Mini-Review

Cytokines in Context

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In the last ten years, an avalanche of new information has flattened much of the conceptual framework erected in the first three decades of cytokine research. This article briefly reviews the concepts that collapsed, then attempts to begin replacing them. We see cytokines as specialized symbols in a language of intercellular communication, whose meaning is controlled by context (Sporn and Roberts, 1988, 1990; Nathan, 1990; Kenyon and Kamb, 1989). To illustrate control by context, we summarize new evidence that the response of cells to cytokines can be markedly affected by the extracellular matrix in which most cells are normally embedded.

Legacy: Concepts Crushed by Complexity

Immunologists often date the start of the cytokine era from the description of lymphocyte-derived mediators or "lymphokines" (Dumonde et al., 1969) in the late 1960s (David, 1966; Bloom and Bennett, 1966). However, the roots go much farther back. Nerve growth factor was discovered in 1951 (Levi-Montalcini and Hamburger), and interferon, whose relevance to immunology is indisputable, was discovered in 1954 (Nagano and Kojima). As this illustrates, until recently, investigators in each of four different areas—immunology (interleukins), virology (interferons), hematology (colony-stimulating factors), and cell biology (peptide growth factors)—have worked in relative isolation from parallel developments in the other areas. In this article, we will refer to all of the above polypeptide regulatory factors as "cytokines" (Bigazzi et al., 1975), an enlarged term that took root in immunologic parlance as the perception spread that interferons, colony-stimulating factors (CSFs),[1] and growth factors play a central role in immunology (see Table I). Nonetheless, the persistent legacy of the historical isolation is a terminology imbued with defunct assumptions, notably that a cytokine functions largely within the category in which it came to light; arises chiefly from one type of cell; has a principal action reflected in its name; can be categorized as either a stimulator or an inhibitor; and has a set of additional actions that are related to each other in some obvious way.

By the standards of those concepts, cytokine research is in chaos. Most cytokines arise from seemingly unrelated types of cells. Most have bioactivities so diverse as to seem unrelated; these usually include the ability both to promote and inhibit cellular proliferation and differentiation. Most activities manifest by a given cytokine can be exerted by others. Many cytokines that subserve familiar functions postnatally play different or unknown roles embryologically. Given the amino acid sequence of a cytokine and any of its actions, we cannot predict when or where it will do what else. This last point is an operational definition of the inadequacy of current concepts.

Meaning in Context: Messages from Matrix

We define a cytokine as a soluble (glyco)protein, nonimmunoglobulin in nature, released by living cells of the host, which acts nonenzymatically in picomolar to nanomolar concentrations to regulate host cell function. Cytokines make up the fourth major class of soluble intercellular signaling molecules, alongside neurotransmitters, endocrine hormones, and autacoids. The physiologic importance of cytokines is no less than that of the other classes.

We suggest that a central role of cytokines is to control the (re)modeling of tissues, be it developmentally programmed, constitutive, or unscheduled. Unscheduled remodeling is that which accompanies inflammation, infection, wounding, and repair (Vlassara et al., 1988). In the immune system, the relevant tissues are not just those within fixed organs like lymph nodes, thymus, marrow, and spleen, but also the transient cell assemblages that can infiltrate any organ that is wounded, infected, or inflamed. From this perspective, it is not surprising that a given tissue may exert a profound influence on how cells within it respond to cytokines. Recent evidence documents at least seven types of interaction between cytokines and cell matrix.

Adherence to Matrix Induces Cells to Make Cytokines

This has been clearly demonstrated with monocytes and macrophages. Adherence to fibronectin induces transcription of granulocyte-macrophage (GM)-CSF (Thorens et al., 1987), and CSF-1 (Eierman et al., 1989); adherence to collagen induces IL-1 (Dayer et al., 1986) and TNF-α (Eierman et al., 1989); interaction with proteins (postulated to include matrix proteins) that have been modified with advanced glycosyla-

1. *Abbreviations used in this paper*: CSF, colony-stimulating factor; GM, granulocyte-macrophage; TGF, transforming growth factor; TNF, tumor necrosis factor.

Table I. Cytokines Mentioned in this Article

Abbreviation	Major or alternative names
Interleukins*	
ETA-1	Early T cell activation antigen-1
IL-1α,β	Lymphocyte-activating factor, endogenous pyrogen, catabolin
IL-2	T cell growth factor
IL-3	Multipotential growth factor, mast cell-stimulating factor
IL-6	Hepatocyte stimulating factor, B cell growth factor
IL-8	Neutrophil-activating peptide-1
TNF-α	Tumor necrosis factor, cachectin
Interferons*	
IFN-γ	Type II or immune interferon, macrophage-activating factor
Colony-stimulating factors*	
CSF-1	Macrophage CSF
GM-CSF	Granulocyte/macrophage-CSF
Peptide growth factors*	
EGF	Epidermal growth factor
FGF	Fibroblast growth factor
PDGF	Platelet-derived growth factor
TGF-α	Transforming growth factor-α
TGF-β	Transforming growth factor-β

* This classification now appears arbitrary and misleading (see text).

