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Expression and Function of Interleukin-6 in Epithelial Cells

James Krueger, Anuradha Ray, Igor Tamm, and Pravinkumar B. Sehgal

The Rockefeller University, New York, New York 10021

Abstract Epithelial cells both produce and are affected by interleukin-6 (IL-6). Experiments with an adenocarcinoma-derived cell line (HeLa) reveal that activation of the transfected human IL-6 promoter occurs largely through two partially overlapping second messenger (cAMP, phorbol ester)- and cytokine (IL-1, TNF, serum)-responsive enhancer elements (MRE I, −173 to −151 and MRE II, −158 to −145). MRE I contains the typical GACGTCA cAMP and phorbol ester-responsive (CRE/TRE) motif, whereas MRE II defines a new CRE/TRE motif that contains an imperfect dyad repeat. The mechanism of dexamethasone-mediated repression of IL-6 gene expression in epithelial cells involves occlusion of the entire MRE enhancer region and of the core-promoter elements (TATA-box and RNA start site) by ligand-activated glucocorticoid receptor. Enhanced levels of IL-6 expression are observed in many solid tumors and in the hyperproliferative (and glucocorticoid-suppressible) lesions of psoriasis. In cell culture, IL-6 enhances, inhibits, or has no effect on the proliferation of epithelial cells depending upon the cell-type examined. IL-6 enhances proliferation of keratinocytes but inhibits that of breast carcinoma cell lines ZR-75-1 and T-47D. In these breast carcinoma cells, IL-6 elicits a major change in cell phenotype which is characterized by a fibroblastoid morphology, enhanced motility, increased cell-cell separation, and decreased adherens type junctions (desmosomes and focal adhesions). The new data identify IL-6 as a regulator of epithelial cell growth and of cell-cell association.

Key words: multiple-cytokine responsive enhancer (MRE), glucocorticoid repression, promoter occlusion, keratinocytes, breast carcinoma cell lines, cell proliferation, cell motility, cell-cell association

Human interleukin-6 (IL-6) cDNA was originally cloned more than 10 years ago as the DNA copy of a poly(I).poly(C)-inducible 1.3-kb long mRNA present in fibroblasts [1]. At that time this molecule was termed "interferon-β_2" [2,3]. Extensive sections of the amino acid sequence of human IL-6 were described in 1985 (3–5) and the IL-6 gene was assigned to human chromosome 7 in the spring of 1986 [6]. Four different laboratories reported the complete nucleotide sequence of the cDNA essentially simultaneously in the fall of 1986 [7–10]. The discovery that IL-6 was strongly induced by inflammation-associated cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and platelet-derived growth factor (PDGF) [11–13] suggested that IL-6 participated in the host response to infection and injury. The realization that "IFN-β_2" was the same cytokine as B-cell differentiation factor-2 [14] pointed to the critical role of this cytokine in B-cell function. The landmark discovery that this cytokine was also the "hepatocyte stimulating factor," a term that had been coined by Fuller and colleagues several years earlier to refer to a cytokine that elicited the acute phase alterations in plasma protein secretion by hepatocytes [15,16], made clear the central role of IL-6 in the systemic host response to tissue damage [17].

Murine IL-6 was purified to homogeneity in three different laboratories [18–21] using two different assays (myeloid cell differentiation and enhancement of plasmacytoma/hybridoma growth) and a partial N-terminal sequence was reported in 1986 [21]. However, this N-terminus was highly divergent from the then known complete sequence of human IL-6 and it was not until human IL-6 had been shown to have plasmacytoma/hybridoma growth activity [22–24] and the complete nucleotide and amino acid sequence of murine IL-6 became available that it was recognized to be the murine homolog of human IL-6 [25,26].

Through 1987 and 1988, other investigators independently recognized that the respective human or murine proteins that they had character-

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Address reprint requests to Dr. P.B. Sehgal, The Rockefeller University, 1230 York Avenue, New York, NY 10021.

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ized based on different biological activities were IL-6. As examples, proteins characterized as monocyte-granulocyte inducer type-2 [27], T-cell activating factor [28], monocyte-derived growth factor for human B cells [29], and cytolytic T-cell differentiation factor [30] all turned out to be IL-6 (reviewed in 31).

