprotection Increased stability of E-rosettes

* Induced by both recombinant IL-1β (pI 7·0) and recombinant TNFα.

mia (Malkovský *et al.*, 1986), multiple sclerosis (DeFreitas *et al.*, 1986) and adult T cell leukaemia (Depper *et al.*, 1984). Clearly, further studies are needed to elucidate the nature and clinical relevance of these disorders of the IL-2 system. Nonetheless, the primary focus of current clinical activity with IL-2 has been the area of tumour immunotherapy (Rosenberg, 1986; Malkovský & Sondel, 1987).

IL-2 has no direct cytotoxic or cytostatic effect on most neoplastic cells. Its anti-tumour effect is derived from its ability to stimulate the cytotoxic activity of LAK cells, which is independent of *de novo* DNA synthesis (Malkovský *et al.*,1987a), but can be influenced by immunization (Gao *et al.*, 1987). The LAK cells mediate destruction of a broad range of neoplastic and transformed tissues as well as of some normal tissues (Grimm *et al.*, 1982; Sondel *et al.*, 1986; Chen *et al.*, 1987). Thus, it is not surprising that regimens utilizing immunologically active doses of IL-2 *in vivo* are associated with varying levels of toxicity to normal tissues. In pilot clinical studies utilizing very high doses of IL-2 combined with *in vitro* activated LAK cells, measurable anti-tumour responses were seen in approximately 20% of patients (Rosenberg *et al.*, 1985; 1987; Lotze *et al.*, 1986; West *et al.*, 1987).

Although tumour-specific cytotoxic T cells have been virtually impossible to identify reproducibly in the peripheral blood of patients with cancer (Sondel *et al.*, 1983), more recently evaluations of lymphocytes found infiltrating human tumours (tumour infiltrating lymphocytes or TIL cells) suggest that some of these may be tumour-specific T lymphocytes (Itoh *et al.*, 1986; Rosenberg *et al.*, 1986). Their expansion in IL-2 *in vitro* may generate a population of potent tumour-specific effector cells that could be utilized therapeutically when combined with IL-2 *in vivo*. Clinical trials of this concept are just beginning. Unfortunately, it is not always possible to obtain tumour-specific TIL cells and expand them *in vitro* for many patients with cancer. However, local administration of IL-2 *in vivo* may be able to activate these tumour-specific TIL cells *in vivo* and bypass the *in vitro* activation and expansion step (Pizza *et al.*, 1984; Forni *et al.*, 1986).

If the primary purpose of the immune system is to prevent injury from pathologic microorganisms, then the importance of IL-2 in the activation of immune responses would suggest IL-2 may play a major role in the immune response to infectious agents. The production of specific neutralizing antibody by B cells involves a cooperative role for T cells. Thus the level of specific antibody produced in response to an initial antigenic challenge, may be regulated by the action of IL-2 on helper T cells (and potentially on B cells directly). It is pertinent to mention in this context that immunization with antigen and IL-2 *in vivo* can overcome Ir gene-dependent low antibody responses (Kawamura *et al.*, 1985). In the control of many viral infections, viral antigen-specific T cells are essential and they require IL-2 for adequate activation and expansion. Furthermore, non-specific, genetically unrestricted effector cells (NK and LAK cells), also appear to destroy target cells infected with similar microorganisms. In fact, such activated effector cells can (at least *in vitro*) directly destroy microorganisms (e.g. *Cryptococcus neoformans*) (Murphy *et al.*, 1986; Nabavi & Murphy 1986). Recently, the IL-2 treatment *in vivo* was found to limit mycobacterial infections in mice (Jeevan & Asherson, 1988).

