



REVIEW: SIGNAL TRANSDUCTION

Integrin Signaling

Filippo G. Giancotti¹ and Erkki Ruoslahti²

Cells reside in a protein network, the extracellular matrix (ECM), which they secrete and mold into the intercellular space. The ECM exerts profound control over cells. The effects of the matrix are primarily mediated by integrins, a family of cell surface receptors that attach cells to the matrix and mediate mechanical and chemical signals from it. These signals regulate the activities of cytoplasmic kinases, growth factor receptors, and ion channels and control the organization of the intracellular actin cytoskeleton. Many integrin signals converge on cell cycle regulation, directing cells to live or die, to proliferate, or to exit the cell cycle and differentiate.

Integrins comprise a large family of cell surface receptors that are found in many animal species, ranging from sponges to mammals. They are composed of two subunits, α and β , and each $\alpha\beta$ combination has its own binding specificity and signaling properties. Most integrins recognize several ECM proteins. Conversely, individual matrix proteins, such as fibronectin, laminins, collagens, and vitronectin, bind to several integrins (1). Integrins can signal through the cell membrane in either direction: The extracellular binding activity of integrins is regulated from the inside of the cell (inside-out signaling), while the binding of the ECM elicits signals that are transmitted into the cell (outside-in signaling) (2).

Recent studies have provided a better understanding of the signaling pathways activated by integrins in adherent cells, such as fibroblasts and epithelial cells. Adherent cells must be anchored to an appropriate ECM to survive. Depending partly on signals from the matrix, they either proliferate or exit the cell cycle and differentiate (Fig. 1). This anchorage requirement is lost in neoplastic cells. In this review, we focus on the integrin signals that control these basic cellular behaviors.

The Basic Signaling Machinery

Integrin clustering. The cytoplasmic tails of integrins are generally short and always devoid of enzymatic features. Hence, integrins transduce signals by associating with adapter proteins that connect the integrin to the cytoskeleton, cytoplasmic kinases, and transmembrane growth factor receptors.

Integrin signaling and assembly of the cytoskeleton are intimately linked. As integrins bind to ECM, they become clustered in the plane of the cell membrane and associate

with a cytoskeletal and signaling complex that promotes the assembly of actin filaments (the $\alpha 6\beta 4$ integrin associates with keratin filaments through the uniquely large $\beta 4$ cytodomain). The reorganization of actin filaments into larger stress fibers, in turn, causes more integrin clustering, thus enhancing the matrix binding and organization by integrins in a positive feedback system (Fig. 2). As a result, ECM proteins, integrins, and cytoskeletal proteins assemble into aggregates on each side of the membrane. Well-developed aggregates can be detected by immunofluorescence microscopy and are known as focal adhesions and ECM contacts (3). In this manner, integrins serve as integrators of the ECM and cytoskeleton, the property for which integrins are named.

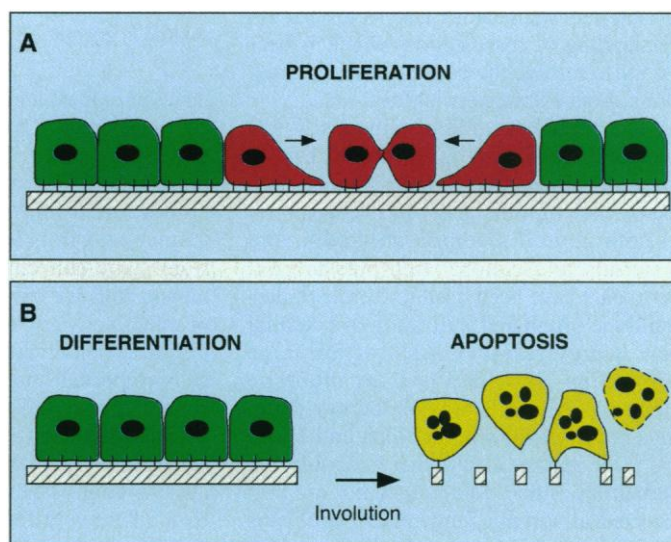
Several integrins have been found to associate laterally with the oligomeric membrane protein caveolin-1, at least in primary cells (4, 5). Although the biochemical nature of this interaction is not known, inhibiting caveolin expression suppresses the formation of focal adhesions and integrin signaling (4,

5). Because of its ability to associate into oligomers, caveolin-1 may help integrins to cluster on the plasma membrane. Integrin-associated structural and signaling proteins also aggregate with the integrins, and signaling is facilitated by the resulting high local concentrations of these proteins (6).

