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Emerging Views of Integrin Signaling: Implications for Prostate Cancer

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Abstract Integrins are heterodimeric transmembrane cellular receptors that link the cell to its underlying substratum. Alterations in integrin expression and signaling have been implicated in many aspects of tumorigenesis and metastasis including cell survival, migration, and invasion. In prostate cancer, the progression from normal to metastatic cells is accompanied by changes in the repertoire of integrins expressed and up-regulation of key adhesion-dependent signaling pathways. Recent work from several laboratories indicates the emergence of new mechanisms for the regulation of growth and migratory pathways by integrin engagement. These pathways are likely to provide novel sites of therapeutic intervention for the treatment of prostate cancer. J. Cell. Biochem. 91: 41–46, 2004.

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Integrins are transmembrane receptors that function as sensors of the environment, and as such, are responsible for directing cellular responses including biochemical signals and cellular forces, which together regulate cellular migration, growth, differentiation, and survival [Hynes, 1992]. One of the hallmarks of cancer is the profound change in how cells sense their local environment, no longer responding to the environmental signals that tightly regulate growth and cell motility. This loss of adhesion-dependent growth control is due in part to changes in integrin signaling. Indeed, whereas attachment of normal cells to the appropriate extracellular matrix (ECM) stimulates contact inhibited proliferation or differentiation, loss of adhesion-dependent growth regulation is an early indicator of progression to the malignant state. Alterations in integrin expression and signaling have been implicated in many aspects of tumorigenesis and metastasis including cell survival, migration, and invasion. In prostate cancer, the progression from normal to metastatic cells is accompanied by changes in the repertoire of integrins expressed and up-regulation of key adhesion-dependent signaling pathways. Recent work from several laboratories indicates the emergence of new mechanisms for the regulation of growth and migratory pathways by integrin engagement. These pathways are likely to provide novel sites of therapeutic intervention for the treatment of prostate cancer.

INTEGRINS

Integrins are a family of heterodimeric, transmembrane receptors that mediate the attachment of cells to the surrounding ECM [Hynes, 1992]. Integrins are comprised of α and β subunits. Currently, 18 α subunits and 8 β subunits have been identified, and different combinations of α and β subunits dictate specificity for the extracellular ligands [Calderwood et al., 2000]. As transmembrane receptors, each subunit contains a large extracellular domain, a single membrane spanning segment and a short cytoplasmic tail. The cytoplasmic tail of the β subunit is necessary and sufficient to mediate the linkage of integrins to the actin cytoskeleton. Although α subunits can bind to cytoskeletal proteins, current evidence indicates that the major functional role of the α cytoplasmic tail is to modulate cytoskeletal interactions by directly interacting in a ligand-

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dependent fashion with the cytoplasmic region of the β subunit [Calderwood et al., 2000].

The repertoire of integrin subunit expression is cell type specific and determines the ECM proteins with which cells interact. Changes in integrin subunit expression and the composition of surrounding ECM often are observed in cells with increasing metastatic potential when compared to normal counterparts. Prostate adenocarcinomas and metastatic lesions exhibit increased expression of β_3, β_1, and α_{IIb} integrins and decreased expression of β_{1C}, β_4, α_2, α_3, α_4, and α_5 integrins [Cress et al., 1995; Fornaro et al., 2001]. For example, the β_{1C} integrin (an alternatively spiced isoform of β_1) functions as a negative regulator of cell growth by influencing expression of $p27^{kip1}$, a cell-cycle inhibitor [Fornaro et al., 1999]. Loss of β_{1C} expression occurs early in prostate tumorigenesis and correlates with increased proliferation of neoplastic lesions [Fornaro et al., 1996, 1999].