The human IL-6 gene consists of five exons and is located at 7p21 in the genome [31]. The deduced amino acid sequence for human IL-6 contains an open reading frame for 212 amino acids; from within this reading frame the 184–186 C-terminal amino acids form the major mature IL-6 species [7–10]. Mature IL-6 species range in molecular mass from 19 to 30 kDa and are differentially *N*-glycosylated, *O*-glycosylated, and serine-phosphorylated [31]. IL-6 is readily detected in the peripheral circulation in patients with infection, injury, or neoplasia at levels higher than those at which this cytokine elicits effects on cells in culture [31]. This is in contrast to cytokines such as TNF and IL-1 which are found at very low levels and only transiently in the peripheral circulation. To a first approximation, TNF and IL-1 primarily have paracrine effects, whereas IL-6 stands out as a systemic cytokine. It is now clear that IL-6 is produced by a wide variety of cells and that IL-6 affects the function of numerous different cell types [31]. In this overview we summarize new information on the expression and function of IL-6 in epithelial cells.

THE IL-6 PROMOTER IN EPITHELIAL CELLS

The function of the IL-6 promoter has been studied extensively by us following transfection into HeLa cervical adenocarcinoma cells [32–35]. Fig. 1 summarizes the transcription-regulatory elements present in the 5′ flanking region of the human IL-6 gene. We and others find that this promoter contains two inducible RNA start sites (a major start site at +1 and a minor one at approximately −21 [8,33,35]); we find no evidence for a start site at approximately −65 nor for one further upstream [37]. The IL-6 and c-*fos* promoters are strikingly similar in their overall function [33]. The c-*fos* serum-responsive element (SRE) enhancer region displays strong nucleotide sequence similarity with the multiple cytokine (IL-1, TNF, serum)- and second messenger (cAMP, phorbol ester)-responsive enhancer region in IL-6 (−173 to −145) [33,35,36]. The complex IL-6 enhancer region consists of two partially overlapping DNA elements, each of which is responsive to these stimuli [33,34]. One of these, MRE I, −173 to

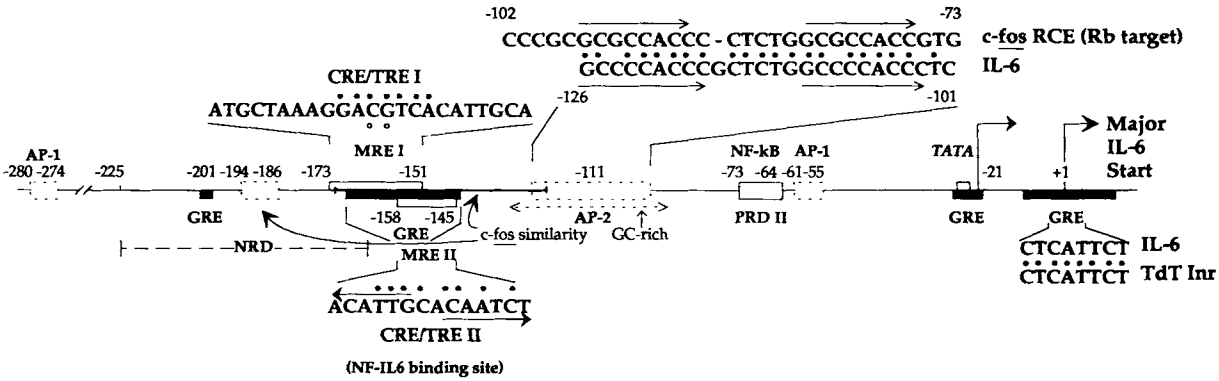

Fig. 1. Schematic representation of positive and negative transcription-regulatory elements in the 5′ flanking region of the IL-6 gene. Solid lines (either boxes or arrows) indicate DNA regulatory elements that have already been functionally implicated in IL-6 gene expression while those marked by broken lines or boxes are based on DNA sequence analyses. MRE I and II, multiple second messenger- and cytokine-responsive element; GRE, glucocorticoid receptor binding elements; CRE, cAMP-responsive element; TRE, phorbol ester-responsive element; NRD, negative regulatory domain; PRD II, NF-κB-like positive regulatory domain II in the IFN-β promoter. Mutation of the CG residues (open circles) to GT reduces the responsiveness of MRE I to phorbol ester and forskolin. The typical GACGTCA CRE/TRE motif in MRE I and the nucleotides in the new CRE/TRE element in MRE II which match with nucleotides in the CRE identified in the bovine cytochrome P450 gene bCYP17 (see 34 for details) are highlighted by filled circles. The sequence from −3 to +5 across the major RNA start site (CTCATTCT) corresponds exactly to the functional Inr ("initiator") transcription-regulatory element. 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. NF-IL6 is a member of the C/EBP family of transcription factors. (Adapted from Ray et al. [34] with permission of *Mol Cell Biol.*.)