The clinical utility of IL-2 in augmenting deficient protective immune responses depends upon the existence of cells that are responsive to IL-2. In the acquired immune deficiency syndrome, the destruction of helper T cells (bearing the CD4 marker) by the human immunodeficiency virus (HIV) (Wong-Staal & Gallo, 1985; Dalgleish & Malkovský, 1988) causes a severe deficiency in IL-2 production, with resultant severe immune defects, leading usually to death from opportunistic infection (Ho *et al.*, 1987). Since the CD4 surface molecule can function as a specific receptor for cell entry by the HIV itself (Dalgleish *et al.*, 1984; 1988) the provision of IL-2 may add 'fuel to the fire' by activating the population of cells susceptible to HIV infection. This would enable more rapid virus replication and spread. Clinical trials will need to test IL-2 in this setting for AIDS patients (to augment immune function by circumventing the IL-2 production defect), while simultaneously administering agents which could inactivate HIV.

A variety of other naturally occurring immune deficient states are of clinical relevance. However, for many of these (aging, malnutrition, multiple myeloma, chronic Epstein–Barr infection, autoimmune disease associated immune deficiency, etc.), the mechanism of the immune dysfunction does not appear to be simply the result of an IL-2 production defect, as a component of IL-2 response is also impaired. It remains unclear whether pharmacological dosing of IL-2 can override these immune defects. It is noteworthy that a considerable fraction of opportunistic infections, occurs due to iatrogenically induced, rather than naturally acquired, immune deficiencies, such as those associated with general anaesthesia, surgery and certain anti-neoplastic therapies. The mechanism is not certain, but provision of pharmacological doses of IL-2 could prevent the development (or enable more rapid restoration) of these immunodeficiencies. Finally, IL-2 may some day play a role in the induction of protective immunity. Vaccines for a number of pathogens are being developed utilizing recombinant DNA and peptide synthesis techniques. For such vaccines where material is limited or only weakly immunogenic, the local administration of IL-2 with the vaccine may augment the cascade of immune activation and potentially provide the ability to make a stronger specific protective immune response.

Although the purpose of the immune response is protection from pathogenic microorganisms, this same immune response can become auto-destructive. A wide clinical spectrum of autoimmune diseases is the result of immune responses directed at normal, non-infected tissues. Moreover, tissue transplantation as treatment for specific organ failure has added tissue rejection as well as graft-vs-host disease to the list of undesired immune responses requiring immunosuppressive therapy. In many experimental systems *in vivo* (Malkovský *et al.*, 1984; 1985; Colizzi, 1984; Colizzi *et al.*, 1985; Loveland *et al.*, 1986; Holáň, 1988) and *in vitro* (Asherson *et al.*, 1985; Lehtonen *et al.*, 1986; Essery *et al.*, 1988), IL-2 interferes with immunological unresponsiveness. Therefore, mechanisms which block the induction or action of IL-2 should blunt these undesired immune responses (Malkovský *et al.*, 1982; Malkovský & Medawar, 1984; de Boer & Hogeweg, 1987; Holáň, 1987). Other molecular manipulations attempting to block IL-2 signalling are currently being studied. Nevertheless, many basic questions regarding the role of IL-2 in acquired disease remain unanswered. In particular, the molecular mechanism of IL-2 signalling, the *in vivo* purpose of non-specific, genetically unrestricted

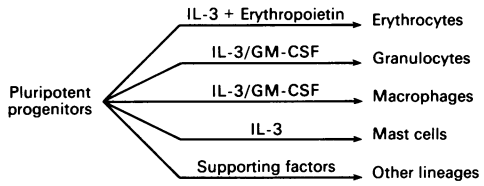

Fig. 2. Differentiation of haematopoietic progenitor cells.

Table 3. Interleukin signals in B cell development and differentiation

B-cell maturation stages	Induced by
Activation	IL-1, IL-4, IL-5
Proliferation	IL-2, IL-4, IL-5
Differentiation	IL-2, IL-5, IL-6

It should be noted that although human IL-5 appears to stimulate IgM synthesis in human B cells (Azuma *et al.*, 1986), in many other experimental systems, unlike in the mouse, human IL-5 has virtually no direct effect on human B cells (Clutterbuck *et al.*, 1987).

IL-2-responsive effector cells and the actions of IL-2 (both direct and indirect) on B cells (Waldmann *et al.*, 1984; Malkovska *et al.*, 1987) and monocytes (Thurman *et al.*, 1986; Malkovský *et al.*, 1987b), all require further clarification.