Alterations in subunit expression have an impact on integrin heterodimer usage. The best studied of these is the switch in laminin receptors from $\alpha_6\beta_4$ to $\alpha_6\beta_1$ [Cress et al., 1995]. In normal prostate epithelium, the α_6 subunit pairs with the β_4 integrin in hemidesmosomes, unique structures located at the interface of the cell with the surrounding basal lamina. In tumor cells decreased β_4 expression results in the pairing of α_6 with β_1 and redistribution of α_6 from hemidesmosomes. Concomitantly, tumor cells, while remaining in contact with the basal lamina, fail to express laminin 5, a key ECM protein associated with hemidesmosomes [Cress et al., 1995]. Loss of hemidesmosomes results in less stable interaction of the cell with the underlying matrix thus providing increased potential for tumor cells to invade and migrate to distal organ sites [Hao et al., 1996]. The migration and localization of prostate tumors to metastatic sites is accompanied by additional changes in integrin expression. Prostate adenocarcinomas isolated from bone metastases express $\alpha_V\beta_3$ integrin receptors, which regulate adhesion to and migration on bone ECM proteins vitronectin and osteopontin, [Zheng et al., 1999; Cooper et al., 2002].

INTEGRIN SIGNALING

Alterations in integrin-mediated signal transduction cascades accompany the changes in integrin subunit usage by prostate carcinomas. Since integrins lack catalytic activity, their ability to relay signals from the ECM to intracellular activities relies on interactions with intracellular signaling and adaptor molecules [Liu et al., 2000]. One such protein is focal adhesion kinase (FAK), a non-receptor protein tyrosine kinase that is activated upon integrin engagement and has been demonstrated to play a role in propagation of intracellular signal transduction cascades [Parsons, 2003]. Binding of integrins to ECM results in integrin clustering and initiates FAK autophosphorylation on tyrosine 397 (Tyr397). Phosphorylation of Tyr397 creates a high affinity binding site for the Src homology 2 (SH2) domain of Src-family tyrosine protein kinases and leads to the formation of stable complexes and activation of Src catalytic activity. FAK mutants deficient in Src binding (e.g., Tyr397Phe) fail to effectively induce the translocation of Src to focal adhesion structures and activate downstream signals. Phosphorylation of Tyr397 correlates with increased catalytic activity of FAK and is required for the subsequent adhesion-dependent tyrosine phosphorylation of FAK on other tyrosine residues as well as other focal complex-associated proteins including paxillin and Cas. In addition to binding Src, phosphorylation of FAK on Tyr397 promotes the interaction with several other SH2-containing signaling proteins, including phosphatidylinositol 3-kinase (PI3K), phospholipase C (PLC)-γ, and the adapter protein Grb7.

Alterations in the FAK/Src signaling pathway are observed in prostate cancer. Elevated FAK expression is evident in the earliest preinvasive prostate cancer lesions as well as in adenocarcinoma and lymph node metastases [Tremblay et al., 1996; Rovin et al., 2002]. When compared to normal and hyperplastic prostates, FAK mRNA and protein levels are elevated in prostate cancer samples isolated from patients who had metastases [Tremblay et al., 1996]. Moreover, FAK expression is observed in the basal epithelial cell layer in normal prostate glands compared to the even distribution of expression within the cytoplasm of all cells within the tumor [Rovin et al., 2002]. In addition to increased FAK expression, prostate cancer cell lines with increasing metastatic potential have elevated Src activity, which correlates with increased cell migration [Slack et al., 2001]. In these cells, inhibition of FAK activity resulting from over expression of a dominant negative

form of FAK, FRNK, leads to inhibition of cell migration and growth arrest and inhibition of tumorigenicity in xenograph models [Slack et al., 2001; Rovin et al., submitted]. These observations are consistent with increased FAK expression playing a role in activating integrin signaling in prostate cancer.