Table II. Adhesion Molecules Mentioned in this Article

Designation	Alternative names/descriptions*
Integrins	
$\alpha1\beta1$	VLA-1 ($\beta1$ component is CD29)
$\alpha2\beta1$	VLA-2, CD49b/CD29, extracellular matrix receptor II; binds collagen types I, IV
$\alpha3\beta1$	VLA-3, extracellular matrix receptor I; binds fibronectin, laminin, collagen
$\alpha5\beta1$	VLA-5, extracellular matrix receptor VI; binds fibronectin
$\alpha6\beta1$	VLA-6, CD49f/CD29; binds laminin
CD11a/CD18	LFA-1, $\alpha L\beta2$
CD11b/CD18	$\alpha M\beta2$; complement receptor type 3
$\alpha v\beta3$	CD51/CD61; binds vitronectin
gpIIb/IIIa	$\alpha IIb\beta3$, CD41/CD61; binds fibronectin, fibrinogen, vitronectin, von Willebrand factor, thrombospondin
Selectins	
LAM-1	Mel-14, LECCAM-1
ELAM-1	Endothelial-leukocyte adhesion molecule-1, LECCAM-2
Immunoglobulin superfamily	
LFA-3	Lymphocyte function-associated antigen-3, CD58; binds CD2 (LFA-2)
ICAM-1	Intercellular adhesion molecule-1, CD54; binds CD11a/CD18
Class II MHC	Major histocompatibility complex class II; binds T cell antigen receptor
CD3	Complex of 5 constant chains of the T cell antigen receptor; binds complexes of MHC with antigen
Unclassified	
CD44	Phagocyte glycoprotein 1, lymph node homing receptor; HERMES antigen, extracellular matrix receptor III; binds hyaluronate

* Abbreviations: CD, cluster of differentiation; LECCAM, lectin/epidermal growth factor/complement regulatory protein-cell adhesion molecule (referring to homologies of domains); LFA, lymphocyte function-associated antigen; VLA, very late antigen. For review, see Springer, 1990.

tion endproducts induces tumor necrosis factor (TNF)-α and IL-1β (Vlassara et al., 1988); adherence to serum-coated plastic induces PDGF-B (Shaw et al., 1990*a*); and adherence to uncoated plastic generates artefactual but powerful signals for induction of TNF-α, IL-1, and CSF-1 (Eierman et al., 1989). Such effects may explain the influence of matrix proteins on the phenotype of macrophages in culture (Kaplan and Gaudernack, 1982).

Intercellular adhesion, like adhesion of cells to matrix, can also induce cytokines. Thus, binding of macrophages to tumor cells induces TNF-α (Jänicke and Mannel, 1990), and binding of human monocytes to surfaces coated with antibodies to the intercellular adhesion molecules LFA-3 or CD44 (the latter is also an extracellular matrix receptor; see Table II) induces release of TNF-α and IL-1β (Webb et al., 1990). Induction of cytokines by cell–cell interactions could account for the fact that some lymphocyte responses, normally dependent on cell–cell contact, can alternatively be driven by exogenous cytokines.

Cytokines Induce Cells to Alter Matrix

TGF-β markedly stimulates deposition of type I collagen into normal rat kidney cell matrix, which may account for its ability to inhibit growth of these cells in monolayer. Exogenous type I collagen mimics, and collagenase abolishes, this antiproliferative action of TGF-β (Nugent and Newman, 1989). Effects of TGF-β on collagen deposition can be ascribed, in part, to repression of interstitial collagenase and the reciprocal induction of tissue inhibitor of metalloproteinases (Stetler-Stevenson et al., 1990); conversely, other cytokines, such as EGF and FGF, are potent inducers of metalloproteinases, which alter matrix (Edwards et al., 1987). IL-6 also induces tissue inhibitor of metalloproteinases in human chondrocytes, synoviocytes and fibroblasts (Lotz and Guerne, 1991).

Cytokines Affect Cell Adhesion Receptors

TGF-β increases the expression of $\alpha1\beta1$, $\alpha2\beta1$, $\alpha3\beta1$, and $\alpha5\beta1$ integrins in fibroblasts (Heino et al., 1989), the CD11a/CD18 integrin in monocytic leukemia cells, and the $\alpha V\beta3$ integrin in fibroblasts and osteosarcoma cells (Ignotz et al., 1989). IL-1β enhances $\beta1$ integrin expression in osteosarcoma cells (Dedhar, 1989). IFN-γ enhances macrophage binding to laminin (Shaw and Mercurio, 1989), an effect that may be mediated by enhanced function of the $\alpha6\beta1$ integrin associated with its phosphorylation (Shaw et al., 1990*b*). GM-CSF and TNF-α induce neutrophils and monocytes to shed one type of adhesion receptor, the LAM-1 or MEL-14 selectin, while the cells mobilize intracellular pools of another type of adhesion receptor, the $\beta2$ (CD11/CD18) integrins (Arnaout et al., 1986; Griffin et al., 1990). The $\beta2$ integrins may act as receptors for a variety of matrix proteins

(Nathan et al., 1989). TNF-α (Lo et al., 1989) and IL-8 (Detmers et al., 1990) activate β2 integrins so as to promote transient attachment of neutrophils to endothelium, an effect distinct from increased surface expression of the integrins. On endothelial cells, TNF-α and IL-1 induce the ELAM-1 selectin (Bevilaqua et al., 1989). Whether selectins can act as receptors for matrix proteins is not yet known.

In a noteworthy variation on this theme, the place of cytokine receptors can be taken by antigen receptors. For example, engagement of the primary antigen receptor on T cells enhances the binding of the β2 family integrin CD11a/CD18 (LFA-1) to its ligand, intercellular adhesion molecule-1 (ICAM-1) (Dustin and Springer, 1990), as well as the binding of the β1 family integrins VLA-4, -5, and -6 to their ligands fibronectin and laminin (Shimizu et al., 1990*b*). Likewise, binding of superantigens, or certain antibodies, to the class II MHC antigen-presenting receptor of T cells, B cells, and macrophages enhances LFA-1-dependent adhesion of these cells (Mourad et al., 1990).

