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Perspectives in Cancer Research

Signaling by Integrins: Implications for Tumorigenesis[1]

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Acquisition of a fully malignant phenotype by normal cells is thought to require mutations in a number of cellular genes. Much research has led to the view that these mutations can induce overexpression or constitutive activation of regulatory proteins that stimulate cell growth (oncogenes). Alternatively, mutations can induce the loss or inactivation of proteins that inhibit cell growth (tumor suppressor genes) (1). In those systems that are best characterized, *e.g.*, colorectal and breast cancer, 4 or more mutations appear to be required for transition of normal cells to frank carcinoma, involving both activation of oncogenes and loss of tumor suppressor functions (2).

In normal cells, these stimulatory and inhibitory events are believed to be under the control of growth factors or growth inhibitory factors. A considerable body of evidence supports the view that protooncogenes can represent critical points in the pathways that mediate growth regulation by soluble factors (3). Though the evidence is less extensive, available data point towards a similar role for tumor suppressors (4). Consequently, much research has focused on the role of oncogene products and tumor suppressors in the action of growth factors and growth inhibitory factors. Indeed, this set of hypotheses has been a powerful tool for investigating growth control and cancer.

Unanswered Questions

Despite the utility of this conceptual framework, certain key aspects of oncogenesis remain unexplained. Growth of normal adherent cell types *in vitro* requires not only growth factors, but also adhesion to a solid surface coated with extracellular matrix proteins such as collagen or fibronectin (5). Furthermore, transformation of cells by a variety of oncogenes and viral transforming proteins diminishes cells' requirements not only for growth factors, but also for anchorage (6). In fact, anchorage independence of growth is often regarded as the aspect of growth *in vitro* that provides the best marker for tumorigenicity in animal models (7).

In vivo, the situation is more complex but appears to be analogous. Cancer is defined clinically not by growth rate, but by the breakdown of tissue organization and the acquisition of invasiveness (8). At late stages, tumor cells usually become metastatic, often migrating to quite distant sites. These changes toward invasive and metastatic behavior are generally accompanied by loss of differentiated cellular structure and functions (9). By contrast, benign tumors show abnormal growth regulation, but preserve a higher degree of tissue organization and cellular structure. Benign tumors, however, frequently progress to full-blown cancer, demonstrating that, although growth control and spatial control are not equivalent, they are closely linked.

These considerations suggest that 2 unanswered questions are central to our understanding of cancer. These questions are: (*a*) How is growth control linked to spatial control mechanisms for normal cells? and (*b*) How does loss of growth control in cancer cells lead to the loss of spatial controls that underlie anchorage independence of growth *in vitro*, and invasiveness and metastasis *in vivo*.

Integrins and Growth Control

Adhesion of cells to proteins of basement membranes and other extracellular matrices is mediated largely, though not entirely, by members of the integrin family of receptors (reviewed in Refs. 10 and 11). These are heterodimeric transmembrane proteins, comprised of an α- and a β-chain; 13 α- and 7 β-subunits have been described, which form the 21 known integrins, but new integrins are still being discovered. Integrins bind to extracellular matrix proteins (such as collagens, laminin, entactin, fibronectin, vitronectin, and fibrinogen or fibrin) outside the cell, and associate with cytoskeletal proteins inside the cell. They therefore serve as linkages between extracellular matrix and structural elements inside the cell.

Integrins are essential for cell adhesion *in vitro* and *in vivo*. Antibodies or peptides that block binding of integrins to their extracellular matrix protein ligands often induce complete detachment of cultured cells from their substratum (12, 13). Such antibodies and peptides can also inhibit a variety of adhesive and migratory events *in vivo* (14, 15). Blockade of integrin-ligand interactions by several means completely inhibits growth of anchorage-dependent cells in culture (5, 13). These results argue that anchorage-dependent growth is a specific regulatory mechanism mediated by integrins.

Signaling by Integrins

Recent work has shown that integrins have a second functional role as signaling receptors (for recent reviews, see Refs. 11 and 16). Integrin-mediated adhesion of cells to extracellular matrix proteins has been shown to activate a number of intracellular signaling events or second messengers. The first event identified was activation of the Na/H antiporter. Elevation of intracellular pH due to the Na/H antiporter was observed to be a rapid and reversible consequence of adhesion to the extracellular matrix protein fibronectin (17), and to be due to clustering of integrins, as occurs at sites of adhesion (18). This effect of adhesion on intracellular pH is of some interest, since activation of the antiporter can be triggered by a variety of growth factors and oncogenes, and is closely linked to mitogenesis (reviewed in Ref. 19).

Adhesion of cultured cells to fibronectin, or clustering of integrins with antibodies, also triggers phosphorylation of proteins on tyrosine (20, 21). In leukocytes, cell adhesion is associated with transient elevations of intracellular calcium, which can be either blocked by anti-integrin antibodies or triggered by antibodies if they are used to cluster receptors (22). Elevations of intracellular calcium are also triggered by spreading of endothelial cells on extracellular matrix proteins or on anti-integrin antibodies (23). Finally, cell spreading leads to an increase in inositol lipid turnover.[3]

It is noteworthy that growth factors trigger a similar spectrum of intracellular signals. Furthermore, they do so by inducing local clustering of their receptors. It would appear, therefore, that signaling by

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integrins shares, at least superficially, common features with signaling by growth factor receptors.