ADHESION-DEPENDENT SIGNALING TO MITOGEN ACTIVATED PROTEIN KINASE (MAPK)

The significance of increased FAK expression and elevated Src activity in prostate cancer has yet to be determined but newly emerging data suggest a role for integrin signaling pathways, including FAK and Src, in the regulation of MAPK activity. MAPK, a serine/threonine kinase, is the terminal kinase of the Ras signal transduction cascade, which includes Raf and MAPK kinase (MEK) [Schaeffer and Weber, 1999]. The Ras/MAPK pathway is a central regulator of growth, migration, and survival. Indeed, activating Ras mutations lead to unregulated growth and are observed in many tumors. While Ras mutations are not associated with prostate cancer, MAPK activity is elevated in high-grade prostate tumors [Gioeli et al., 1999].

Growth factor-stimulation of cells involves consecutive activation of Ras, Raf, MEK, and finally MAPK [Schaeffer and Weber, 1999]. Historically, integrin engagement was reported to activate MAPK through three different Ras-dependent pathways [Chen et al., 1994; Schlaepfer et al., 1994; Wary et al., 1996]. More recent data indicate a role for Rac/p21 activated kinase (PAK) signaling pathways in the regulation of MAPK activation. Rac signaling to PAK synergizes with Raf to regulate MAPK activity [Frost et al., 1997]. The PAK effects on MAPK signal transduction appear to be mediated by phosphorylation of Raf on S338 and MEK1 on S298 [Frost et al., 1997; King et al., 1998; Chaudhary et al., 2000; Coles and Shaw, 2002; Slack-Davis et al., 2003]. PAK phosphorylation of c-Raf has been reported to stimulate its activity and enhance its interaction with MEK1 and has been reported to be regulated by cell adhesion [King et al., 1998; Chaudhary et al., 2000; Xiang et al., 2002]. Likewise, PAK phosphorylation of MEK1 on S298 sensitizes MEK1 to activation by Raf [Frost et al., 1997; Coles and Shaw, 2002; Slack-Davis et al., 2003]. Phosphorylation of MEK1 on S298 is adhesion-dependent and necessary for the formation of MEK1–MAPK complexes and subsequent MAPK activation upon cell adhesion to the ECM [Eblen et al., 2002]. Together, these observations indicate a role for PAK activity in regulating the assembly of MAPK signaling module involving c-Raf, MEK1, and MAPK.

Adhesion to the ECM leads to PAK activation and the targeting of PAK to adhesion complexes [Manser et al., 1998; del Pozo et al., 2000; West et al., 2001]. The small GTPases Rac and Cdc42 are potent activators of PAK and are stimulated following integrin ligation. The molecular pathways leading to Rac/Cdc42 and PAK activation are likely numerous, however, recent studies have implicated PI3K and FAK/Src signaling pathways in the regulation of PAK1 phosphorylation of c-Raf and MEK1, respectively [Chaudhary et al., 2000; Slack-Davis et al., 2003].

BIOLOGICAL IMPORTANCE OF ADHESION SIGNALING TO MEK: IMPLICATIONS FOR PROSTATE CANCER

The observations described above provide insights into how changes in integrin signaling may influence the adhesion-dependent regulation of tumor cell growth and migration (Fig. 1). A key aspect of tumor progression is the ability of tumor cells to adapt to changing environmental cues and alterations in both autocrine and paracrine growth factors. Recognition that integrin-dependent PAK phosphorylation of c-Raf and/or MEK1 governs the formation of a c-Raf/MEK1/MAPK "signaling module" suggests that this pathway may contribute to "priming" cells to receive both chemotactic and growth-promoting signals through Ras (Fig. 1). MAPK and PAK activities are both important for cell migration [Klemke et al., 1997; Kiosses et al., 1999; Sells et al., 1999]. The observations that active MAPK and active PAK are found in membrane ruffles and peripheral focal complexes upon ECM stimulation support a role for these kinases in the regulation of focal adhesion dynamics and cell migration [Fincham et al., 2000; Sells et al., 2000; Slack-Davis et al., 2003]. Indeed, Rac over-expression enhances MAPK-dependent migration of cells stimulated with low levels of EGF while having little effect on migration in response to high concentrations of growth factor [Leng et al., 1999]. PAK phosphorylation of MEK1 on S298, which is required for MEK1 activation in the absence