Matrix Presents Cytokines to Cells

Several forms of fibroblast growth factor (FGF) (Rogelj et al., 1989; Baird and Bohlen, 1990), GM-CSF, and IL-3 (Gordon et al., 1987; Roberts et al., 1988) are among the cytokines that are deposited in and function when bound to proteoglycans of extracellular matrix. In contrast, the core protein of the proteoglycan decorin (whose synthesis TGF-β induces) binds and neutralizes TGF-β (Yamaguchi et al., 1990). Binding of vitronectin to surfaces induces it to bind β-endorphin (Hildebrand et al., 1989). Differentiation inhibiting activity/leukemia inhibitory factor is produced in two forms by alternate usage of the first exon. One form is diffusible; the other binds to matrix (Rathjen et al., 1990).

Some Adhesion Receptors Can Act Like Cytokine Receptors

Treatment of mouse macrophages with mAb to β2 integrins induces changes in phenotype over several days that are indistinguishable from responses to IFN-γ (Ding et al., 1987). Fibronectin, fibronectin fragments, anti-fibronectin receptor mAbs, or laminin can mimic FGF, PDGF, or IL-1 by inducing some cells to become alkaline (Ingber et al., 1990), transcribe protooncogenes (Dike and Farmer, 1988), divide (reviewed by Martin and Sank, 1990), and secrete collagenase and stromelysin (Werb et al., 1989); presumably, these act through adhesion receptors.

A macrophage-activating cytokine termed Eta-1 depends on an RGD sequence for its interaction with macrophages (Singh et al., 1990). This is reminiscent of the dependence of several matrix proteins on RGD sequences for their binding to integrins (Ruoslahti and Pierschbacher, 1986). It will be interesting to determine if the Eta-1 receptor is an integrin, and if the effects of Eta-1 can be mimicked by binding of macrophages to certain matrix proteins.

Some Cytokine Receptors Can Promote Cell–Cell Adhesion

EGF receptors can promote the binding of hematopoietic cells to bone marrow stromal cells expressing the transmembrane form of the ligand, pro-TGF-α (Anklesaria et al., 1990). The cytokine remains anchored in the membrane of the producer cell, enabling close interaction with the responder cell, a process termed "juxtacrine secretion."

Adhesion Can Control How Cells Respond to Cytokines

A variety of physiologic peptides, including the cytokine TNF-α, act as secretagogues for neutrophils, but only if the neutrophils are adherent (Nathan, 1987; Luedke and Humes, 1989) to matrix proteins (Nathan et al., 1989) via β2 integrins (Nathan and Sanchez, 1990; Shappell et al., 1990; Richter et al., 1990). Likewise, the survival of embryonic sensory neurons requires not only brain-derived neurotrophic factor but also laminin (Kalcheim et al., 1987). The ability of ciliary neurotrophic factor to induce type-2 astrocyte development depends on matrix (Lillien et al., 1990). The amount of fibronectin or collagen on the substratum dictates whether endothelial cells will proliferate or differentiate in response to FGF (Ingber and Folkman, 1989*b*). Whether endothelial cells respond to TGF-β by proliferating to form tubes resembling capillaries, or cease to grow, likewise depends on the nature of the extracellular matrix (Madri et al., 1990). Pretreatment of monocytes with IFN-γ depresses the binding capacity of their receptors for complement component C3bi (comprised of the CD11b/CD18 β2 family integrins), but this effect is promptly reversed when the cells are plated on fibronectin (Wright et al., 1986).

In an important variation on this theme, similar to that noted above, the place of cytokine receptors is taken by antigen receptors. Thus, activation of T lymphocytes via the CD3 component of the antigen receptor is enhanced synergistically by binding of matrix proteins to β2 integrins (Carrerra et al., 1988; Wacholz et al. 1989; Van Seventer et al., 1990), interaction with collagen (Dang et al., 1990), or binding to fibronectin, laminin or vitronectin via β1 integrins (Nojima et al., 1990; Shimizu et al., 1990*a*,*b*; Roberts et al., 1991). In contrast, the matrix protein tenascin seems to inhibit rather than augment the activation of T cells (Ruegg et al., 1989).

Underlying Mechanisms

What signals from matrix induce cells to make and respond to cytokines? These are new questions. To answer them is emerging as a major goal in cytokine and cell adhesion research. To date, several mutually compatible mechanisms have received experimental support.

(*a*) Engagement of adhesion receptors alone by their ligands or by anti-receptor antibodies (we will refer to both means of engaging receptors as "ligation") may trigger second messenger responses. For example, spreading of cells on fibronectin can induce intracellular alkalinization (Ingber and Folkman, 1989*b*). Lymphocytes whose CD11a/CD18 integrins are cross-linked by antibodies have responded with increases in intracellular Ca^{2+} and accumulation of inositol triphosphate (Pardi et al., 1989). A preliminary report involving a single time point showed a higher ratio of inositol mono-, di-, and tetrakis-phosphate (but not inositol triphosphate) in baby hamster kidney cells that had spread on fibronectin-coated plastic compared with those remaining rounded on uncoated plastic (Breuer and Wagener, 1989). However, the mechanisms underlying these infrequently described responses are far from clear. Adhesion receptors have not been

shown to be linked to phospholipases nor associated with kinase activity.