INTERLEUKIN 3

Studies of the clonal proliferation of haematopoietic progenitor cells *in vitro* have led to the discovery of a family of growth factors known as the colony stimulating factors or CSFs (Metcalf, 1984). They are named according to the cell types which they support. For example, haematopoietins known as erythropoietin, thrombopoietin, macrophage CSF (M-CSF), granulocyte CSF (G-CSF) and granulocyte-macrophage CSF (GM-CSF) have been identified. IL-3 can promote the proliferation and development of many haematopoietic lineages (multi-CSF) (Yang *et al.*, 1986). Its broad spectrum of activities (Fig. 2) is in agreement with the concept that IL-3 regulates the growth and differentiation of early haematopoetic and lymphoid progenitors (Schrader, 1986; Ihle & Weinstein, 1986). However, *nu/nu* (athymic) mice, which lack a detectable source of IL-3 (IL-3 is produced predominantly by activated T lymphocytes), have normal haematopoiesis suggesting that haematopoiesis *in vivo* may be capable of utilizing an alternative pathway, which is independent of IL-3

Specific clinical situations associated with IL-3 production or response defects have not been clearly identified. Nevertheless, the recent production of human recombinant IL-3 (Yang *et al.*, 1986), as well as other recombinant myeloid growth factors, is opening a new line of clinical investigations. The provision of appropriate quantities of these recombinant molecules (at appropriate doses and schedules, which require clarification), may enable stimulation of dysfunctional bone marrow in a number of clinical settings. These include acquired specific stem cell dysfunction (such as pure red cell aplasia), as well as stimulation of marrow function in pancytopenia (acquired aplastic anaemia), provided that at least some myeloid stem cells remain. IL-3 by itself or in combination with other haematopoietins may prove useful in treating cytopenias associated with certain viral infections as well as in accelerating recovery following bone marrow transplantation or iatrogenic marrow dysfunction following chemotherapy/radiation therapy for neoplasms. Since current chemotherapeutic protocols are limited by the haematologic toxicity of the agents which are used, the provision of marrow stimulatory factors such as IL-3 and other CSFs following chemotherapy, could enable more rapid recovery of myeloid function without the significant periods of pancytopenia. If this indeed proves to be the case, doses and regimens of currently utilized chemotherapeutics can be altered dramatically to increase the functionally administered dose to the point where non-haematologic toxicity is the dose-limiting factor. Hopefully, this will increase the anti-tumour effect.

INTERLEUKIN 4

Table 3 shows a scheme illustrating the involvement of interleukins in the B-cell development. For a comprehensive review on the regulation of B-cell growth and differentiation by soluble factors see Hamaoka & Ono, (1986); Jelinek & Lipsky, (1987); O'Garra *et al.*, (1988). Apart from being active on B cells, IL-4 also increases the viability and stimulates the growth of T lymphocytes and some T-cell lines (Paul & Ohara, 1987; Yokota *et al.*, 1988; Sideras *et al.*, 1988). Recently, Crawford *et al.*, (1987) have shown that IL-4 activates macrophages for increased tumoricidal activity and expression of Ia antigens. IL-4 can also act as a co-stimulant for growth of some macrophage and mast cell lines and synergizes with erythropoietin and other CSFs to stimulate erythroid, granulocytic and megakaryocytic colonies (Lee *et al.*, 1986; Paul & Ohara 1987). These activities of IL-4 are somewhat similar to those of IL-3, as both IL-4 and IL-3 can essentially act on all cells of haematopoietic origin. Finally, IL-4 may play an important role in cognate T cell–B cell interactions (Paul & Ohara, 1987).