−151, contains the typical GACGTCA cAMP/phorbol ester-responsive (CRE/TRE) motif. Mutations at CG in this CGTCA motif block induction by cAMP and phorbol ester but not by serum, IL-1 or TNF [33]. The other DNA element, MRE II, −158 to −145, contains an imperfect dyad repeat and bears little resemblance to a CRE/TRE motif. Nevertheless, a chimeric construct containing MRE II is strongly induced by both phorbol ester and forskolin, suggesting that this DNA defines a new cAMP- and TPA-responsive element ("CRE/TRE II"). The fact that both MRE I and MRE II are independently strongly induced by TPA and forskolin demonstrates extensive interactions between components of the two major signal transduction pathways. 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 [38,39]; we have been unable to assign a clear function to this site using transfection experiments in HeLa cells [32–34]. The observation that the IL-6 promoter sequence from −126 to −101 contains a 21 out of 26 nucleotide match 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 [34].

An important aspect of IL-6 gene expression is its repression by glucocorticoids and estradiol-17β [40,41]. In footprinting experiments the glucocorticoid receptor (GR) binds to the entire MRE region and to the core promoter elements (TATA-box and RNA start site) in the IL-6 promoter [34]. The actual locations of the GR-binding regions in the IL-6 promoter are different from the assignments previously reported based on computer analyses [37]. In functional assays carried out in HeLa cells, dexamethasone-activated GR (expressed in HeLa cells using a constitutive expression vector containing human GR cDNA) 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 [34]. 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 GR rendering these elements unavailable to positive transcription factors. Sequence motifs weakly related to the consensus GRE motif are present at the major RNA start site, the TATA-box and the MRE II site in the IL-6 promoter; however, MRE I does not display any discernable similarity to the consensus GRE motif [34]. Strikingly, the major RNA start site in the IL-6 gene contains the motif CTCATTCT from −3 to +5 which has been shown to define the functional "initiator" (Inr) transcriptional control element [34].

The ability of glucocorticoids to suppress IL-6 gene expression is likely to contribute to the therapeutic efficacy of these drugs as topical and systemic anti-inflammatory agents.

ENHANCED IL-6 EXPRESSION IN PSORIATIC AND NEOPLASTIC TISSUES

The availability of immunohistochemical techniques to detect IL-6 antigen in frozen sections of tissues using high affinity rabbit anti-rIL-6 antibody has made it possible to evaluate the local presence of IL-6 in abnormal tissues. High levels of immunoreactive IL-6 have been observed in the epidermis and dermis in psoriatic plaques [42]. The hyperproliferative keratinocytes not only stained intensely for IL-6 but were shown to contain IL-6 mRNA by in situ nucleic acid hybridization [42]. Furthermore, circulating levels of IL-6 were elevated in patients with psoriasis. Therapy with antimetabolites such as methotrexate was accompanied by a decrease in hyperkeratosis and a reduction in IL-6 staining of the plaques.

IL-6 immunoreactivity is observed in frozen sections of most solid tumors [43]. As examples, neoplastic elements in primary squamous cell carcinomas, in adenocarcinomas of mammary, colonic, ovarian, and endometrial origin, and in various adenocarcinomatous metastases to lymph nodes display moderate to strong IL-6 immunoreactivity.

Elevations of circulating levels of IL-6 are observed in patients with multiple myeloma and other B cell dyscrasias (reviewed in 37) and in a significant proportion of cancer patients with solid tumors [44]. IL-6 may contribute to systemic alterations observed in cancer patients (e.g. an increased erythrocyte sedimentation rate, increased serum levels of acute phase plasma proteins, decreased serum albumin levels, fever and weight loss/cachexia).