The FAK and Fyn/Shc pathways. Integrins activate various protein tyrosine kinases, including focal adhesion kinase (FAK), Src-family kinases, and Abl, and a serine-threonine kinase, integrin-linked kinase (ILK) (4, 7). The integrin-dependent pathways involving FAK and Src-family kinases have been studied in some detail.

The FAK pathway is activated by most integrins. The activation of FAK is not well understood, but it is coupled to the assembly of focal adhesions. FAK may be recruited to nascent focal adhesions because it interacts, either directly or through the cytoskeletal proteins talin and paxillin, with the cytoplasmic tail of integrin β subunits (8). Upon activation, FAK autophosphorylates Tyr³⁹⁷, creating a binding site for the Src homology 2 (SH2) domain of Src or Fyn (9, 10). The Src kinase then phosphorylates a number of focal adhesion components. The major targets include paxillin and tensin, two cytoskeletal proteins that may also have signaling functions, and p130^{CAS}, a docking protein that recruits the adapter proteins Crk and Nck (11, 12). FAK also combines with, and may activate, phosphoinositide 3-OH kinase (PI 3-kinase), either directly or through the Src kinase (13). Finally, there is evidence that Src

Fig. 1. Cell survival and cell proliferation require interaction with the extracellular matrix. (A) Epithelial cells in some tissues, such as skin and gut, are continuously renewed from stem cells that rest on a basement membrane. Neighboring cells migrate into the space left empty by cells that have moved away to differentiate. (B) Certain epithelia, such as those of the mammary gland and prostate, are not continuously renewed. In this case, interaction with the matrix appears to promote differentiation. During involution, the basement membrane is dissolved by proteolysis, and the cells undergo apoptosis.



¹Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA. E-mail: f-giancotti@ski.mskcc.org ²Cancer Research Center, The Burnham Institute, La Jolla, CA 92027, USA. E-mail: ruoslahti@burnham.inst.org

phosphorylates FAK at Tyr⁹²⁵, creating a binding site for the complex of the adapter Grb2 and Ras guanosine 5'-triphosphate exchange factor mSOS (10). These interactions link FAK to signaling pathways that modify the cytoskeleton and activate mitogen-activated protein kinase (MAPK) cascades (Fig. 3A). Whereas FAK is phosphorylated on tyrosine upon assembly of focal adhesions, it becomes phosphorylated on serine and disassociates from Src and p130^{CAS} during mitosis (14). These events may loosen cell-substrate

contacts and allow cells to divide and move apart.

In addition to activating FAK, some $\beta 1$ and αv integrins also activate the tyrosine kinase Fyn and, through it, the adapter protein Shc (4). In this pathway, caveolin-1 appears to function as a membrane adapter, which couples the integrin α subunit to Fyn. This function of caveolin-1 is consistent with its ability to bind cholesterol and glycosphingolipids and organize specialized plasma membrane "rafts," which are enriched in the

Src-family kinases that carry both a myristoyl and a palmitoyl lipid group, such as Fyn, Yes, and Lck (15). Upon integrin binding to ECM, Fyn becomes activated, and its SH3 domain interacts with a proline-rich site in Shc. Shc is then phosphorylated by Fyn at Tyr³¹⁷ and combines with the Grb2-mSOS complex (4) (Fig. 3B). Although most integrins interact with caveolin-1 and Fyn, only a subset of integrins can activate Fyn and thereby recruit Shc: Perhaps these integrins are associated with an activator of Fyn, such as a phosphatase that removes the phosphate group from the autoinhibitory tyrosine residue in Fyn. Yes and Lck are known to be enriched in rafts and may mediate the activation of Shc when Fyn is not expressed.

It is likely that both FAK and Shc contribute to the activation of the Ras-extracellular signal-regulated kinase (ERK) MAPK cascade when Shc-linked integrins bind to ECM. The relative contribution of each pathway may depend on the cell type and perhaps also on how far the adhesion process has progressed. In many cell types, Shc appears to be responsible for the initial high-level activation of ERK upon cell adhesion. FAK, which is activated more slowly, may sustain the ERK activation (4, 12, 16, 17). The integrins that do not activate Shc are weak activators of ERK and cell proliferation (4, 17, 18). The ability of integrins to activate ERK may be especially important when the concentration of growth factors available to the cell is limited. In this setting, proliferation is likely to require costimulation of ERK through integrins and growth factor receptors.