It is now clear that IL-4 is a T cell product which affects the expression of various genes and consequently the activation, growth and differentiation of lymphoid cells and of haematopoietic precursors. Therefore, Il-4 may have a broad range of regulatory effects on haematopoiesis and numerous immune reactions. Although there have been no IL-4 disorders reported *in vivo*, a first evidence that IL-4 is involved in the in-vivo regulation of IgE production in experimental animals was provided by Finkelman *et al.* (1986). In order to determine whether *in vivo* IgG1 and IgE antibody responses are IL-4 dependent, they studied the ability of a monoclonal rat IgG1 anti-IL-4 antibody, 11B11, to influence polyclonal IgG1 and IgE production in mice infected with the nematode parasite *Nippostrongylus brasiliensis* or injected with a purified goat antibody to mouse IgD. 11B11 strongly inhibited IgE production in both systems but did not affect IgG1 production, whereas control rat IgG1 had no IgE-inhibitory activity. Those results provide experimental basis for potential therapeutic manipulations to limit the production of antibodies responsible for

allergic reactions without diminishing protective antibody responses in patients. Furthermore, the provision of IL-4 in combination with other interleukins and various haematopoietins could be a useful therapeutic intervention in patients with compromised functions of the immune and haematopoietic systems.

INTERLEUKIN 5

Studies of a soluble factor originally termed T cell-replacing factor (TRF) or B-cell growth factor II (BCGF-II) (now more appropriately called IL-5) went a long way toward establishing that IL-5 was a functionally unique material that was distinct from other T cell lymphokines (Swain & Dutton, 1982; Swain *et al.*, 1983; Swain, 1985; Sanderson *et al.*, 1985; O'Garra *et al.*, 1986). IL-5 was distinguishable from IL-4 in that it did not co-stimulate with anti-μ and, IL-4, in turn, did not co-stimulate with dextran sulfate or cause differentiation of BCL_1 cells. IL-5-enriched supernatants were lacking in IL-1, IL-2, IL-3 and IFN-γ activities and the latter lymphokines also did not cause differentiation of BCL_1 cells. IL-5 was clearly distinguishable from lymphokines that act on resting cells (e.g. IL-4) or B-cell factors that cause differentiation in the absence of proliferation (e.g. IL-6). The fact that TRF/BCGF-II can manifest both differentiation- and proliferation-inducing activities was finally demonstrated when this factor was obtained by recombinant techinques and shown to mediate both activities (Kinashi *et al.*, 1986; Azuma *et al.*, 1986). As far as the intracellular events occurring in the B cell following its stimulation via the IL-5 receptor are concerned, it has been shown that B cell stimulation in the presence of IL-5 leads to the appearance of both IL-2 receptors (Loughnan *et al.*, 1987) and secretory μ mRNA in cells having only the membrane form of this message (Matsumoto *et al.*, 1987).

If experience with other T cell lymphokines is any guide, IL-5 might be expected to have activity on a variety of cells other than B cells. It therefore comes as no surprise that a T cell factor having colony-stimulating activity for eosinophils in liquid bone marrow cultures has been shown to be indentical to IL-5 (Kinashi *et al.*, 1986; Sanderson *et al.*, 1986). In addition, it has been reported that IL-5 (both purified material and recombinant material) causes thymocytes to manifest increased cytotoxic activity (Takatsu *et al.*, 1987) and that recombinant IL-5 enhances the IL-2 receptor expression of T cells (Sideras *et al.*, 1988). It is noteworthy that several investigators have shown recently that human recombinant IL-5 has no activity in standard human B-cell growth factor assays (Clutterbuck *et al.*, 1987, J. Farrant, personal communication).

IL-5 is a 'late acting' factor (Table 3) whose receptors are not present on resting cells. However, it does not have an effect on anti-μ antibody activated B cells, suggesting that its main function is to augment the development of murine B cells that have received more specific kinds of activation signals. Finally, while the effect of IL-5 is clearly to enhance cell proliferation, there is emerging evidence that IL-5 also causes distinct and specific types of murine B cell differentiation. No immunopathological syndromes in man associated with disorders of IL-5 production or responsiveness have been identified. Nonetheless, because of its development-promoting function, IL-5 alone or in combination with other interleukins could be considered for treatment of immunodeficiencies.