ENHANCEMENT OF KERATINOCYTE PROLIFERATION BY IL-6

The realization that IL-6 is a growth factor for transformed human B cell lines [29] raised the possibility that IL-6 may also enhance the prolif-

eration of non-lymphoid human cells. The detection of markedly enhanced levels of IL-6 in psoriatic plaques [42], a disease state characterized by hyperproliferative keratinocytes, led to an evaluation of the effect of IL-6 on keratinocyte proliferation. When normal human adult skin keratinocytes were maintained in basal medium, the addition of IL-6 stimulated thymidine incorporation into DNA [42,45]. The increase in thymidine incorporation is accompanied by an increase in cell numbers (Tables I and II and Fig. 2). In the experiment described in Table I, keratinocytes were first seeded in complete growth medium for 18 hours and then shifted to basal medium in the presence of IL-1 or IL-6 for another 5 days. Under these experimental conditions there is a marked stimulation of cell proliferation in the IL-6-treated cultures (also see Fig. 2); this stimulation far exceeds that observed in IL-1-treated cultures. Table II illustrates data obtained using a different protocol in which previously seeded keratinocytes were treated for 5 days with different cytokines in the presence of insulin and hydrocortisone. Again, IL-6 enhances keratinocyte proliferation to an extent comparable to that seen with IL-1 and FGF and exceeding that observed in the continued presence of EGF. These data suggest that local production of IL-6 may contribute to the pathogenesis of hyperproliferative epithelial lesions such as the psoriatic plaque and, in principle, to that of cutaneous neoplasia. The cellular and molecular mechanisms that lead to the IL-6-stimulated enhancement of keratinocyte proliferation remain to be explored.

TABLE I. IL-6 Enhances Keratinocyte Proliferation*

Experimental conditions		Cell number after 5 days
Cytokine	Concentration (ng/ml)	($\times 10^5$)
None		0.3
IL-1α	10	0.7
IL-6	1	2.4
IL-6	10	5.3

*10^5 human keratinocytes were seeded in 25 cm^2 flasks in keratinocyte basal medium (KBM, ref. 42) containing epidermal growth factor (EGF, 10 ng/ml), insulin (5 μg/ml) and hydrocortisone (0.5 μg/ml) for 18 hours. The average number of cells that attached after 18 hours was 33,600 per flask (mean of two replicates). The cultures were then washed and the medium replaced with KBM supplemented with the appropriate cytokine. Five days later, the number of cells in each group of cultures (mean of two flasks) was enumerated using a Coulter counter after trypsinization.

INHIBITION OF EPITHELIAL CELL PROLIFERATION BY IL-6

IL-6 has a dual action on cell proliferation. IL-6 strongly inhibits the proliferation of certain breast carcinoma cell lines [46–49]. It is unclear why IL-6 inhibits proliferation of some epithelial cells, but stimulates that of others. Proliferation of ductal breast carcinoma lines MCF-7, T-47D and ZR-75-1 is inhibited by IL-6. Among these, the ZR-75-1 cell line employed in our laboratory is the most sensitive to IL-6-induced inhibition of cell growth. Cell lines such as T-47D represent mixed populations of cells with differing relative sensitivities to inhibition by IL-6 [48]. In the highly sensitive ZR-75-1 cells, baculovirus vector-derived IL-6 causes substantial inhibition of DNA synthesis and colony formation at a concentration of 0.1 ng/ml; a maximal inhibitory effect (70–80% inhibition) is observed at 3–10 ng/ml IL-6. The cellular mechanisms involved in IL-6-mediated inhibition of cell proliferation in these carcinoma lines remain to be determined.

IL-6 ENHANCES MOTILITY OF BREAST CANCER CELLS

In addition to and independent of the inhibition of cell proliferation, treatment of breast duct epithelial cells T-47D and ZR-75-1 induces a cellular phenotype characterized by fibroblastoid morphology, enhanced motility, increased cell-cell separation, and decreased adherens type junctions (desmosomes and focal adhesions) [47,49].

The great majority of T-47D cell colonies consist largely of contiguous flat polygonal cells with typical epithelial appearance (Fig. 3). IL-6 causes a marked increase in the proportion of T-47D cells that are deficient in junction formation. The IL-6-treated cells scatter and are angular in shape (Fig. 3). Time-lapse cinemicrography shows increased local movement of IL-6-treated cells and also movement by these cells over considerable distances [47]. T-47D cells grown for several days in culture show numerous desmoplakin-containing desmosomal attachments between adjacent cells. IL-6-treated T-47D cells show a marked reduction in the number of desmosomal attachments. IL-6 also causes perinuclear retraction of cytokeratin filaments and greatly diminishes peripheral keratin filament

TABLE II. Action of IL-6 and Other Keratinocyte Mitogens in Enhancing Keratinocyte Proliferation*

Experimental conditions			Cell number after 5 days
Medium used	Cytokine	Concentration (ng/ml)	($\times 10^5$)
KBM	None		0.3
KHI[a]	None		3.2
KHI	EGF	100	3.8
KHI	EGF	10	4.6
KHI	bFGF	100	6.9
KHI	bFGF	10	5.0
KHI	bFGF	1	4.4
KHI	IL-1α	10	5.4
KHI	IL-1α	1	3.4
KHI	IL-6	10	5.9
KHI	IL-6	1	5.5

*Experimental conditions were as described in the legend to Table I.
[a]Keratinocytes were incubated in KBM medium containing insulin and hydrocortisone (designated KHI) throughout the five day experimental period. All growth factors and cytokines are purified protein of human origin from recombinant sources.