Control of Cell Function

It is well documented that extracellular matrix proteins can regulate cellular gene expression, differentiation, and other functions (reviewed in Refs. 24–26). These cases can be divided into 2 categories: "direct" regulation by adhesion, in which extracellular matrix can induce appropriate responses rapidly and independently of soluble factors, and "indirect" or "permissive" effects, in which both extracellular matrix and soluble factors must be present to obtain a response. Examples of direct regulation include activation of growth-related genes in fibroblasts (27) and immediate-early gene expression in monocytes (28). Examples of permissive roles include secretion of milk proteins in response to prolactin by mammary epithelial cells (29), and activation of leukocytes by cytokines (30). Control of cell growth may fall into both categories, since in some instances, adhesion can promote growth in the presence of minimal growth factors (31), whereas in others, adhesion enhances cellular responses to soluble factors (6).

Regulation of intracellular signaling pathways by integrins can also be divided into direct, soluble factor-independent effects, and indirect, soluble factor-dependent effects. Elevation of intracellular pH in endothelial cells (31), protein tyrosine phosphorylation in fibroblasts (20, 21), and elevation of intracellular calcium (22, 23, 32) fall into the direct category, since they occur quite rapidly and in the absence of serum or growth factors. The effect of adhesion on inositol lipid metabolism in fibroblasts falls into the "indirect" category.[3] In that system, adhesion to extracellular matrix proteins is required for synthesis of PIP_2[4] but has no effect on PIP_2 breakdown. Platelet-derived growth factor is able to stimulate phospholipase C, independent of adhesion, but significant PIP_2 hydrolysis occurs only if PIP_2 is first synthesized in response to adhesion. Thus, release of second messengers due to hydrolysis of PIP_2 requires both adhesion and platelet-derived growth factor.

For cell growth, a reasonable case can be made that integrin-regulated signals mediate the control by extracellular matrix. In fibroblasts and endothelial cells, activation of the Na-H antiporter and elevation of intracellular pH require adhesion. Not only does blockade of the antiporter inhibit progression through the cell cycle (31, 33), but transfecting cells with the gene for a yeast proton pump to elevate intracellular pH is sufficient to induce anchorage-independent growth and tumorigenicity *in vivo* (34). These results strongly suggest that activation of the antiporter mediates, at least in part, the stimulation of growth by adhesion. The argument that integrin-mediated signals are important in growth control is further strengthened by the results from inositol lipid studies. Since inositol lipid hydrolysis in fibroblasts requires adhesion, and since second messengers from this pathway are closely linked to growth stimulation (35), it would seem that this signaling pathway is also likely to play a significant role in anchorage dependence of growth. The necessary data are not yet available analyzing the control of gene expression, differentiation, and other cell functions by extracellular matrix. It seems very likely, however, that these effects are also mediated by signaling pathways that are controlled by integrins.

Nonintegrin Adhesion Receptors

Though integrins are the adhesion receptors for which signaling has been studied most extensively, there is evidence that other adhesion receptors can trigger intracellular second messengers. N-CAM appears to be able to trigger changes in intracellular pH, calcium, and inositol lipids (36). The neural cell adhesion molecule L-1 has been shown to trigger the same second messengers (37). It, therefore, seems that the ability to regulate various signaling pathways inside cells is not unique to integrins, but may be shared by many or most cell adhesion receptors.

Connections to Oncogenes

Two lines of evidence suggest a connection between integrin-mediated signals and certain oncogenes that localize to the plasma membrane. First, it has been shown that normal cells of many types have a low intracellular pH when poorly adherent, and a high intracellular pH when tightly adhered to extracellular matrix proteins, due to the increased activity of the Na/H antiporter. By contrast, a number of cell lines that were transformed by *v-ras*, *v-src*, or the polyoma middle T oncogene had an elevated intracellular pH in suspension. This anchorage-independent elevation of intracellular pH occurred in direct proportion to the ability of the cell lines to form colonies in suspension culture (38). Cells transformed by the nuclear oncogene *myc*, however, had normal regulation of intracellular pH (17), showing that the effect is not a nonspecific consequence of oncogenic transformation, but it is due to the action of specific oncogenes.

Second, the protein that is phosphorylated on tyrosine most prominently when cells are plated on extracellular matrix proteins, or when integrins are cross-linked with antibodies, is a M_r 125,000 protein that is itself a tyrosine kinase (39). Furthermore, this protein (called FAK, for focal adhesion kinase) was first identified as a substrate of *v-src* (40). This protein shares no homology with other nonreceptor tyrosine kinases outside of its kinase domain, and therefore appears to comprise a new kinase family. Phosphorylation of this protein either by *v-src* or in response to cell adhesion has been found to increase its kinase activity towards substrates (41).

