MINIREVIEW

Interleukin 6 in Infection and Cancer (43129D)

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Localized tissue disruption quickly elicits systemic alterations in the biochemical, physiologic, and immunologic status of the host (1–3). The hypothesis that a circulating mediator(s) produced by injured tissues orchestrates the "acute phase" alterations in the "chemistry of the host" (1–4) has now been extensively validated (5, 6). It has become amply clear in the last 3 years that the cytokine interleukin 6 (IL-6) plays a pivotal role in mediating the host response to tissue injury. Elevated levels of IL-6 are readily detected in body fluids during the course of microbial infections, autoimmune diseases, and neoplasia (6). It is the purpose of this review to highlight some recent advances in experimental IL-6 research and to discuss new clinical insights on the role of IL-6 in the pathophysiology of infection and cancer. The thesis that IL-6, in addition to mediating the systemic host response to neoplastic disease, may itself promote the proliferation of neoplastic cell elements adds a novel dimension to this discussion.

Historical Comments

Clinical observations that we would today ascribe in large part to the effects of IL-6 were recorded at least 2500 years ago. The central tenet of Hippocratic medicine (approximately 400 B.C.) was based on the empirical observation that blood withdrawn from an acutely ill person, when allowed to stand, separated into four distinct layers or "humors" as it clotted (melancholia, sanguis, phlegm, and cholera) (7). The scientific basis for the appearance of a phlegm or crusta inflammatoria (the fibrin clot or "buffy coat") in blood from diseased individuals was elucidated in 1921 and is the enhanced sedimentation of erythrocytes (7–9). It is understood today that the enhancement of the erythrocyte sedimentation rate during acute infections largely reflects a change in plasma protein composition (particularly an increase in the fibrinogen level) that is collectively referred to as the "acute phase" plasma protein response (5, 6, 9, 10). This response is also accompanied by other systemic changes in the host such as fever, increased levels of circulating glucocorticoids, and a negative protein balance (1, 2, 10, 11). Similar systemic alterations have also long been recognized in patients with neoplastic disease (12). IL-6 produced at the site of injury or infection or by the tumor tissue itself is now recognized to be a major mediator of the altered hepatic plasma protein gene expression (6, 13, 14). Additionally, IL-6 also appears to be involved in mediating the increase in body temperature (15, 16), that of circulating levels of glucocorticoids (17, 18), and the alteration in tissue metabolism (11).

The cDNA for human IL-6 was originally isolated more than 10 years ago by Weissenbach *et al.* (19) in an investigation of poly(I)·poly(C)-induced mRNA in fibroblasts (β_2-interferon) (19, 20) and, by early 1986, the *IL-6* gene had been characterized and assigned to human chromosome 7 (21). Although IL-6 was initially recognized as a poly(I)·poly(C)- and virus-inducible gene (19, 22), its induction by cytokines such as tumor necrosis factor (TNF) and interleukin 1 (IL-1), described in 1985 and 1986 (23–25) and by growth factors such as serum, platelet-derived growth factor (25) and epidermal growth factor (26), attracted particular attention. By late 1987, studies in a number of different laboratories led to a rapid increase in our understanding of the biologic properties of IL-6. IL-6 was recognized to have the ability to enhance acute phase plasma protein synthesis by hepatocytes (hepatocyte stimulating factor) (13), to enhance the proliferation and differentiation of B cells (hybridoma/plasmacytoma growth factor and B cell differentiation factor type 2) (27–29), to enhance the proliferation and activation of cytotoxic function of T cells (cytolytic T cell differentiation factor) (30, 31), to enhance differentiation of monocytes (monocyte granulocyte inducer type 2) (32), to enhance neuronal cell differentiation (33), to inhibit or enhance the proliferation of epithelial cells depending on the

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experimental system used (34, 35), and to alter the social behavior of some breast cancer cells (increase in motility and decrease in cell-cell association) (35).