(*b*) Ligation of adhesion receptors may interact synergistically with ligation of cytokine receptors to induce changes in the levels of second messengers. To our knowledge, the one example reported to date involves the dependence of the neutrophil respiratory burst on simultaneous ligation of TNF-α receptors and β2 integrins. This response is mediated, in part, by a fall in cAMP (Nathan and Sanchez, 1990). In experiments on platelets that did not involve cytokines, glycoprotein IIb/IIIa (a β3 family integrin) was required for epinephrine to activate phospholipases (Banga et al., 1986) and for thrombin to induce a subset of tyrosine phosphorylation reactions (Ferrell and Martin, 1989). In each of these examples, the biochemical basis for the interdependence of two distinct receptor systems remains a mystery.

(*c*) Ligation of some adhesion receptors might mimic ligation of cytokine receptors, or regulate the cellular response to ligation of cytokine receptors, by virtue of a physical association between both types of receptors. For example, a physical if not functional association has been demonstrated for intercellular adhesion molecule-1 and the IL-2 receptor (Burton et al., 1990).

(*d*) Complexes formed by some matrix proteins with cytokines (for example, glycosaminoglycans with basic FGF) may have higher affinity for specific receptors than do the cytokines themselves (Yayon et al., 1991).

(*e*) Alteration of cell shape by interaction with the matrix may activate stretch-sensitive ion channels, or transduce other mechanochemical signals in ways that remain to be defined (Ingber and Folkman, 1989*a*,*b*).

(*f*) Interaction of cells with the extracellular matrix promotes reorganization of the cytoskeleton. The cytoskeleton can control the number of cytokine receptors on the plasma membrane (Ding et al., 1990*a*), the secretion of cytokines (Ding et al., 1990*b*), ribosome function, and gene transcription (reviewed in Ingber and Folkman, 1989*a*; Ding et al., 1990*a*).

Conclusion

The extracellular matrix of a cell reflects its metabolic history. As a relatively stable engram of past experiences, the matrix furnishes the cell with a rudimentary memory useful in responding appropriately to incoming stimuli. Elsewhere it was suggested that cytokines can be viewed as symbols in an intracellular language (Sporn and Roberts, 1988, 1990). Here we suggest that the extracellular matrix is part of the same language. In semantics, language itself is regarded as "time-binding," that is, a mechanism for recording past experience (Korzybski, 1958). The participation of the extracellular matrix in the language of intercellular communication is one way that multicellular organisms can use past experience to help determine how their cells respond to cytokines. The amount of information potentially stored in the specific array of carbohydrate moieties in the macromolecules of the matrix may exceed that in the genome (Rademacher et al., 1988). Thus, interactions with matrix enable cytokines to elicit adaptive responses that are rich in complexity to a degree not available to prokaryotes or unicellular eukaryotes.

The physiologic target of cytokines has conventionally been regarded as the individual responding cell. We propose a shift in perspective, such that the targets of cytokines are seen as tissues. Individual cells are seen not as targets but as mediators of cytokine action. In this view, cytokines are intercellular signaling proteins whose physiologic role is to coordinate the modeling and remodeling of tissues—developmentally programmed, constitutive, and unscheduled. This shift in perspective leads to a corresponding shift in predictions regarding the major determinants of cytokine action. For example, as we argue above, the effects of cytokines can be profoundly influenced by reciprocal interactions of responding cells with the extracellular matrix.

In homeostasis, cytokines act vicinally in surface-bound or diffusible form. In pathologic states, cytokines may circulate to act beyond the organ of origin. A combined requirement for diffusible (cytokine) and nondiffusible (matrix) signals may be an important mechanism for localizing the responses of cells to a cytokine that is widely distributed. Similarly, the ability of matrix to present cytokines in either an active or inactive form may contribute to the spatial control that a tissue can exert over the cytokine responses of cells within it. Finally, the ability to produce a cytokine either in diffusible, cell surface-bound, or matrix-bound forms may give a cell some control over that cytokine's sphere of influence (Rathjen et al., 1990). Since matrix can present cytokines, and since binding of cells to matrix proteins can both induce cytokines and synergize with them, it is possible that the apparent induction of cell differentiation by matrix proteins alone (Ingber and Folkman, 1989*a*,*b*; Grant et al., 1989) may sometimes result from the combined action of matrix proteins with cytokines acting in an autocrine or paracrine manner. Thus, combined control of cell function by matrix proteins and cytokines may be a widespread phenomenon.

A shift in emphasis from the actions of cytokines on individual cells to their actions on tissues raises the difficult problem of how to study cytokine actions in vitro. Experiments with isolated cell populations exposed to cytokines in vitro have led to the description of countless, often contradictory bioactivities, among which it is difficult to discern those of physiologic and pathophysiologic relevance. Ad hoc criteria include the magnitude of a given effect and the potency with which it is induced, its robustness as experimental conditions are varied (reflected in the ease of its confirmation), and the existence of countereffects that can be construed as regulatory. However, definitive evidence for the physiologic relevance of a given action of a cytokine requires tests in intact organisms. Here, the cardinal criterion is the association of natural or induced states of cytokine deficiency with pathologic effects, and the reversal of these effects with cytokine repletion (e.g., Nathan et al., 1986; Kodama et al., 1991). A secondary criterion is the association of natural or induced states of cytokine excess with therapeutic or pathologic effects, and their correction with depletion. Obviously, such tests are difficult to carry out. A major practical problem is how to conduct tests of cytokine action in vitro that can best inform the design of studies in vivo, if not predict their outcome. Perhaps experiments with cytokines in vitro will yield physiologically more relevant information as investigators take increasingly into account the extracellular milieu of the responding cells.