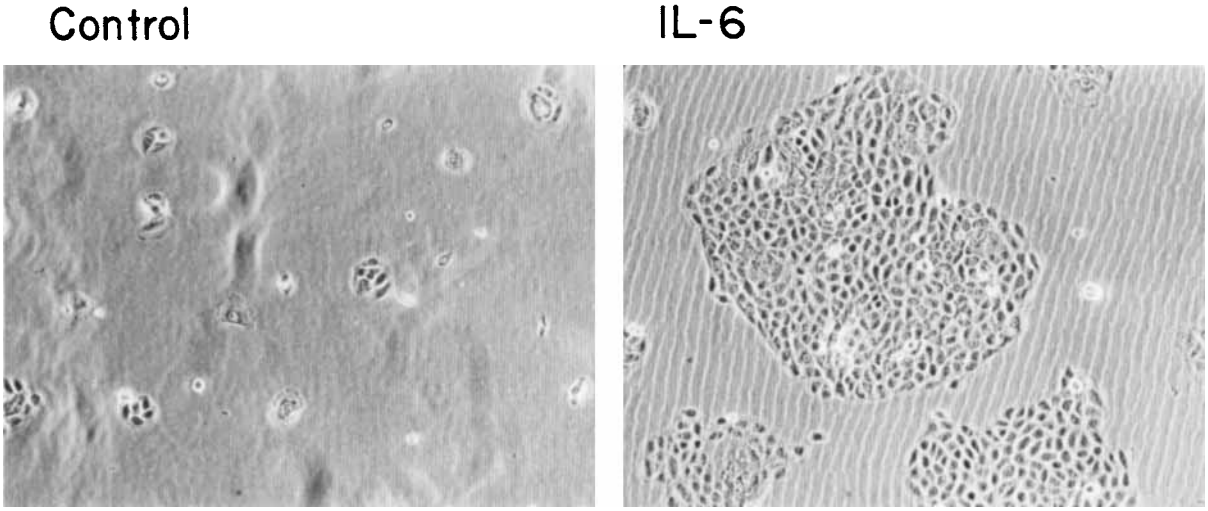

Fig. 2. Effect of IL-6 on human keratinocyte growth and colony morphology. Phase-contrast photomicrographs correspond to experiment in Table I and were taken at the end of 5 days' incubation. Keratinocytes in control cultures (left) formed only small, isolated colonies. Keratinocytes in the baculovirus vector-derived rIL-6 (10 ng/ml) formed large colonies in which the cells retained a typical epithelial morphology.

attachments commensurate with the decrease in the number of desmosomes [47].

Control T-47D cells show numerous prominent vinculin-containing focal adhesions distributed over most of the ventral cell surface [47]. IL-6-treated T-47D cells show a marked reduction in the number of focal adhesions. Furthermore, there is a marked decrease in the number of microfilament bundles (stress fibers) in IL-6-treated cells. Overall, these changes in cytoskeletal structures and adherens junctions are consistent with the altered morphology and increased motility of IL-6-treated cells.

Colonies of ZR-75-1 cells are densely packed with polygonal or cuboidal cells that often form what appear to be multi-layered, elongated, and convoluted aggregates [47]. IL-6-treated ZR-75-1 cells become stellate or fusiform in shape and often display long filopodia. By time-lapse cinemicrography, IL-6-treated ZR-75-1 cells can be seen to separate from each other and to move apart [47]. In denser cultures, the IL-6-treated