The Human IL-6 mRNA and Gene

The 1.3-kb IL-6 mRNA contains a 212-amino acid long open reading frame; the N-terminal 27–30 amino acids are hydrophobic and represent the secretory signal peptide (28, 36–38). The deduced amino acid sequence of the mature IL-6 protein contains regions of similarity with granulocyte-colony stimulating factor (multiple cysteine residues are aligned) (28) and β-interferon (IFN-β) (region aligned and identical is highly conserved among all IFN-α and β species) (38). The IL-6 open reading frame contains two potential *N*-glycosylation sites and several potential *O*-glycosylation and serine-phosphorylation sites. The 3′-untranslated region of the IL-6 mRNA contains multiple copies of the AUUUA-repeat motif considered important in regulating mRNA turnover.

The human *IL-6* gene is located at 7p21 in the genome (21, 39, 40). It consists of five exons which have the same overall exon/intron pattern as the gene for granulocyte-colony-stimulating factor (41). Immediately upstream of the 3′-most exon (exon V) is an Alu-repetitive DNA motif (40). There is considerable polymorphism in the human *IL-6* gene—three *Msp*I, two *Bgl*I, and at least four *Bst*NI alleles that segregate independently have been identified by restriction fragment length polymorphism (40). Thus, theoretically, there exist up to 24 different *IL-6* haplotypes in the human population; many of these have already been identified (40). The *Msp*I and *Bgl*I RFLP appear to be due to point mutations in introns; the *Bst*NI polymorphism is the result of insertions/deletions in an AT-rich region immediately downstream of exon V (42). Recombination analyses using these polymorphisms have helped place the *IL-6* gene within the linkage map of human chromosome 7 (40).

IL-6 Gene Expression

Expression of the *IL-6* gene is readily induced in different cell types by a wide range of "noxious" stimuli (43). Bacterial products such as endotoxin strongly enhance IL-6 gene expression in human fibroblasts and monocytes/macrophages. *IL-6* gene expression in different cell types is also enhanced by infection with different RNA- and DNA-containing viruses and by inflammation-associated cytokines such as IL-1, TNF, platelet-derived growth factor, and interferons (43). Endothelial cells, keratinocytes, and a variety of other epithelial and mesenchymal cells also express IL-6 in response to these stimuli (43). Some neoplastic cells (transformed B and T cell lines, multiple myeloma cells, follicular lymphoma cells, various carcinomas, and sarcoma cells) appear to express IL-6 "constitutively" (43, 44). Glucocorticoids, which can be produced secondarily to an IL-6-induced increase in ACTH production (18), strongly inhibit *IL-6* gene expression (45); this appears to be an important negative feedback loop that limits the acute phase response. 17β-Estradiol has also been shown to inhibit *IL-6* gene expression in endometrial stromal cells (46).

Figure 1 summarizes the transcription regulatory elements present in the 5′-flanking region of the human *IL-6* gene (26, 43, 47–50). The IL-6 and c-*fos* promoters are strikingly similar in their overall function. The c-*fos* serum-response element enhancer region exhibits strong nucleotide sequence similarity to that of the multiple cytokine (IL-1, TNF, serum) and second messenger (cAMP, phorbol ester)-responsive enhancer (MRE) region in IL-6 (−173 to −145) (26, 43, 47, 49, 50). The complex IL-6 enhancer region consists of two partially overlapping DNA elements, each of which is responsive to these stimuli (50). MRE I, −173 to −151, contains the typical GACGTCA cAMP/phorbol ester-responsive (CRE/TRE) motif. MRE II, −158 to −145, contains an imperfect dyad repeat which bears little resemblance to a CRE/TRE motif. That a chimeric construct containing MRE II is nevertheless strongly induced by both phorbol ester and forskolin suggests that this DNA defines a new cAMP and phorbol ester-responsive element (CRE/TRE II). This element is highly similar to an atypical cAMP-responsive element recently identified in the bovine cytochrome P-450$_{17\alpha}$ gene (50, 51). The fact that both MRE I and MRE II are independently strongly induced by phorbol ester and forskolin demonstrates extensive "cross-talk" between components of the two major signal transduction pathways that are involved in activation of the IL-6 promoter. The NF-κB site in the IL-6 promoter also appears to contribute to the activation of this gene in transfected U937 cells and in some batches of L cells in response to lipopolysaccharide and IL-1 (52, 53).