The FAK and Shc pathways are regulated both positively and negatively by tyrosine phosphatases. Integrin-mediated activation of ERK is suppressed in cells that lack the re-

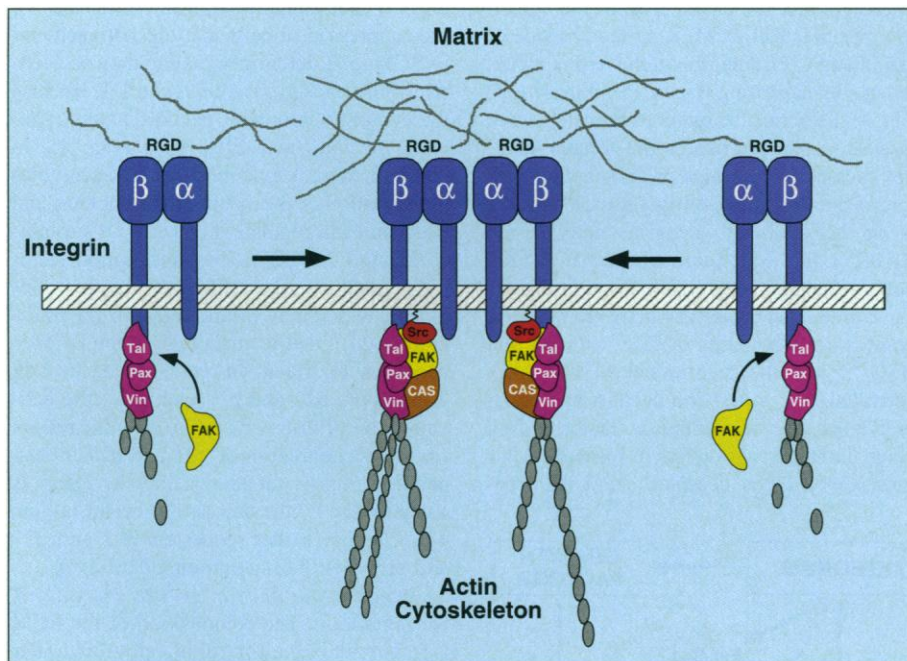


Fig. 2. Matrix binding promotes integrin clustering and association with the cytoskeleton. This in turn promotes further integrin clustering and matrix organization in a positive feedback system. RGD, Arg-Gly-Asp integrin-binding motif; Tal, talin; Pax, paxillin; Vin, vinculin; CAS, p130^{CAS}.