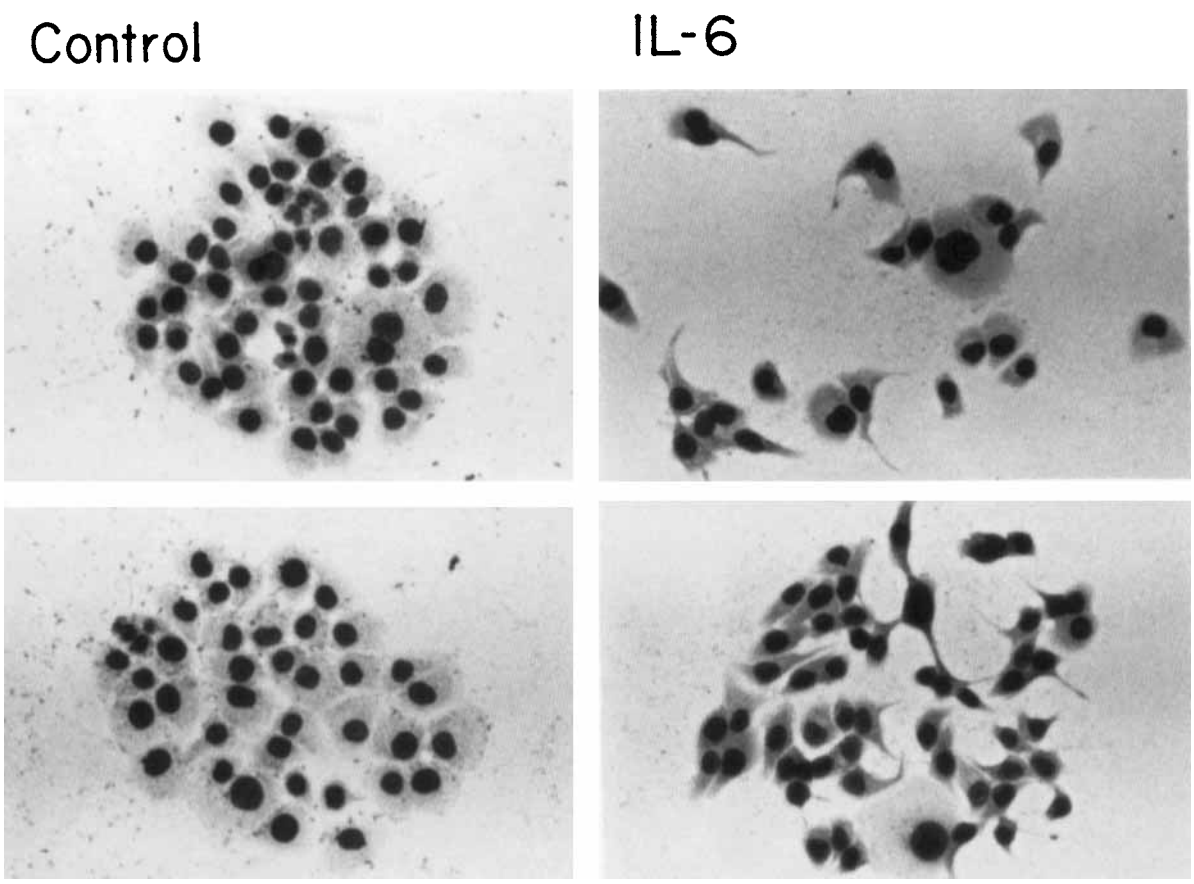

Fig. 3. Cell "scattering" effect of IL-6. T-47D ductal breast carcinoma cells planted at a density of 42 cells/cm^2 were incubated for 11 days in the absence (left) or presence (right) of rIL-6. Figure illustrates photomicrographs of Giemsa-stained cultures. (Adapted from Tamm et al. [47] with permission of Rockefeller University Press.)

cells tend to form networks with numerous individual cells within open spaces.

The IL-6-induced changes in these breast carcinoma cell lines develop over the course of several days and persist as long as IL-6 is present in the culture medium. On removal of IL-6 from the medium, these changes are reversible and the cells reassume epithelial morphology and reattach to each other [47].

The IL-6-induced phenotypic change in epithelial cells is of particular interest because it resembles the change that certain groups of epithelial cells undergo in early embryogenesis as they detach from the epithelium, move, and become "mesenchymal," and because it raises the question whether such IL-6-induced changes may contribute to the invasiveness and metastasizing ability of carcinoma cells. In fact, IL-6-treated cells (Fig. 3) have an appearance that resembles cells of the more "malignant" or "anaplastic" phenotype seen in cytological preparations of breast ductal carcinoma tissue. The molecular and biochemical alterations that underlie the development of the IL-6-induced fibroblastoid phenotype in epithelial cells and the enhancement of cell motility remain to be explored. It is already clear that the scattering effect of IL-6 is restricted to particular epithelial cells. Fig. 2 shows that IL-6 does not scatter keratinocytes or affect their morphology.