In footprinting experiments, the glucocorticoid receptor binds to the entire MRE region and to the core promoter elements (TATA box and RNA start site) in the IL-6 promoter (50). In functional assays, dexamethasone-activated glucocorticoid receptor strongly represses the activity of each of the IL-6 functional elements (MRE I, MRE II, and the core promoter) in an inducer independent manner (50). These data indicate that the highly efficient repression of the IL-6 promoter is the consequence of the occlusion of both the enhancer and the core promoter by glucocorticoid receptor rendering them unavailable as positive transcription factors. Imperfect palindromic sequence motifs related to the consensus glucocorticoid responsive element (GRE) motif are present at the major RNA start site, the TATA box, and the MRE II site in the IL-6 promotor (50).

The observation that the *IL-6* promoter sequence from −126 to −101 contains a 21/26 nucleotide match

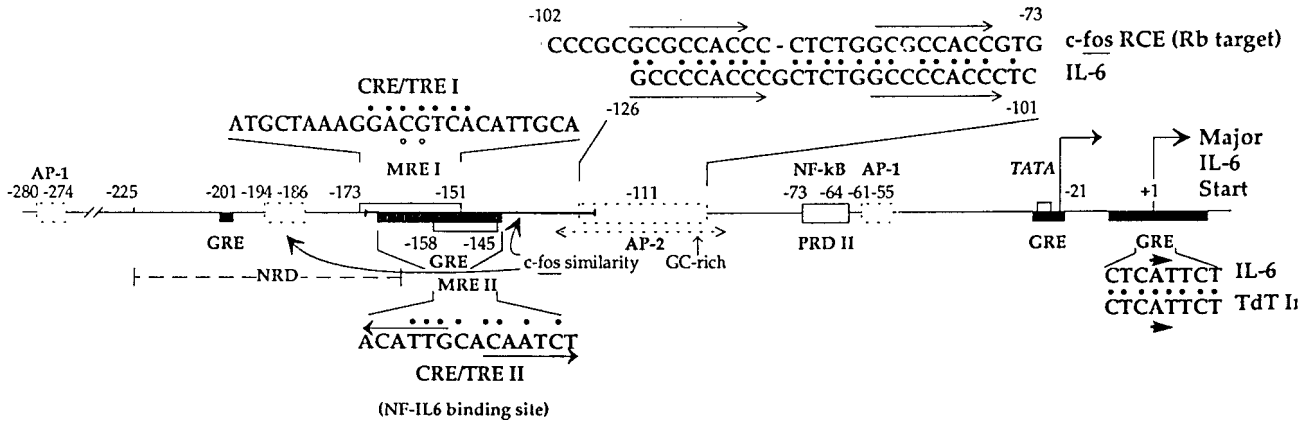

Figure 1. Schematic representation of positive and negative transcription regulatory elements in the 5′-flanking region of the *IL-6* gene. Solid lines (either boxes or arrows) indicate DNA regulatory elements that have already been functionally implicated in *IL-6* gene expression while those marked by broken lines or boxes are based on DNA sequence analyses. The inducible transcription start sites were derived by S1 nuclease mapping (ratio of major +1 to minor −21 sites is 100:1) (43). The upstream start site at −21 confirms data reported in ref. 37 but is different from that reported in ref. 41. Also, we have been unable to confirm the presence of the so-called "third upstream start site" reported to be present at approximately −110 in ref. 41. The presence of a negative regulatory domain (NRD) between −225 and −165 was inferred by deletion analyses (49). The typical GACGTCA CRE/TRE motif in MRE I and the nucleotides in the new CRE/TRE in MRE II which match with nucleotides in the CRE identified in bCYP17 (50) are highlighted by filled circles. The mutation of the CG residues (open circles) to GT reduces the responsiveness of MRE I to TPA and forskolin (49). PRD II refers to an NF-κB-like motif in the IFN-β promoter that is also present in the IL-6 promoter (26). RCE is the DNA element in the *c-fos* promoter that has been functionally identified as a target for repression by wild-type but not mutant retinoblastoma susceptibility gene product Rb (50). Adapted from Ray *et al.* (50).

with the retinoblastoma susceptibility gene product (Rb) repressible element in *c-fos* raises the possibility that Rb may be involved in the regulation of *IL-6* gene expression during development and oncogenesis (50).