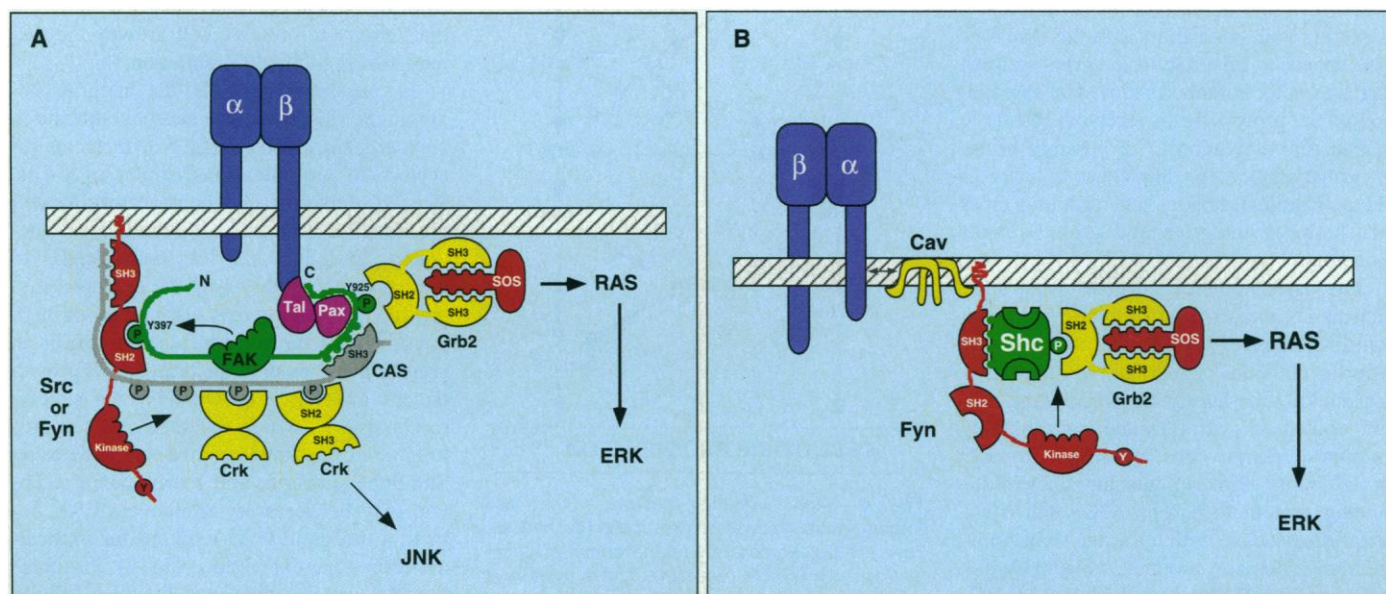


Fig. 3. Model of the (A) FAK and (B) Shc pathways. N, NH₂-terminal; C, COOH-terminal; Y397, Tyr³⁹⁷; P, phosphotyrosine; Y, tyrosine; Cav, caveolin.

ceptor-type protein tyrosine phosphatase α or the cytosolic phosphatase SHP-2 (19). These enzymes dephosphorylate the negative regulatory site in Src-family kinases and thus, presumably, amplify both FAK and Shc signaling. Two cytoplasmic protein tyrosine phosphatases, PTP-PEST and PTP-1B, target p130^{CAS} and may specifically inhibit some of the signals downstream of FAK (20). PTP-PEST has a COOH-terminal extension that anchors it to the cytosolic aspect of the endoplasmic reticulum. Integrin-mediated adhesion activates calpain, a protease that cleaves this extension and allows the phosphatase to relocate to focal adhesions (21). PTEN, a cytoplasmic phosphatase encoded by a tumor suppressor gene, dephosphorylates inositol lipids generated by PI 3-kinase (22). It can, however, also dephosphorylate protein substrates, such as FAK and Shc, and suppress integrin signaling when overexpressed in cells (23). Hence, the lack of functional PTEN may contribute to tumorigenicity by enhancing both PI 3-kinase and integrin signaling.

Partnerships with growth factor receptors and other membrane proteins. Integrins not only signal on their own but are also necessary for optimal activation of growth factor receptors. The receptors for insulin, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF) are optimally activated by their ligands only under appropriate cell attachment conditions (24–28). Although a systematic analysis has not been conducted, certain integrins appear to be preferentially associated with specific growth factor receptors. Thus, the $\alpha\beta3$ integrin can be immunoprecipitated in complexes with the insulin, PDGF, and VEGF receptors (26, 28), whereas $\alpha5\beta1$ and perhaps other $\beta1$ integrins associate with the EGF receptor (25, 27). Integrin clustering and association with the cytoskeleton appear to give rise to integrin–growth factor receptor complexes (25). The aggregation of the growth factor receptors results in their partial activation (27), possibly bringing growth factor signaling closer to a threshold of manifest activity and enabling cross talk between integrins and growth factor receptors.

The association of integrins with other transmembrane proteins provides additional coordinate signals to cells that are also specific for individual integrins. IAP, an immunoglobulin superfamily transmembrane protein, cooperates with $\beta3$ integrins in binding thrombospondin to cells, and it also activates an inhibitory trimeric guanine nucleotide-binding protein (29). The $\alpha3\beta1$ and $\alpha6\beta1$ integrins associate with tetraspan (four transmembrane domain) proteins, which may link these integrins to phosphatidylinositol signaling pathways (30). There is also a connection

between integrins and various types of ion channels (31), but the physiological importance of these connections is still unclear.