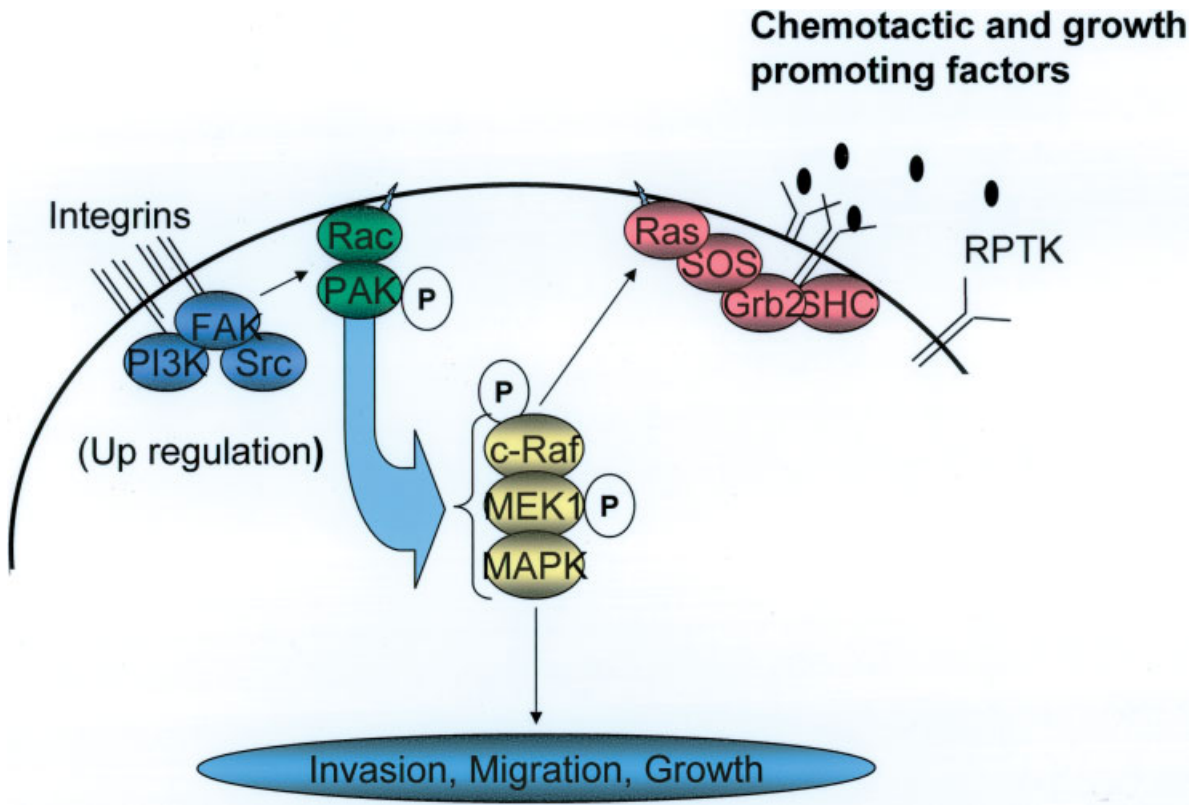

Fig. 1. Model of integrin signaling to mitogen activated protein kinase (MAPK) activation. As discussed in the text, integrin binding to the extracellular matrix (ECM) stimulates focal adhesion kinase (FAK) activity, the recruitment and activation of Src and/or PI3K, and subsequent activation of Rac. Activated Rac interacts with p21 activated kinase (PAK) stimulating autophosphorylation of PAK and PAK phosphorylation of c-Raf and MEK1, which promotes interactions between c-Raf, MEK1, and MAPK. This MAPK ''signaling module'' is ''primed'' to receive signals from Ras initiated by growth or chemotactic factors interacting with receptor protein tyrosine kinases (RPTK). In metastatic prostate cancer cells, the FAK/Src signaling pathway is upregulated resulting in amplification of this signaling pathway. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com]

of inducible Raf activity, provides a mechanism whereby suboptimal Raf activation (likely achieved with shallow gradients of chemotactic factor stimulation) could promote maximal MAPK activity in a localized manner [Slack-Davis et al., 2003]. The ability of tumor cells to respond to threshold levels of chemotactic signals may contribute to progression and selection of metastatic cells.