17β-Estradiol inhibits *IL-6* gene expression in endometrial stromal cells at concentrations in the physiologic range (10^{-9} *M*) (46). The involvement of IL-6 in the biology of the reproductive tract is now attracting particular attention.

IL-6 Proteins and Assays

Human IL-6 consists of a set of differentially modified phosphoglycoproteins of molecular mass in the range of 19–30 kDa (54–56). IL-6 polypeptides of length 184–186 amino acids are differentially modified by *O*-glycosylation, *N*-glycosylation, and serine-phosphorylation in a cell type-specific manner and can be resolved by sodium dodecyl sulfate-polyacrylamide gel electrophoresis into several *O*-glycosylated species of mass 19–25 kDa and several *O*- and *N*-glycosylated species of mass 27–30 kDa. These IL-6 species exist in a multimeric state (45–70 kDa) in culture medium and in human body fluids as judged by gel filtration analyses or by polyacrylamide gel electrophoresis under nondenaturing or partially denaturing conditions (57–59).

It is not yet clear how titers of biologically active IL-6 in human body fluids that are determined using the hybridoma growth factor assay (in B9 or 7TD1 or equivalent cells) and expressed as units per milliliter relate numerically to those obtained using other biologic and immunologic assays for IL-6. Indeed, it is quite clear that certain enzyme-linked immunoabsorbent assays for IL-6 detect particular forms of IL-6 with very low efficiency; it is also clear that human body fluids, serum/plasma in particular, interfere with many of the currently available bioassays and enzyme-linked immunoabsorbent assays for IL-6.

The IL-6 Cell Surface Receptor

The complex IL-6 receptor appears to consist of at least two polypeptides (60, 61). The p80 protein (dubbed IL-6R) binds IL-6 but does not by itself function in signal transduction. It associates with a p130 which is hypothesized to function as the major signal transducer. Soluble forms of the p80 IL-6 binding protein are found in urine and, when added to IL-6 preparations, enhance their biologic activity (62).

Dexamethasone up-regulates IL-6 receptor numbers in hepatocytes (63). This phenomenon may contribute to the synergism observed between IL-6 and glucocorticoids in enhancing acute phase plasma protein gene expression in the liver. The numbers of IL-6 receptors are also regulated during cell differentiation—resting B cells have few receptors; activated B cells exhibit a considerable increase in the number of IL-6 receptors (64). The possibility that there exist IL-6 receptors distinct from the p80 + p130 complex in cell types such as the fibroblast remains to be explored.

Biologic Effects of IL-6

The broad range of effects exerted by IL-6 is exemplified by the numerous names used by different investigators to describe its activities. IL-6 elicits the acute phase alterations in plasma protein gene expres-

sion in hepatic and nonhepatic (fibroblasts and monocytes) tissues, enhances the proliferation and differentiation of B cells, contributes to the activation of T cell function (particularly that of cytotoxic T cells), enhances the activity of natural killer cells (65), enhances hematopoiesis (66), and stimulates monocytic and neuronal cell differentiation. In animal experiments, administration of IL-6 is pyrogenic (16), leads to an increase in ACTH levels secondary to the increased production of corticotropin-releasing factor (18), elicits alterations of plasma protein composition reminiscent of the acute phase response (67, 68), and causes megakaryocytosis (68).

Depending on the cell type investigated, IL-6 can either enhance, inhibit, or have no effect on cell proliferation (34, 35). On the one hand, IL-6 can enhance the proliferation of normal keratinocytes (69) and of different carcinoma and myeloma cells (44). On the other hand, IL-6 can strongly inhibit the growth of several breast carcinoma cell lines (34, 35). IL-6 has been reported to inhibit the proliferation of endothelial cells (70) and of diploid fibroblasts (71) under particular experimental conditions.

Although IL-6 inhibits the proliferation of T-47D and ZR-75-1 ductal breast carcinoma cell lines, it increases cell motility and decreases cell-cell association (35). T-47D and ZR-75-1 cells are typically epitheliod in shape and form compact colonies in culture. Time-lapse cinemicrography shows that IL-6-treated cells become stellate or fusiform ("fibroblastoid") and show increased motility. This results in a dispersal or scattering of cells within colonies. IL-6-treated T-47D cells display diminished adherens-type cell junctions as indicated by markedly decreased vinculin-containing adhesions and intercellular desmosomal attachments. The IL-6-induced phenotypic change, which is reversible, is of interest because (i) this change resembles that which certain epithelial cells undergo in early embryogenesis as they detach from the epithelium, move, and become mesenchymal in character; and (ii) it raises the question whether such changes may play a role in the invasiveness and metastasizing ability of tumor cells.