Control of Cell Cycle by Integrins

Dependence of cell growth on integrin signals. Cells require anchorage to ECM to proliferate. Integrins activate growth-promoting signaling pathways that are responsible for the anchorage requirement. Two such pathways appear to be activated by most integrins. In one of them, integrins facilitate growth factor–mediated activation of ERK. In some cells, signaling along the Ras-ERK cascade is blocked at the level of the activation of either Raf or MEK in the absence of attachment (32). Integrins remove this block, perhaps by activating Rac or PI 3-kinase (33) (Fig. 4). ERK may be required for cell growth because it phosphorylates the ternary complex factor (TCF), which promotes transcription of the immediate-early gene *c-Fos* (34). In another pathway, integrins activate the MAPK *c-Jun* NH₂-terminal kinase (JNK), which regulates progression through the G₁ phase of the cell cycle. The activation of JNK requires the association of FAK with Src and p130^{CAS} and the recruitment of Crk (35). Activated JNK enters the nucleus and phosphorylates the transcription factor *c-Jun*, which combines with *c-Fos* to form the AP-1 transcription factor complex. AP-1 then reg-

ulates genes that are important for cell proliferation (34). Because most growth factors are poor activators of JNK, the ability of integrins to activate this kinase may explain why cell proliferation requires integrin-mediated adhesion (Fig. 4).

Integrin connections to the cell cycle machinery. Integrin signals are necessary for cells to traverse the cell division cycle. Progression through the G₁ phase of the cell cycle requires the sequential activation of the cyclin-dependent kinases (Cdk's) Cdk 4/6 and Cdk 2. The activities of these kinases are regulated by integrins. The expression of cyclin D1 and, thus, the activation of Cdk 4/6 are suppressed in cells that are not anchored to ECM (36). Integrin signaling may be needed for the transcription of cyclin D1, because the cyclin D1 promoter is coordinately regulated by JNK and ERK (37) (Fig. 4). In addition, there is evidence that ILK promotes translocation of β -catenin to the nucleus, and β -catenin can regulate the cyclin D1 promoter through the TCF/LEF transcription factor (38). Integrins also stimulate the p70 S6-kinase, which may promote cyclin D1 translation (39). Finally, anchorage to the ECM is necessary for the down-regulation of the Cdk 2 inhibitors p21 and p27 and, thus, the activation of cyclin E–Cdk 2 (36, 40). The reason for the accumulation of p21 and p27 in suspended cells is not known, but its effect is compounded by the decrease in cyclin D–Cdk 4/6, a complex that sequesters p21 and p27 and prevents their action on Cdk 2 (41).

Integrin specificity of growth and cell cycle regulation. The composition of the ECM is important in the control of cell growth. For example, myoblasts proliferate on fibronectin but stop growing on laminin and form myotubes; mammary epithelial cells are also induced to differentiate on laminin (42). These observations imply that integrins differ in their ability to promote cell growth and that they also regulate differentiation.

In many primary cells, the integrins belonging to the Shc-linked subset cooperate in a synergistic manner with growth factor receptors to promote transcription of *c-Fos*. This costimulation may be necessary for cell proliferation because ECM binding of Shc-linked integrins enables these cells to progress through the G₁ phase in response to growth factors, whereas attachment through integrins that do not activate Shc results in growth arrest, even in the presence of growth factors (4, 17, 18). Although the precise mechanism by which Shc regulates cell proliferation is not known, stimulation of Ras by Shc-linked integrins and growth factor receptors may be necessary to activate ERK beyond a threshold level required for immediate-early gene expression (Fig. 4). Proliferation deficiencies displayed by mice lacking the integrin $\alpha1$ subunit or the cytodomain of

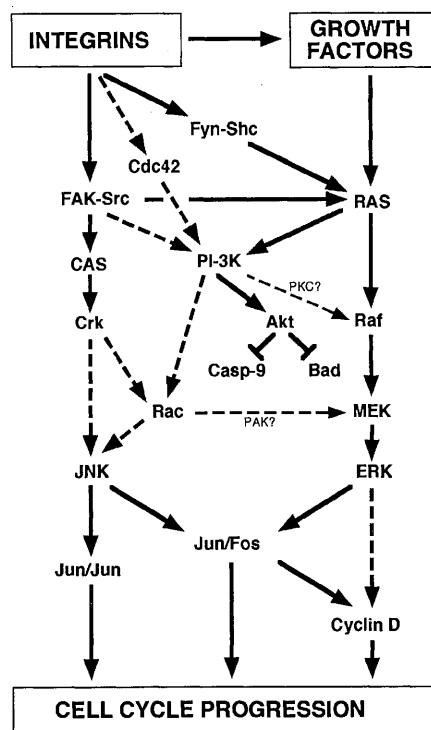


Fig. 4. Major signaling pathways that are known (solid arrows) or presumed (dashed arrows) to be coordinately regulated by integrins and growth factors receptors. These pathways control immediate-early gene expression, the cell cycle machinery, and cell survival.