In addition to regulating cell migration, cell adhesion regulates sustained MAPK activity necessary for growth [Assoian and Schwartz, 2001]. In the absence of an appropriate ECM, addition of growth factors stimulates Ras activity, however, cell adhesion is required to maximally activate Raf, MEK, and MAPK [Lin et al., 1997; Renshaw et al., 1997; Slack-Davis et al., 2003]. Observations that adhesion-dependent activation of Rac and PAK1 are required to enhance the propagation of signals from c-Raf to MEK1 and subsequently MAPK [Frost et al., 1997; King et al., 1998; Chaudhary et al., 2000; Coles and Shaw, 2002; Eblen et al., 2002; Xiang et al., 2002; Slack-Davis et al., 2003] provide a mechanism to account for the disconnect between Raf and MEK in serum stimulated, suspended cells, and thereby render MAPK activation dependent on cell adhesion. The observation that the adhesion requirement for growth factor-induced MAPK activation is abrogated in cells over-expressing activated FAK [Renshaw et al., 1999] or PAK [Howe and Juliano, 2000] suggests that up-regulation of FAK or PAK activity may be important for anchorage-independent growth of tumor cells. Indeed, PAK has been implicated in regulating anchorage-independent growth [Tang et al., 1997, 1999; Vadlamudi et al., 2000].

Activation of Rac plays a central role in both growth and migratory responses. While the pathways from integrin engagement to Rac activation have not been elucidated, signals

from PI3K and FAK/Src play a prominent role [Chaudhary et al., 2000; Slack-Davis et al., 2003]. This is of particular relevance to prostate cancer in light of observed alterations in PI3K and FAK/Src signaling pathways in advanced tumors. In addition to elevated FAK expression and Src activity [Tremblay et al., 1996; Slack et al., 2001; Rovin et al., 2002], signaling downstream of PI3K is constitutively activated in prostate cancer cells due to the inactivation of a negative regulator of PI3K, the phosphoinositide 3-phosphate lipid phosphatase PTEN [Dong, 2001]. While the contribution of elevated PI3K and FAK/Src signaling to PAK and/or MAPK signaling in prostate cancer has not formally been tested, elevated PAK-directed MEK1 S298 phosphorylation has been observed in highly tumorigenic human prostate cell lines in the absence of integrin engagement [Slack-Davis et al., 2003]. This coupled with the observation that MAPK activity is elevated in high grade prostate tumors [Gioeli et al., 1999] provides insights as to how changes in integrin repertoire and signaling contribute to regulation of anchorage-independent growth and metastasis (Fig. 1).

PERSPECTIVES

Recently, interest has turned to integrins for anti-cancer therapeutics. The unique patterns of integrins expressed on tumor cells create specific targets for drug delivery, gene therapy, and immune based tumor elimination [Rust et al., 2002]. Additionally, integrins provide unique chemotherapeutic targets themselves. Blocking antibodies and synthetic cyclic peptides mimicking integrin ligands, which function as antagonists of integrin function, are currently in clinical trials [Tucker, 2002]. While anti-integrin therapy shows promise to halt tumor progression, tumors often overcome integrin requirements through up-regulation of integrin-initiated intracellular signaling pathways. Therefore, integrin-dependent signaling components, including FAK, Src, and PI3K may serve as complementary chemotherapeutic targets. Identification of key signaling components will provide new avenues for intervention in prostate tumorigenesis and metastasis.

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