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References

Anklesaria, P., J. Teixido, M. Laiho, J. H. Pierce, J. S. Greenberger, and J. Massagué. 1990. Cell-cell adhesion mediated by binding of membrane-anchored transforming growth factor α to epidermal growth factor receptors promotes cell proliferation. *Proc. Natl. Acad. Sci. USA.* 87:3289–3293.

Arnaout, M. A., E. A. Wang, S. C. Clark, and C. A. Sieff. 1986. Human recombinant granulocyte-macrophage colony-stimulating factor increases cell-to-cell adhesion and surface expression of adhesion-promoting surface glycoproteins on mature granulocytes. *J. Clin. Invest.* 78:597–601.

Baird, A., and P. Bohlen. 1990. Fibroblast growth factors. *In* Peptide Growth Factors and Their Receptors. M. B. Sporn and A. B. Roberts, editors. Springer-Verlag, Berlin. Vol. 1. pp. 369–418.

Banga, H. S., E. R. Simons, L. F. Brass, and S. E. Rittenhouse. 1986. Activation of phospholipases A and C in human platelets exposed to epinephrine: role of glycoproteins IIb/IIIa and dual role of epinephrine. *Proc. Natl. Acad. Sci. USA.* 83:9197–9201.

Bevilaqua, M. P., S. Strengelin, M. A. Gimbrone, Jr., and B. Seed. 1989. Endothelial leukocyte adhesion molecule 1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science (Wash. DC).* 243:1160–1165.

Bigazzi, P. E., T. Yoshida, P. A. Ward, and S. Cohen. 1975. Production of lymphokine-like factors (cytokines) by simian virus 40-infected and simian virus 40-transformed cells. *Am. J. Pathol.* 80:69–78.

Bloom, B. R., and B. Bennett. 1966. Mechanism of a reaction in vitro associated with delayed type hypersensitivity. *Science (Wash. DC).* 153: 80–82.

Breuer, D., and C. Wagener. 1989. Activation of the phosphatidylinositol cycle in spreading cells. *Exp. Cell Res.* 182:659–663.

Burton, J., C. K. Goldman, P. Rao, M. Moos, and T. A. Waldmann. 1990. Association of intercellular adhesion molecule 1 with the multichain high-affinity interleukin 2 receptor. *Proc. Natl. Acad. Sci. USA.* 87:7329–7333.

Carrerra, A. C., M. Rincon, F. Sanchez-Madrid, M. Lopez-Botet, and M. O. de Landazuri. 1988. Triggering of co-mitogenic signals in T cell proliferation by anti-LFA-1 (CD18, CD11a), LFA-3, and CD7 monoclonal antibodies. *J. Immunol.* 141:1919–1924.

Dang, N. H., Y. Torimoto, K. S. F. Schlossman, and C. Morimoto. 1990. Human CD4 helper T cell activation: functional involvement of two distinct collagen receptors, 1F7 and VLA integrin family. *J. Exp. Med.* 172:649–652.

Dayer, J.-M., S. Ricard-Blum, M.-T. Kaufmann, and D. Herbage. 1986. Type IX collagen is a potent inducer of PGE_2 and interleukin 1 production by human monocyte macrophages. *FEBS (Fed. Eur. Biochem. Soc.) Lett.* 198: 208–212.

David, J. R. 1966. Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. *Proc. Natl. Acad. Sci. USA.* 56:72–77.

Dedhar, S. 1989. Regulation of expression of the cell adhesion receptors, integrins, by recombinant human interleukin-1β in human osteosarcoma cells: inhibition of cell proliferation and stimulation of alkaline phosphatase activity. *J. Cell Physiol.* 138:291–299.

Detmers, P. A., S. K. Lo, E. Olsen-Egbert, A. Walz, M. Baggiolini, and Z. A. Cohn. 1990. Neutrophil-activating protein 1/interleukin 8 stimulates the binding activity of the leukocyte adhesion receptor CD11b/CD18 on human neutrophils. *J. Exp. Med.* 171:1155–1162.

Ding, A., S. D. Wright, and C. Nathan. 1987. Activation of mouse peritoneal macrophages by monoclonal antibodies to Mac-1 (complement receptor type 3). *J. Exp. Med.* 165:733–749.

Ding, A. H., F. Porteu, E. Sanchez, and C. F. Nathan. 1990*a*. Downregulation of tumor necrosis factor receptors on macrophages and endothelial cells by microtubule depolymerizing agents. *J. Exp. Med.* 171:715–727.

Ding, A. H., F. Porteu, E. Sanchez, and C. F. Nathan. 1990*b*. Shared actions of endotoxin and taxol on TNF receptors and TNF release. *Science (Wash. DC).* 248:370–372.

Dike, L. E., and S. R. Farmer. 1988. Cell adhesion induces expression of growth-associated genes in suspension-arrested fibroblasts. *Proc. Natl. Acad. Sci. USA.* 85:6792–6796.

Dumonde, D. C., R. A. Wolstencraft, G. S. Panayi, M. Matthew, J. Morley, and W. T. Howson. 1969. "Lymphokines:" non-antibody mediators of cellular immunity generated by lymphocyte activation. *Nature (Lond.).* 224: 38–42.