$\beta 4$ may result from defects in the Shc pathway (17, 43), as both of these subunits form integrins capable of activating Shc.

Certain integrins may regulate proliferation by additional mechanisms. For example, the $\alpha 6 \beta 1$ integrin may in part promote exit from the cell cycle in myoblasts, because the cytoplasmic domain of $\alpha 6$ inhibits paxillin signaling (44). Selective interaction of integrins with growth factor receptors may provide yet another mechanism for matrix-specific growth regulation. For example, $\alpha \nu \beta 3$ associates with the PDGF receptor, and fibroblasts show greater proliferation in response to PDGF β when adhering to the $\alpha \nu \beta 3$ ligand vitronectin than when they adhere to the $\beta 1$ integrin ligand collagen (26).

Cell attachment through integrins may also facilitate exit from the cell cycle and provide signals for differentiation. Withdrawal from the cell cycle is a prerequisite for differentiation. Several mechanisms ensure that proliferation and differentiation are mutually exclusive. For example, the cyclin D-dependent kinases suppress the function of the muscle-inducing transcription factor MyoD in proliferating myoblasts, thereby preventing the expression of muscle-specific genes. Conversely, MyoD maintains cell cycle arrest in differentiated skeletal muscle by inducing expression of the Cdk2 inhibitor p21 (45). Hence, integrins that do not efficiently activate Shc or FAK or that lack the ability to cooperate with growth factor receptors may facilitate differentiation by inducing exit from the cell cycle. However, integrin signals alone are likely to be only permissive for differentiation. For example, differentiated functions of primary mammary epithelial cells require both adhesion to a basement membrane and exposure to lactogenic hormones (46). Thus, whereas interaction with a specific matrix seems sufficient to promote exit from the cell cycle, differentiation is likely to require the integration of signals from integrins and soluble differentiation factors. These signals play an important role in tissue morphogenesis and various tissue repair processes.

Control of Life and Death by Integrins

Loss of attachment to the matrix causes apoptosis in many cell types (47, 48). This phenomenon, referred to as "anoikis" (a Greek word meaning "homelessness"), may help maintain the integrity of tissues; it would prevent cells that have lost contact with their surroundings from establishing themselves at inappropriate locations. The physiological involution of tissues, such as the mammary gland, in which periods of high activity alternate with inactivity, may also depend on anoikis (49) (Fig. 1B).

FAK appears to play a major role in conveying survival signals from the ECM

(50, 51). Because FAK binds PI 3-kinase, the protective effect against anoikis may be the result of PI 3-kinase-mediated activation of protein kinase B/Akt (52). Akt promotes survival, at least in part, by phosphorylating and thereby inactivating two proapoptotic proteins, Bad and caspase-9 (53) (Fig. 4). Inhibition of p53 prevents FAK-deficient cells from undergoing anoikis when deprived of growth factors, suggesting that p53 mediates the death signal under FAK deficiency (51). FAK-expressing cells that are growth arrested because of a loss of matrix adhesion accumulate hypophosphorylated Rb, apparently because of the inactivity of cyclin D-Cdk 4/6 and cyclin E-Cdk 2. Inhibiting the activity of the Rb target E2-F transcription factor protects these cells from apoptosis, suggesting that hypophosphorylated Rb can, under some conditions, provide an apoptotic signal (54).

Like cell growth, anoikis can be controlled by the ECM in an integrin-specific manner. The $\alpha 5 \beta 1$ integrin, which binds to fibronectin, induces expression of the antiapoptotic protein Bcl-2, protecting cells from apoptosis from stresses such as the lack of growth factors (55). Other integrins, including another fibronectin receptor, $\alpha \nu \beta 1$, do not provide this survival effect. The $\alpha \nu \beta 3$ integrin promotes endothelial and melanoma cell survival; this effect correlates with suppression of the p53 pathway and activation of the nuclear factor kappa B transcription factor (56). The activation of Shc by $\alpha 1 \beta 1$, $\alpha 5 \beta 1$, and $\alpha \nu \beta 3$ may also contribute to protection from apoptosis (4, 17). Thus, integrin-mediated attachment to ECM is a general requirement for cell survival, but survival under special circumstances may require a particular integrin.