IL-6 in Human Disease

Infections. Body fluids of patients with acute local bacterial or viral infections and serum of patients with gram-negative or positive bacteremia contain elevated levels of biologically active IL-6 (72–75). The levels observed in the peripheral circulation can be in the range from 5 to 100 ng/ml; those in body fluids in localized infected compartments such as cerebrospinal fluid, synovial fluid, or amniotic fluid (AF) can be ≧500 ng/ml (71, 75, 76; Santhanam *et al.*, submitted for publication). In patients with both meningitis and bacteremia, the concentrations of IL-6 in the cerebrospinal fluid can be 10- to 100-fold higher than that in serum, suggesting considerable local production of IL-6 (72). In cell culture experiments, crude bacterial extracts as well as purified lipopolysaccharide directly induce IL-6 in fibroblasts, monocytes, and endothelial cells (43). The administration of lipopolysaccharide or TNF to human volunteers leads to an increase in IL-6 levels in the peripheral circulation in 30–45 min and the levels peak by approximately 2 hr (57, 58). The ready detection of circulating IL-6 is consistent with the long distance systemic role of IL-6 in mediating the host response to infection. This is in contrast to the essentially local or paracrine role of IL-1 or TNF which have, at best, a transient presence in the peripheral circulation.

Elevated serum levels of IL-6 have been reported in patients with acquired immunodeficiency syndrome (77). This observation is of particular interest because IL-6 and TNF (alone or together) are two cytokines that can lead to reactivation of latent human immunodeficiency virus infection in monocytic cell lines (78).

Obstetric Infections. IL-6 has emerged as a reporter cytokine *par excellence* for intraamniotic infection. Second or third trimester amniotic fluid contains detectable but low levels of IL-6 (range 50–1500 pg/ml) (76). AF samples collected during normal parturition showed a modest increase in IL-6 levels (range 200–15,600 pg/ml); a small subgroup (10–15%) showed significant elevations in AF IL-6 and may represent the group of women in whom apparent "normal" parturition was precipitated due to subliminal intraamniotic infection. AF samples collected from women with premature rupture of membranes but no apparent microbial infection also had modest elevations of IL-6 levels (Santhanam *et al.*, submitted for publication). Among women with preterm labor (76), those who were not responsive to tocolysis and went on to deliver premature babies had high AF IL-6 levels (up to 5 μg/ml; Fig. 2). The latter contained the subgroup of women in preterm labor with provable microbial infection (Fig. 2). In a pilot study of the prognostic value of AF IL-6 measurements in patients with preterm labor (76), it was observed that all 10 out of 56 consecutive patients with markedly elevated AF IL-6 levels (≧46 ng/ml) delivered preterm; in these 10 patients the pregnancy was not salvageable by tocolytic therapy. All four patients with culture-provable AF microbial infection were in this group of 10 patients that had markedly elevated AF IL-6 levels. Similarly, in women with premature rupture of membranes (Santhanam *et al.*, submitted for publication), the presence of markedly elevated AF IL-6 levels correlated with the presence of provable intraamniotic infection. Markedly elevated levels of IL-6 have also been detected in fetal plasma (Santhanam *et al.*, submitted for publication), particularly in the presence of neonatal or amniotic cavity infection. The prognostic implications of IL-6 in the