INTERLEUKIN 6

IL-6 (originally called BCDF of BSF-2) is produced by T lymphocytes upon mitogen stimulation and acts in the late stages of B-cell differentiation (Table 3), leading to the biosynthesis of a secretory type of immunoglobulin (Kishimoto, 1985). It induces immunoglobulin secretion in very low concentrations (pM), which can be augmented by the addition of IL-2 (Hirano *et al.*, 1985). IL-6 also functions as a potent growth factor for myeloma cells, induces differentiation of pheochromocytoma cells into neuronal cells, augments synthesis of acute-phase proteins by hepatocytes, synergizes for proliferation of myeloid leukaemic blast cells and for IL-3 dependent haematopoietic blast cell colony formation. It acts as a T-cell activation factor (Taf) as well as a cytolytic T cell differentiation factor (CDF) and as a co-stimulator of thymocyte proliferation, supports the growth of EBV-transformed B cells, displays some anti-viral activity, has a GM-CSF activity in the mouse and induces fever in rabbits (summarized in Wong & Clark, 1988).

Brenner *et al.*, (1984) studied the responsiveness to IL-6 preparations of B cells from patients with late onset primary acquired hypogammaglobulinaemia. They found that the patients' B cells responded to IL-6 preparations with increased synthesis of IgM, but overall levels of secreted IgM were 10–50 fold lower than in normal B cells. Also, in contrast to control B cells, the patients' B cells secreted little or no IgG. No pathological situations associated with a decrease in the production of IL-6 have been identified. However, increased levels of IL-6 have been found in the serum of children with Still's disease and in the synovial fluid of patients with rheumatoid arthritis (T. Kishimoto, personal communication). Hirano *et al.*, (1987) have shown that cardiac myxoma and uterine cervical carcinoma cells produce IL-6-like factor. Also, the T24 cell line derived from human urinary bladder carcinoma produces a molecule with IL-6 activity (Rawle *et al.*, 1986). Moreover, IL-6 mRNA is transcribed in T24 cells and myxoma cells at a much higher level than in activated lymphocytes and the mRNA in myxoma cells is larger than that of lymphocytes (Hirano *et al.*, 1986). These results indicate that the IL-6 gene can be expressed in non-lymphoid tissues.

The production of IL-6 by cardiac myxoma cells is intriguing, since cardiac myxoma patients often display connective tissue disease-like symptoms, including the presence of autoantibodies and hypergammaglobulinaemia. The symptoms usually disappear after the surgical removal of the tumour. Similarly, a patient, whose cervical carcinoma produced IL-6, had autoantibodies (Hirano *et al.*, 1987). Therefore, it appears that a constitutive production of IL-6 by synovial or tumorous tissues could be responsible for the induction of auotimmunity *in vivo*.

OTHER CLONED PRODUCTS OF LYMPHOID CELLS

Several cloned cytokines, which share many common characteristics with the interleukin family, but do not have 'an interleukin number' at the moment, are of clinical importance: tumour necrosis factors (TNFs) α and β (monocyte tumour necrosis factor and lymphocyte-derived lymphotoxin, respectively), GM-CSF and interferons. To provide any meaningful summary

of countless published articles about the action of interferons (see e.g.Pestka *et al.*, 1987) and their clinical use in the treatment of cancers, viral diseases and other disorders is beyond the scope of this article. Therefore, in the rest of this article we will briefly describe only why TNFs and GM-CSF are now the focus of newly initiated clinical oncologic investigations.