Results from these 2 experimental approaches lead to the same conclusion that oncogenes can substitute for adhesion in the activation of early signaling events. These effects are presumably related to the ability of oncogenes to effectively substitute for adhesion when they promote anchorage-independent cell growth. A corollary of these ideas is that some protooncogenes are likely to be on integrin-stimulated rather than growth factor-stimulated pathways. Other protooncogenes and their cognate oncogenes are likely to be located after the intersection of integrin- and growth factor-mediated pathways; constitutive activation of such postintersection oncogenes should enable cells to grow without both growth factors and anchorage. *ras* and *src* may very well fit into this category.

Connections to Tumor Progression

How these concepts pertain to the complex process of oncogenesis *in vivo* is less clear, but consideration of current models of tumor progression does suggest a testable hypothesis. It has been proposed that approximately 4 or more mutations are needed to convert normal epithelial cells to highly invasive or metastatic carcinomas (2). Furthermore, it appears that these mutations are often in known oncogenes and tumor suppressors, as these genes have been found to be mutated in human cancers with high frequency. In the systems that have been best studied, primarily colorectal and mammary carcinomas, mutations do not occur in a rigid order. Mutations in both oncogenes and tumor suppressor genes can be found at relatively early, premalignant stages (42, 43), suggesting that such mutations play a causative role in tumorigenesis. The theory of tumor progression put forward in light of these results is that activating mutations in oncogenes and inactivating mutations in suppressor genes increase the rate of cellular growth, leading to clonal expansion. Increased cell number and growth rate provide further opportunity for mutations.

[4] The abbreviation used is: PIP_2, phosphatidylinositol bisphosphate.

The final transition to frank carcinoma, and then to metastatic cancer, is less well understood. It is by no means clear that classic oncogenes and tumor suppressor genes are responsible for these later stages. In this regard, it is of considerable interest that adhesion receptors have been shown to function as tumor suppressors. Conceptually similar results were obtained with integrin $\alpha_5\beta_1$, a high affinity fibronectin receptor (44), and with E-cadherin, an epithelial cell-cell adhesion molecule (45). In both of these instances, the adhesion receptors are expressed at high levels on normal cells and low levels on highly malignant cells. When malignant cells were transfected to induce expression of adhesion receptors at high levels, formation of tumors in animals was strongly diminished. In both cases, the receptors exerted either no or rather modest effects on cell growth.

The *DCC* gene is of particular interest in this regard. This gene was identified by genetic analysis of colorectal cancer as a tumor suppressor gene, *i.e.*, a gene that was frequently lost during tumorigenesis (46). Analyses of tissue samples taken from different stages of colorectal carcinogenesis suggest that *DCC* plays a role primarily in the later stages of tumorigenesis, facilitating the transition from adenoma to frank carcinoma (42). Sequencing of the gene revealed it to have strong homologies to a number of cell adhesion proteins. The available data therefore suggest that *DCC* is an adhesion protein whose loss promotes invasiveness.

A Model for Tumor Progression

These observations suggest that early events in carcinogenesis activate specific signaling pathways, including those normally regulated by integrins, and thereby promote cell growth that is independent of growth factors and adhesion. Subsequent mutations could induce diminished adhesion and increased motility, leading to an invasive or metastatic phenotype. These later mutations might induce loss of adhesion receptors, expression of enzymes that degrade extracellular matrix, or alterations in the cytoskeleton. In all cases, mutations would result in a decrease in the adhesive interactions that have ceased to be essential for cell growth and survival. Acquisition of invasive and/or metastatic behavior might not confer a direct growth advantage, but could confer an advantage by enabling the cell to escape the nutrient-depleted tumor mass and colonize other, more favorable environments. Conditions *in vivo* could therefore select for such mutations and favor the progression to cancer.

This model therefore proposes that the relationship between mutations in genes that control growth and those that control adhesion and motility can be best characterized as permissive. Mutations in oncogenes and tumor suppressor genes permit cells to survive and grow with diminished adhesion. In the absence of the early mutations in oncogenes and tumor suppressor genes, the later mutations in adhesion systems would be disadvantageous, or perhaps even fatal to the afflicted cell. This notion is consistent with data indicating that mutations do not occur in a strict order, but that changes in certain genes, some of which code for adhesion receptors, generally occur late in tumorigenesis.

Summary and Prospectives

Cancer cells exhibit abnormal control of both growth and location. Indeed, clinical morbidity and mortality are primarily consequences of abnormal location, *i.e.*, the spread of cancer cells. Why these 2 aspects of cellular regulation should be linked has not been readily understood. Recent work showing that adhesion receptors also function as signaling receptors may provide a link. I propose that because integrins both promote adhesion and trigger intracellular signals that regulate cellular growth, when cells become independent of growth-regulatory signals they also become independent of adhesion. They can therefore develop invasive and metastatic behavior without adverse consequences.

Clearly, this hypothesis leaves much to be tested and more to be elucidated. Little is known about the details of integrin-regulated pathways in cells, the roles of specific oncogenes on these pathways, or how specific pathways relate to tumor progression *in vivo*. What little we do know, however, indicates that signals from integrins play an important role in control of growth, development, and tissue organization. They are also likely to play a role in tumorigenesis. In short, the connections between integrins, oncogenes, and tumor progression appear to be well worth investigating.

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