Because most cells in adult organisms are not actively dividing, it is likely that other cell surface proteins, such as the cadherins, override the growth-promoting, but not the survival-promoting, effects of integrins and growth factor receptors. This contact inhibition of growth, combined with an integrin-mediated survival signal, can ensure the survival of differentiated cells that are correctly positioned within tissues (Fig. 1B).

Anoikis is likely to be important in the maintenance of tissue architecture, as it would ensure the demise of cells that detach from their original site in tissue. The requirement for a specific integrin as the mediator of the attachment may provide an additional safety factor, because it would facilitate the destruction of cells that have attached at an inappropriate tissue location. Tumor cells are generally resistant to anoikis and can proliferate in the absence of anchorage to ECM (2, 48). This may explain their propensity to leave their original site and metastasize.

Control of Cell Shape, Growth, and Survival by Integrins

When cells come in contact with the ECM, their usual response is to extend filopodia, apparently to sample the terrain. Integrins at the tip of filopodia bind to the ECM and initiate the formation of focal adhesions. Actin-rich lamellipodia are then generated, often between filopodia, as the cell spreads on the ECM. Fully developed focal adhesions and associated actin stress fibers ensue. These same events occur cyclically during cell migration as cells extend lamellipodia and form focal adhesions to derive the traction necessary for movement.

Integrins and receptors for soluble mitogens, such as lysophosphatidic acid and growth factors, regulate cell spreading and migration through activation of the Rho-family of small guanine nucleotide-binding proteins (57). Among the Rho-related guanosine triphosphatase, Cdc42 induces filopodia, Rac induces lamellipodia, and Rho induces focal adhesions and associated stress fibers. Each of these Rho-related proteins controls the actin cytoskeleton by interacting with multiple downstream effectors (58). The FAK-Src complex also plays a role in cell migration, perhaps by promoting the disassembly of focal adhesions at the trailing edge of the cell (59). Rho activity is also required for the assembly of a fibronectin matrix (60). Conversely, interaction with a natural fibronectin ECM, but not with fibronectin coated on a culture plate, facilitates Rho activation and cell proliferation (61). Thus, the ECM and the cytoskeleton are interdependent, and the geometry and physical properties of the ECM available to the cell are important for cell spreading and motility.

Cell spreading is closely linked to cell survival and growth (62). Rho-related proteins are likely candidates for mediators of this cell-spreading requirement. Rac promotes cell cycle progression, an effect that correlates with its ability to organize the cytoskeleton and promote spreading, rather than with its ability to activate MAP kinases (63). This suggests that integrins and integrin-associated actin filaments may be the origin of the Rac-mediated growth stimulatory signal, but the nature of this signal and its mechanism of action are unclear. Rac also promotes integrin clustering, and this effect may cause further Rac activation, spreading, and integrin clustering, establishing a positive feedback loop (64). Thus, the failure of certain cells to thrive when spreading is prevented (62) may reflect the inhibition of Rac signaling. Alternatively, physical forces exerted on the nucleus by integrin-induced changes in the cytoskeleton may regulate nuclear events without cytoplasmic chemical intermediates (65). The coordinated control of cell shape, survival, and growth by inte-

grins is likely to be important in the establishment and maintenance of tissue architecture (Fig. 1).

Conclusion and Future Prospects

Because integrins assemble large signaling complexes and activate multiple signaling pathways, they may well serve as one class of "master regulators" of cell function. Future biochemical studies will provide a better understanding of the integrin signaling complexes, and they may reveal new organizational principles at the cell membrane. Most of the current knowledge on integrin signaling is based on the analysis of established fibroblastic and epithelial cell lines, many of which are either highly transformed or immortalized by an unknown mechanism. As more normal cell types are analyzed, variations to the now established pathways will probably be discovered. Genetic studies will be particularly important in assessing the relative contributions of the integrin signaling pathways to embryonic development, tissue architecture, and various disease and repair processes.

Advances in the integrin field are also being translated into practical applications. Three integrin-directed drugs are presently available. As our understanding of integrin signaling advances, intracellular targets for integrin-modifying drugs should emerge. For example, eliciting an anoikis response in tumor neovasculation and restoring it in tumor cells would seem to be a particularly attractive possibility.

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