FUTURE DIRECTIONS

The role of IL-6 in embryonic development represents an area of research in its initial stages. Biologically active IL-6 has been detected in human amniotic fluid in the second and third trimesters of pregnancy [50]. In the mouse, IL-6 mRNA is transiently expressed in perifollicular vascular tissue around the developing ovum and in the developing endothelial cords in decidual tissue in the post-implantation uterus [51]. These tissues are characterized by self-limiting

angiogenesis; IL-6 gene expression occurs during the proliferative phase of angiogenesis. The effects of IL-6 on epithelial and mesenchymal cells in the developing embryo are unclear. Gene deletion experiments using murine embryonal stem cells (ES cells) are likely to provide new insights into the contribution of IL-6 to embryonic development.

The participation of IL-6 in the host-tumor interaction is clearly established. The contribution of IL-6 to the regulation of growth of human neoplastic cells in vivo and to the modulation of their invasive and metastisizing capability remain to be directly tested. Nevertheless, in cell culture experiments, IL-6 has emerged as a critical regulator of epithelial cell growth and of cell-cell association.

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REFERENCES

1. Weissenbach J, Chernajovsky Y, Zeevi M, Shulman L, Soreq M, Nir U, Wallach D, Perricaudet M, Tiollais P, Revel M: Proc Natl Acad Sci USA 77:7152–7156, 1980.
2. Sehgal PB, Sagar AD: Nature 287:95–97, 1980.
3. Zilberstein A, Ruggieri M, Revel M: In Rossi GB, Dianzani F, (eds): "The IFN System." Serono Symposia. New York: Raven Press, 1985, pp 73–83.
4. Zilberstein A, Nissim A, Ruggieri R, Shulman L, Chen L, Revel M: In Stewart WE, Schellekens H, (eds): "The Biology of the Interferon System 1985." Amsterdam: Elsevier, 1986, pp 119–124.
5. Revel M, Ruggieri R, Zilberstein A: In Stewart WE, Schellekens H, (eds): "The Biology of the Interferon System 1985." Amsterdam: Elsevier, 1986, pp 207–216.
6. Sehgal PB, Zilberstein A, Ruggieri R, May LT, Ferguson-Smith A, Slate DL, Revel M, Ruddle FH: Proc Natl Acad Sci USA 83:5219–5222, 1986.
7. Haegeman C, Content J, Vilckaert G, Derynck R, Tavernier J, Fiers W: Eur J Biochem 159:625–632, 1986.
8. Zilberstein A, Ruggieri R, Korn JH, Revel M: EMBO J 5:2529–2537, 1986.
9. Hirano T, Yasukawa K, Taga T, Watanabe Y, Matsuda T, Kashiwamura S, Nakajima K, Iwamatsu K, Tsunasawa S, Sakiyama F, Matsui H, Takahara Y, Taniguchi T, Kishimoto T: Nature 324:73–76, 1986.
10. May LT, Helfgott DC, Sehgal PB: Proc Natl Acad Sci USA 83:8957–8961, 1986.
11. Content J, DeWit L, Poupart P, Opdenakker G, Van Damme J, Billiau A: Eur J Biochem 152:253–257, 1985.
12. Kohase M, Henriksen-DiStefano D, May LT, Vilček J, Sehgal PB: Cell 45:659–666, 1986.
13. Kohase M, May LT, Tamm I, Vilček J, Sehgal PB: Mol Cell Biol 7:273–280, 1987.
14. Sehgal PB, May LT, Tamm I, Vilček J: Science 235:731–732, 1987.
15. Fuller GM, Ritchie DG: Ann NY Acad Sci 389:308–322, 1982.
16. Ritchie DG, Fuller GM: Ann NY Acad Sci 408:490–502, 1983.
17. Gauldie J, Richards C, Harnish D, Lansdorp P, Baumann H: Proc Natl Acad Sci USA 84:7251–7255, 1987.
18. Lotem J, Lipton JH, Sachs L: Intl J Cancer 32:127–134, 1980.
19. Lipton JH, Sachs L: Biochim Biophys Acta 673:552–569, 1981.
20. Nordan RP, Potter M: Science 233:566–569, 1986.
21. Van Snick J, Cayphas S, Vink A, Uttenhoye C, Coulie P, Simpson RJ: Proc Natl Acad Sci USA 83:9679–9683, 1986.
22. Van Damme J, Opdenakker JR, Simpson MR, Rubira S, Cayphas S, Vink A, Billiau A, Van Snick J: J Exp Med 165:914–922, 1987.
23. Poupart P, Vandenabeele P, Cayphas S, Van Snick J, Haegeman G, Kruys V, Fiers W, Content J: EMBO J 6:1219–1224, 1987.
24. Brakenhoff JPJ, DeGroot ER, Evers RF, Pannekoek H, Aarden LA: J Immunol 139:4116–4121, 1987.
25. Van Snick J, Cayphas S, Szikora J-P, Renauld J-C, Van Roost E, Boon T, Simpson RJ: Eur J Immunol 18:193–198, 1988.
26. Chiu CP, Moulds C, Coffman RL, Rennick D, Lee F: Proc Natl Acad Sci USA 85:7099–7103, 1988.
27. Shabo Y, Lotem J, Rubinstein M, Revel M, Clark SC, Wolf SF, Kamen R, Sachs L: Blood 72:2070–2073, 1988.
28. Garmen RD, Jacobs KA, Clark SC, Raulet DH: Proc Natl Acad Sci USA 84:7629–7633, 1987.
29. Tosato G, Seamon KB, Goldman ND, Sehgal PB, May LT, Washington GC, Jones KD, Pike SE: Science 239: 502–504, 1988.
30. Cernetti C, Steinman RM, Granelli-Piperno A: Proc Natl Acad Sci USA 85:1605–1609, 1988.
31. Sehgal PB, Grieninger G, Tosato G: Ann NY Acad Sci 557:1–583, 1989.
32. Ray A, Tatter SB, May LT, Sehgal PB: Proc Natl Acad Sci USA 85:6701–6705, 1988.
33. Ray A, Sassone-Corsi P, Sehgal PB: Mol Cell Biol 9:5537–5547, 1989.
34. Ray A, LaForge KS, Sehgal PB: Mol Cell Biol 10:5736–5746, 1990.
35. Ray A, Tatter SB, Santhanam U, Helfgott DC, May LT, Sehgal PB: Ann NY Acad Sci 557:353–362, 1989.
36. Walther Z, May LT, Sehgal PB: J Immunol 140:974–977, 1988.
37. Hirano H, Kishimoto T: In Sporn M, Roberts A, (eds): "Peptide Growth Factors and Their Receptors." Berlin: Springer-Verlag, Hdbk Pharmacol 95:633–665, 1990.
38. Shimizu H, Motomo K, Watanabe T, Okamoto S, Yamamoto KI: Mol Cell Biol 10:561–568, 1990.
39. Liebermann TA, Baltimore D: Mol Cell Biol 10:2327–2334, 1990.
40. Kohase M, Henriksen-DiStefano D, Sehgal PB, Vilcek J: J Cell Physiol 132:271–278, 1987.