Dustin, M. L., and T. A. Springer. 1989. T-cell receptor cross-linking transiently stimulates adhesiveness through LFA-1. *Nature (Lond.).* 341:619–624.

Edwards, D. R., G. Murphy, J. J. Reynolds, S. E. Whitham, A. J. P. Docherty, P. Angel, and J. K. Heath. 1987. Transforming growth factor beta modulates the expression of collagenase and metalloproteinase inhibitor. *EMBO (Eur. Mol. Biol. Organ.) J.* 6:1899–1904.

Eierman, D. F., C. E. Johnson, and J. S. Haskill. 1989. Human monocyte inflammatory mediator gene expression is selectively regulated by adherence substrates. *J. Immunol.* 142:1970–1976.

Ferrell, J. E., Jr. and G. S. Martin. 1989. Tyrosine-specific protein phosphorylation is regulated by glycoprotein IIb-IIIa in platelets. *Proc. Natl. Acad. Sci. USA.* 86:2234–2238.

Gordon, M. Y., G. P. Rile, S. M. Watt, and M. F. Greaves. 1987. Compartmentalization of a haemopoietic growth factor (GM-CSF) by glycosaminoglycans in the bone marrow microenvironment. *Nature (Lond.).* 326:403–405.

Grant, D. S., K.-I. Tashiro, B. Segui-Real, Y. Yamada, G. R. Martin, and H. K. Kleinman. 1989. Two different laminin domains mediate the differentiation of human endothelial cells into capillary-like structures in vitro. *Cell.* 58:933–943.

Griffin, J. D., O. Spertini, T. J. Ernst, M. P. Belvin, H. B. Levine, Y. Kanakura, and T. F. Tedder. 1990. Granulocyte-macrophage colony-stimulating factor and other cytokines regulate surface expression of the leukocyte adhesion molecule-1 on human neutrophils, monocytes, and their precursors. *J. Immunol.* 145:576–584.

Heino, J., R. A. Ignotz, M. E. Hemler, C. Crouse, and J. Massagué. 1989. Regulation of cell adhesion receptors by transforming growth factor-β. Concomitant regulation of integrins that share a common β1 subunit. *J. Biol. Chem.* 264:380–388.

Hildebrand, A., K. T. Preissner, G. Muller-Berghaus, and J. Teschemacher. 1989. A novel β-endorphin binding protein. Complement S protein (= vitronectin) exhibits specific non-opioid binding sites for β-endorphin upon interaction with heparin or surfaces. *J. Biol. Chem.* 264:15429–15434.

Ignotz, R. A., J. Heino, and J. Massagué. 1989. Regulation of cell adhesion receptors by transforming growth factor-β. Regulation of vitronectin receptor and LFA-1. *J. Biol. Chem.* 264:389–392.

Ingber, D. E., and J. Folkman. 1989*a*. How does extracellular matrix control capillary morphogenesis? *Cell.* 58:803–805.

Ingber, D. E., and J. Folkman. 1989*b*. Mechanochemical switching between growth and differentiation during fibroblast growth factor-stimulated angiogenesis in vitro: role of extracellular matrix. *J. Cell Biol.* 109:317–330.

Ingber, D. E., D. Prusty, J. V. Frangioni, E. J. Cragoe, Jr., C. Lechene, and M. A. Schwartz. 1990. Control of intracellular pH and growth by fibronectin in capillary endothelial cells. *J. Cell Biol.* 110:1803–1811.

Jänicke, R., and D. N. Mannel. 1990. Distinct tumor cell membrane constituents activate human monocytes for tumor necrosis factor synthesis. *J. Immunol.* 144:1144–1150.

Kalcheim, C., Y. A. Barde, H. Thoenen, and N. M. LeDouarin. 1987. *In vivo* effect of brain-derived neurotrophic factor on the survival of developing dorsal root ganglion cells. *EMBO (Eur. Mol. Biol. Organ.) J.* 6:2871–2873.

Kaplan, G., and G. Gaudernack. 1982. In vitro differentiation of human monocytes. Differences in monocyte phenotypes induced by cultivation on glass or on collagen. *J. Exp. Med.* 156:1101–1114.

Kenyon, C., and A. Kamb. 1989. Cellular dialogs during development. *Cell.* 58:607–608.

Kodama, H., A. Yamasaki, M. Nose, S. Niida, Y. Ohgame, M. Abe, M. Kumegawa, and T. Suda. 1991. Congenital osteoclast deficiency in osteopetrotic (*op/op*) mice is cured by injections of macrophage colony-stimulating factor. *J. Exp. Med.* 173:269–272.

Korzybski, A. 1958. Science and Sanity. An Introduction to Non-Aristotelian Systems and General Semantics. 4th ed. Institute of General Semantics, Lakesville, CT. 806 pp.

Levi-Montalcini, R., and V. Hamburger. 1951. Selective growth stimulating effects of mouse sarcoma on the sensory and sympathetic nervous system of the chick embryo. *J. Exp. Zool.* 116:321–361.

Lillien, L. E., M. Sendtner, and M. C. Raff. 1990. Extracellular matrix-associated molecules collaborate with ciliary neurotrophic factor to induce type-2 astrocyte development. *J. Cell Biol.* 111:635–644.