The biologic effects of TNFs are diverse including killing, growth stimulation and induction of differentiation (Sohmura *et al.*, 1986; Trinchieri *et al.*, 1986; Urban *et al.*, 1986; Hemmi *et al.*, 1987; Mannel, 1987; Paul & Ruddle, 1988). These molecules have cytostatic and cytotoxic effect against a wide range of human tumour cells *in vitro* with minimal, if any, toxic effect against most cell lines of normal human tissue. These agents also have anti-tumour effects in murine models and against human xenografts growing in nude mice. TNFs are associated with profound metabolic disturbance and weight loss *in vivo* (with apparent molecular identity of TNFα and a biologic factor previously identified as cachexin). TNF has anti-viral activity, induces the enzyme (2′-5′)-oligoadenylate synthetase similarly to interferon (Pestka *et al.*, 1987), enhances granulocyte function, augments the expression of MHC class I and class II antigens, activates human, monocytes to mediate cytotoxicity *in vitro* and augments expression of IL-2 receptors. Hence, TNF may have an immunologically synergistic role together with IL-2. Furthermore, the *in vivo* anti-tumour effects of TNF are often associated with central necrosis of tumour nodules. This is in contrast to the destruction of tissue at the periphery of tumours by IL-2 activated lymphocytes in animals receiving high-dose IL-2. As such, a potential synergistic action of *in vivo* TNF together with IL-2 is postulated (simultaneously acting on the centre and on the periphery of tumour nodules). The activation and release of TNF during times of metabolic and clinical stress, particularly associated with the 'Shwartzman reaction' is accompanied by profound metabolic defects resulting from the cachexin activity of TNF.

Clinical manipulation of large doses of human recombinant TNF are now being initiated in phase I trials (Blick *et al.*, 1987). Once the toxicity, maximum tolerated dose and immunologically/metabolically effective schedules are obtained in such studies, clinical trials testing the synergistic effects of TNF together with other agents (such as IL-2 and interferons) can proceed.

Very promising results have been obtained using recombinant human GM-CSF. In non-human primates, the administration of human GM-CSF was found to elevate leucocyte counts (Donahue *et al.*, 1986) and to accelerate haematopoietic recovery after total-body irradiation and infusion with autologous bone marrow (Nienhuis *et al.*, 1987). Recently, GM-CSF has been shown to increase circulating leucocytes in leucopenic patients with the acquired immunodeficiency syndrome (Groopman *et al.*, 1987), to accelerate myeloid recovery after high-dose chemotherapy and autologous bone marrow transplantation in patients with breast cancer or melanoma (Brandt *et al.*, 1988) and to expand the circulating haematopoietic progenitor cell compartment in patients with sarcoma (Socinski *et al.*, 1988). These results indicate that haematopoietic growth factors may be useful in reducing the toxicity of high-dose chemotherapy, although caution is required since some tumours express GM-CSF receptors, the function of which is unknown. Interestingly, GM-CSF also induces human neutrophil IgA-mediated phagocytosis by an IgA Fc receptor activation mechanism (Weisbart *et al.*, 1988).

CONCLUSIONS

The availability of cloned and purified interleukins has led not only to their detailed characterization but also to the exciting possibility of testing this new found knowledge *in vivo*. It is obvious that interleukins play a critical role in the activation and expansion of the complete coordinated immune response and some of them are involved in many complex homeostatic mechanisms. Therefore, a detailed analysis of the potential of interleukins in the treatment of cancer, infectious diseases, bone marrow dysfunctions and autoimmune disorders is now a major research priority. Clearly the application of these agents will not be straight forward and the best doses, administration routes and combinations have yet to be worked out in well controlled clinical trials. Indeed not only may the interleukins be useful *in vivo* but antibodies against them or their receptors may also have a therapeutic effect, for example, anti-IL-2 receptor monoclonal antibody in adult T-cell leukaemia (Waldmann *et al.*, 1986) or anti-IL-4 in hypersensitivity states. The interleukins and other cytokines are ushering in new and exciting possibilities for the treatment, diagnosis and investigation of many hitherto untreatable conditions and over the next few years results both in the laboratary and in the clinic are eagerly awaited.

Note added in proof

A novel murine haematopoietic growth factor (termed IL-7) which can stimulate the proliferation of lymphoid progenitors has been cloned recently (Namen *et al.*, 1988).

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Addendum

We would like to dedicate this article *in memoriam* to Sir Peter Medawar, OM, who died on 2nd October 1987. His kindness and charm won the hearts of many people. He inspired and cheered everyone and his diligence, dedication and intense devotion to science will continue to inspire us all.

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