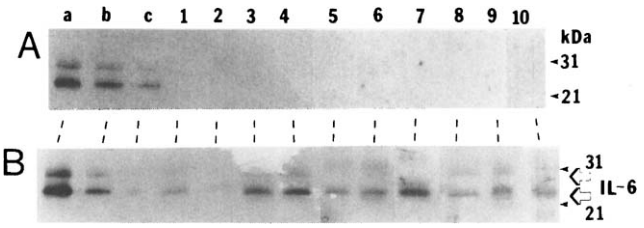

Figure 2. Multiple forms of IL-6 proteins in AF from women in preterm labor. This composite figure illustrates sodium dodecyl sulfate-polyacrylamide gel electrophoresis/immunoblot assays for IL-6 (using a rabbit anti-rIL-6 antiserum) carried out using 10-μl AF aliquots (undiluted) from 10 patients in each of the following two groups: A, AF culture-negative and preterm labor responsive to tocolysis; B, AF culture-positive and preterm labor non responsive to tocolysis. Lanes a, b, and c in each panel illustrate immunoblot assays using natural IL-6 standard preparation at 4, 2, and 1 ng of antigen/lane in A and at 10, 2, and 0.4 ng/lane in B. In additional immunoblot analyses of AF samples, unrelated rabbit serum or the second antirabbit antibody by itself did not react with the 23- to 25- and 28- to 30-kDa anti-rIL-6-immunoreactive proteins. Reproduced from Romero et al. (76), *Journal of Clinical Investigation*.

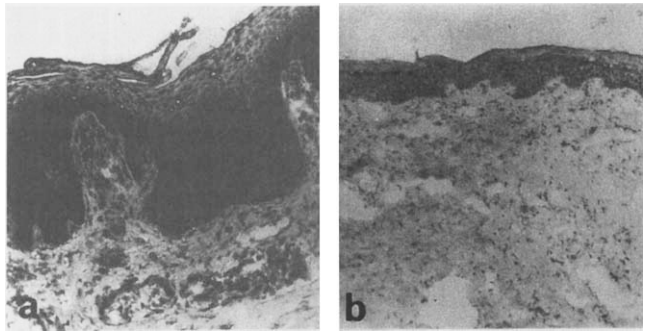

Figure 3. Increased immunoreactive IL-6 in psoriatic plaques and its decrease following medical therapy. Frozen sections of skin biopsies were stained using rabbit anti-rIL-6 antiserum and an immunoperoxidase staining protocol. (a) Active plaque shows diffuse cytoplasmic staining of keratinocytes, the dermal infiltrate, and endothelial cells. (b) After 4 weeks of topical tar and ultraviolet B therapy, acanthosis and IL-6 reactivity are no longer apparent (original magnification ×85). Reproduced from Grossman et al. (69), *Proceedings of the National Academy of Sciences USA*.

fetal circulation remains to be explored. Furthermore, the specific contribution of IL-6 to the physiology of pregnancy and parturition remains to be elucidated.

Diseases Associated with an Altered Immune System. Elevated levels of circulating IL-6 have been detected in patients with cardiac myxoma (79), Castleman's disease (80), rheumatoid arthritis (81–84). IgM gammopathy (85) and in those with acquired immunodeficiency syndrome (77). In the case of rheumatoid arthritis, several investigators have reported the detection of high levels (5–100 ng/ml) of IL-6 in the synovial fluid. These elevations of IL-6 levels in body fluids correlate with the presence of systemic manifestations such as an increased erythrocyte sedimentation rate, fever, increased plasma levels of acute phase plasma proteins like C-reactive protein and serum amyloid A, and an increase in the frequency of activated B cells in the peripheral circulation and increases in the levels of plasma Ig. Treatment of the underlying disease state leads to the diminution of these systemic sequelae.

Proliferative Diseases. The ability of IL-6 to enhance the proliferation of normal and neoplastic cells provides a basis for its participation in the pathophysiology of diseases characterized by increased cell proliferation.

By immunohistochemistry, elevated levels of IL-6 can be detected in psoriatic plaques (69) (Fig. 3). Psoriatic keratinocytes also express elevated levels of IL-6 mRNA as determined by *in situ* nucleic acid hybridization. Elevated plasma levels of IL-6 are observed in patients with psoriasis and are likely to account for the increase in plasma C-reactive protein levels and fever seen in these patients. Strikingly, IL-6 stimulates the proliferation of keratinocytes (69) and may thus account for the hyperkeratosis observed in psoriatic plaques. The diminution of hyperkeratosis following therapy is accompanied by a decrease in IL-6 staining in the psoriatic plaque (Fig. 3).