Lo, S. K., P. A. Detmers, S. M. Levin, and S. D. Wright. 1989. Transient adhesion of neutrophils to endothelium. *J. Exp. Med.* 169:1779–1794.

Lotz, M., and P.-A. Guerne. 1991. Interleukin-6 induces the synthesis of tissue inhibitor of metalloproteinases-1/erythroid potentiating activity (TIMP-1/EPA). *J. Biol. Chem.* 266:2017–2020.

Luedke, E. S., and J. L. Humes. 1989. Effect of tumor necrosis factor on granule release and LTB_4 production in adherent human polymorphonuclear leukocytes. *Agents Actions.* 27:451–454.

Madri, J. A., O. Kochner, J. R. Merwin, L. Bell, A. Tucker, and C. T. Basson. 1990. Interactions of vascular cells with transforming growth factors-β. *Ann. NY Acad. Sci.* 593:243–258.

Martin, G. R., and A. C. Sank. 1990. Extracellular matrices, cells, and growth factors. *In* Peptide Growth Factors and Their Receptors. Vol. 2. M. B. Sporn and A. B. Roberts, editors. Springer-Verlag, Berlin. 463–477.

Mourad, W., R. S. Geha, and T. Chatila. 1990. Engagement of major histocompatibility complex class II molecules induces sustained, lymphocyte function-associated molecule 1-dependent cell adhesion. *J. Exp. Med.* 172: 1513–1516.

Nagano, Y., and Y. Kojima. 1954. Pouvoir immunisant du virus vaccinal inactive par des rayons ultraviolets. *Compt. Rend. Soc. Biol. (Paris).* 148: 1700–1702.

Nathan, C. 1987. Neutrophil activation on biological surfaces. Massive secretion of hydrogen peroxide in response to products of macrophages and lym-