41. Tabibzadeh SS, Santhanam U, Sehgal PB, May LT: J Immunol 142:3134–3139, 1989.
42. Grossman RM, Krueger J, Yourish D, Granelli-Piperno A, Murphy DP, Kupper TS, Sehgal PB, Gottlieb AB: Proc Natl Acad Sci USA 86:6367–6371, 1989.
43. Tabibzadeh SS, Poubouridis D, May LT, Sehgal PB: Am J Path 135:427–433, 1989.
44. Jablons DM, McIntosh, Mule JJ, Nordan RP, Rudikoff S, Lotze MT: Ann NY Acad Sci 557:157–161, 1989.
45. Krueger J, Krane JF, Carter DM, Gottleib AB: J Invest Derm 94:135S–140S, 1990.
46. Chen L, Mory Y, Zilberstein A, Revel M: Proc Natl Acad Sci USA 85:8037–8041, 1988.
47. Tamm I, Cardinale I, Krueger J, Murphy JS, May LT, Sehgal PB: J Exp Med 170:1649–1669, 1989.
48. Chen L, Shulman LM, Revel M: Cancer Res, submitted.
49. Tamm I, Cardinale I, Sehgal PB: Cytokine, submitted.
50. Romero R, Avila C, Santhanam U, Sehgal PB: J Clin Invest 85:1392–1400, 1990.
51. Motro B, Itin A, Sachs L, Keshet E: Proc Natl Acad Sci USA 87:3092–3096, 1990.