Increased local IL-6 levels (by immunostaining) and increased systemic levels of IL-6 have also been detected in patients with mesangial proliferative glomerulonephritis (86). Furthermore, the proliferation of mesangial cells in culture is stimulated by IL-6. At the present time it is not clear whether increased IL-6 is a causative factor in this disease state or whether it is simply an additional participant in its pathophysiology and is induced locally secondary to tissue disruption.

Neoplastic Diseases. IL-6 is a common participant in the host-tumor interaction. It exerts local effects by altering the proliferative properties of the neoplastic cell (increased proliferation of myeloma cells, Lennert's T lymphoma cells, renal carcinoma cells and Kaposi's sarcoma cells) (44, 87) and by eliciting the systemic alterations characteristic of a tumor-bearing host (increased erythrocyte sedimentation rate, increased serum levels of acute phase plasma proteins, decrease in serum albumin, fever, weight loss/cachexia, etc).

The development of immunohistochemical techniques to detect IL-6 antigen in frozen sections of tissues has allowed us to survey human tumor tissue for IL-6 (88). Strong to moderate IL-6 immunoreactivity was observed in the neoplastic elements present in primary squamous cell carcinomas, in adenocarcinomas of mammary, colonic, ovarian, and endometrial origin, in various adenocarcinomas metastatic to lymph nodes, and in soft tissue tumors including leiomyosarcoma and neurofibrosarcoma. Weak to moderate IL-6 immunostaining was observed in Hodgkin's and non-Hodgkin's lymphomas. In brief, most human tumors tested stain positive for IL-6. Where present, the stromal tissue in most of the tumors also stained positive for IL-6 (88). The question that remains open is whether most neoplastic cells secrete IL-6 or simply accumulate

IL-6 from their surroundings. It is likely that it is the presence of neoplastic cell elements in the disrupted host tissue that leads to the local induction of IL-6.

Elevations of circulating levels of IL-6 have also been observed in patients with neoplastic disease. Patients with multiple myeloma, other B cell dyscrasias, Lennert's T lymphoma, Castleman's disease, and various other solid tumors (44, 89, 90) have been reported to have elevated levels of circulating IL-6. In many of these instances, it is the neoplastic cell element that produces the IL-6 which, in turn, has an autocrine enhancing effect on the proliferation of the same cells.

In experimental murine models, it has now been convincingly demonstrated that the growth of several different transplantable solid tumors is accompanied by an increase in the levels of circulating IL-6 (91, 92). The extent of cachexia observed in these animals appears to be correlated with the increase in serum IL-6 levels. Indeed, it has been reported that IL-6 inhibits lipoprotein lipase activity in adipose tissue (93) and this effect may contribute to the observed weight loss seen in the tumor-bearing host. It should be emphasized that in these experimental models, neither IL-1 nor TNF is detected in the sera of tumor-bearing mice (91, 92).

It has been recently reported that administration of IL-6 to mice injected intravenously with cells from transplantable lines of chemically induced murine solid tumors decreased the appearance of tumor nodules in the lungs (94). It is possible that this observation is the *in vivo* correlate of the inhibitory effect of IL-6 on the growth of tumor cells in a clonogenic assay in cell culture (34, 35).

A Network of Cytokines

It is in the nature of a review dealing with a particular cytokine that the contribution of that particular cytokine to disease processes tends to be emphasized. It is important to recognize that the biologic effects of IL-6 occur against a backdrop of other cytokines and hormones. Thus, there exist strong synergistic interactions between IL-6 and IL-1 and between IL-6 and glucocorticoids (6). Additionally, it is common to find that one cytokine induces another, thus recruiting an ever increasing circle of mediators. Nevertheless, in the overall hierarchy of cytokines, IL-6 stands out as a systemic cytokine that mediates a wide array of host responses to disease states. It is key to the elicitation of an altered "host chemistry" (3, 6).

The involvement of IL-6 in human infection and cancer is very clear. What is not so clear is the value of this information in the day to day management of individual patients. It is time for the IL-6 field to make a transition from anecdotal clinical observations to the rigorous evaluation of the diagnostic or prognostic value of IL-6 measurements in clinical practice. The first such rigorous study of the prognostic value of IL-6 measurements, in patients with preterm labor (76), is already under way and is expected to yield management recommendations of direct relevance to the practicing obstetrician.

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