phocytes. *J. Clin. Invest.* 80:1550–1560.
Nathan, C. 1990. Coordinate actions of growth factors in monocytes/macrophages. *In* Peptide Growth Factors and Their Receptors. Vol. 2. M. B. Sporn and A. B. Roberts, editors. Springer-Verlag, Berlin. 427–462.
Nathan, C., and E. Sanchez. 1990. Tumor necrosis factor and CD11/CD18 (β2) integrins act synergistically to lower cAMP in human neutrophils. *J. Cell Biol.* 111:2171–2181.
Nathan, C., G. Kaplan, W. R. Levis, A. Nusrat, M. D. Witmer, S. A. Sherwin, C. K. Job, C. R. Horowitz, R. M. Steinman, and Z. A. Cohn. 1986. Local and systemic effects of intradermal recombinant interferon-γ in patients with lepromatous leprosy. *N. Engl. J. Med.* 315:6–15.
Nathan, C., S. Srimal, C. Farber, E. Sanchez, L. Kabbash, A. Asch, J. Gailit, and S. D. Wright. 1989. Cytokine-induced respiratory burst of human neutrophils: dependence on extracellular matrix proteins and CD11/CD18 integrins. *J. Cell Biol.* 109:1341–1349.
Nojima, Y., M. J. Humphries, A. P. Mould, A. Komoriya, K. M. Yamada, S. F. Schlossman, and C. Morimoto. 1990. VLA-4 mediates CD3-dependent CD4$^+$ T cell activation via the CS1 alternatively spliced domain of fibronectin. *J. Exp. Med.* 172:1185–1192.
Nugent, M. A., and M. J. Newman. 1989. Inhibition of normal rat kidney cell growth by transforming growth factor-β is mediated by collagen. *J. Biol. Chem.* 264:18060–18067.
Pardi, R., J. R. Bender, C. Dettori, E. Giannazza, and E. G. Engleman. 1989. Heterogeneous distribution and transmembrane signalling properties of lymphocyte function-associated antigen (LFA-1) in human lymphocyte subsets. *J. Immunol.* 143:3157–3166.
Rademacher, T. W., R. B. Parekh, and R. A. Dwek. 1988. Glycobiology. *Annu. Rev. Biochem.* 57:785–838.
Rathjen, P. D., S. Toth, A. Willis, J. K. Heath, and A. G. Smith. 1990. Differentiation inhibiting activity is produced in matrix-associated and diffusible forms that are generated by alternate promoter usage. *Cell.* 62:1105–1114.
Richter, J., J. Ng-Sikorski, I. Olsson, and T. Andersson. 1990. Tumor necrosis factor-induced degranulation in adherent human neutrophils is dependent on CD11b/CD18-integrin-triggered oscillations of cytosolic free Ca^{2+}. *Proc. Natl. Acad. Sci. USA.* 87:9472–9476.
Roberts, K., W. M. Yokoyama, P. J. Kehn, and E. M. Shevach. 1991. The vitronectin receptor serves as an accessory molecule for the activation of a subset of γ/δ T cells. *J. Exp. Med.* 173:231–240.
Roberts, R., J. Gallagher, E. Spooncer, T. D. Allen, F. Bloomfield, and T. M. Dexter. 1988. Heparan sulphate bound growth factors: a mechanism for stromal cell mediated haemopoiesis. *Nature (Lond.).* 332:376–378.
Rogelj, S., M. Klagsbrun, R. Atzmon, M. Kurokawa, A. Haimovitz, Z. Fuks, and I. Vlodavsky. 1989. Basic fibroblast growth factor is an extracellular matrix component required for supporting the proliferation of vascular endothelial cells and the differentiation of PC12 cells. *J. Cell Biol.* 109:823–831.
Ruegg, C., R. R. Chiquet-Ehrismann, and S. S. Alkan. 1989. Tenascin, an extracellular matrix protein, exerts immunomodulatory activities. *Proc. Natl. Acad. Sci. USA.* 86:7437–7441.
Ruoslahti, E., and M. D. Pierschbacher. 1986. Arg-Gly-Asp: a versatile cell recognition signal. *Cell.* 44:517–518.
Shappell, S. B., C. Toman, D. C. Anderson, A. A. Taylor, M. L. Entman, and C. W. Smith. 1990. Mac-1 (CD11b/CD18) mediates adherence-dependent hydrogen peroxide production by human and canine neutrophils. *J. Immunol.* 144:2702–2711.
Shaw, L. M., and A. M. Mercurio. 1989. Interferon γ and lipopolysaccharide promote macrophage adherence to basement membrane glycoproteins. *J. Exp. Med.* 169:303–308.
Shaw, L. M., J. M. Messier, and A. M. Mercurio. 1990*a*. The activation dependent adhesion of macrophages to laminin involves cytoskeletal anchoring and phosphorylation of the $\alpha 6\beta 3$ integrin. *J. Cell Biol.* 110:2167–2174.
Shaw, R. J., D. E. Doherty, A. G. Ritter, S. H. Benedict, and R. A. F. Clark. 1990*b*. Adherence-dependent increase in human monocyte PDGF(B) mRNA is associated with increases in *c-fos*, *c-jun*, and ECGR2 mRNA. *J. Cell Biol.* 111:2139–2148.
Shimizu, Y., G. A. Van Seventer, K. J. Horgan, and S. Shaw. 1990*a*. Regulated expression and binding of three VLA (β1) integrin receptors on T cells. *Nature (Lond.).* 345:250–254.
Shimizu, Y., G. A. Van Seventer, K. J. Horgan, and S. Shaw. 1990*b*. Costimulation of proliferative responses of resting CD4$^+$ T cells by the interaction of VLA-4 and VLA-5 with fibronectin or VLA-6 with laminin. *J. Immunol.* 145:59–67.
Singh, R. P., R. Patarca, J. Schwartz, P. Singh, and H. Cantor. 1990. Definition of a specific interaction between the early T lymphocyte activation (Eta-1) protein and murine macrophages in vitro and its effect upon macrophages in vivo. *J. Exp. Med.* 171:1931–1942.
Sporn, M. B., and A. B. Roberts. 1988. Peptide growth factors are multifunctional. *Nature (Lond.).* 332:217–219.
Sporn, M. B., and A. B. Roberts. 1990. The multifunctional nature of peptide growth factors. *In* Peptide Growth Factors and Their Receptors. Vol. 1. M. B. Sporn and A. B. Roberts, editors. Springer-Verlag, Berlin. 3–15.
Springer, T. A. 1990. Adhesion receptors of the immune system. *Nature (Lond.).* 346:425–434.
Stetler-Stevenson, W. G., P. D. Brown, M. Onisto, A. T. Levy, and L. A. Liotta. 1990. Tissue inhibitor of metalloproteinases-2 (TIMP-2) mRNA expression in tumor cell lines and human tumor tissues. *J. Biol. Chem.* 265:13933–13938.
Thorens, B., J.-J. Mermod, and P. Vassalli. 1987. Phagocytosis and inflammatory stimuli induce GM-CSF mRNA in macrophages through posttranscriptional regulation. *Cell.* 48:671–679.
Van Seventer, G. A., Y. Shimizu, K. J. Horgan, and S. Shaw. 1990. The LFA-1 ligand ICAM-1 provides an important costimulatory signal for T cell receptor-mediated activation of resting T cells. *J. Immunol.* 144:4579–4586.
Vlassara, H., M. Brownlee, K. R. Manogue, C. A. Dinarello, and A. Pasagian. 1988. Cachectin/TNF and IL-1 induced by glucose-modified proteins: role in normal tissue remodeling. *Science (Wash. DC).* 240:1546–1548.
Wacholtz, M. C., S. S. Patel, and P. E. Lipsky. 1989. Leukocyte function-associated antigen 1 is an activation molecule for human T cells. *J. Exp. Med.* 170:431–448.
Webb, D. S. A., Y. Shimizu, G. A. Van Seventer, S. Shaw, and T. L. Gerrard. 1990. LFA-3, CD44, and CD45: physiologic triggers of human monocyte TNF and IL-1 release. *Science (Wash. DC.)* 249:1295–1297.
Werb, Z., P. M. Tremble, O. Behrendtsen, E. Crowley, and C. H. Damsky. 1989. Signal transduction through the fibronectin receptor induces collagenase and stromelysin gene expression. *J. Cell Biol.* 109:877–889.
Wright, S. D., P. A. Detmers, M. T. C. Jong, and B. C. Meyer. 1986. Interferon-γ depresses binding of ligand by C3b and C3bi receptors on cultured human monocytes, an effect reversed by fibronectin. *J. Exp. Med.* 163:1245–1259.
Yamaguchi, Y., D. M. Mann, and E. Ruoslahti. 1990. Negative regulation of transforming growth factor-β by the proteoglycan decorin. *Nature (Lond.).* 346:281–284.
Yayon, A., M. Klagsbrun, J. D. Esko, P. Leder, and D. M. Ornitz. 1991. Cell surface, heparin-like molecules are required for binding of basic fibroblast growth factor to its high-affinity receptor. *Cell.* 64:841–848.