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Clinical Cancer Research

Molecular Pathways

β1-Integrin: A Potential Therapeutic Target in the Battle against Cancer Recurrence

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Abstract

Primary cancer treatment, involving both local and often systemic adjuvant therapy, is often successful, especially if the cancer is detected at an early stage of progression. However, for some patients, the cancer may recur either locally or as distant metastases, in some cases many years after apparently successful primary treatment. Significant tumor dormancy has been documented in several cancers, such as breast, melanoma, and renal cancer. Tumor dormancy has long been recognized as an important problem in management of cancer patients. Recent work has clarified biologic aspects of tumor dormancy and has shown that dormant tumor cells may be resistant to cytotoxic chemotherapy and radiation. This work has led to recognition of a key role for β1-integrin in regulating the switch from a dormant state to active proliferation and metastasis. Here we discuss the role of β1-integrin and its signaling partners in regulating the dormant phenotype. We also consider possible therapeutic approaches, such as small molecules or antibodies (ATN-161, volociximab, and JSM6427), directed against β1-integrin signaling to target dormant cancer cells and to prevent metastatic recurrence. *Clin Cancer Res; 17(23); 7219–23. ©2011 AACR.*

Background

The major fear of cancer patients is the propensity of the cancer to recur, sometimes after long latency periods, as metastatic disease. Most therapies fail in the metastatic setting. Thus, it is vital to develop new strategies to confront metastatic disease before it emerges.

Recurrence of cancer after very long latency is explained clinically by the persistence of disseminated dormant tumor cells that are not clinically manifested. Several experimental mouse metastasis models using a variety of cancer cell lines showed the presence of dormant cancer cells, often coexisting in a metastatic site with actively growing metastases (1–9). Furthermore, these 2 populations of cells have been shown to be biologically distinct, with, for example, very different responses to cytotoxic chemotherapy (2, 3, 10). Importantly, accumulating evidence shows that dormant disseminated solitary tumor cells may also be present in patients with no clinical evidence of relapsing tumors, even in some patients who were diagnosed in early stages of the disease (1, 11–13). Although breast and renal cancers, as well as melanoma, are well documented to have late recurrences, patients with other cancer types can also be at risk (11). Moreover, several studies have shown that disseminated solitary dormant cells are quiescent (reviewed in refs. 1, 2, 11) and may be resistant to therapies that target actively dividing cells (3, 10). Hence, the persistent presence of these dormant tumor cells, even after systemic treatment therapy, may lead to outgrowth of the cells years later (14, 15).

During the course of metastatic spread, disseminated tumor cells encounter new and foreign microenvironments that will determine their fate. The majority of disseminated tumor cells will likely meet their death upon colonization of a "nonpermissive" site, because of the well-recognized inefficiency of the metastatic process (2). In contrast, a small proportion of tumor cells may persist and enter a quiescent state of cellular dormancy that can last for years or decades (12, 16). A subset of these cells may eventually escape their dormant state and form metastases. Reciprocal interactions between these cells and their surrounding microenvironment lead to intracellular signaling in the tumor cells that dictates their survival, growth arrest, and resumption of proliferative growth. These interactions involve adhesion molecules on the surface of the tumor cells that sense and engage with the new surroundings.

In this review, we focus on one such adhesion molecule, β1-integrin (Intβ1), which has been shown to play an important role in the switch from cellular dormancy to metastatic growth and in mediating resistance of tumor cells to adjuvant therapy and ionizing radiation. Targeting Intβ1 as potential therapy and translational advances in the field are discussed.

β1-integrin downstream signaling in cellular dormancy and the switch to metastatic growth

Integrins are a family of cell adhesion molecules comprising 18α and 8β subunits that combine into at least 24 heterodimers. Intβ1 partners with α subunits to form 12

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potential integrin receptors, which bind to a wide array of arginine-glycine-aspartic acid (RGD)–containing extracellular matrix (ECM) molecules such as collagens, laminin, and fibronectin (17, 18). Intβ1 consists of a large extracellular domain, a single transmembrane stretch, and a short cytoplasmic domain devoid of an intrinsic enzymatic activity. The cytoplasmic domain transduces bidirectional signals from inside the cell by regulating the conformation and ligand affinities of the extracellular domain of Intβ1 (inside-out signaling), while mediating downstream signaling and interactions with the cytoskeleton (outside-in signaling). The outside-in signaling is initiated upon ligand binding to Intβ1, followed by the formation of adhesion complexes assembled from signaling molecules, such as tyrosine kinases, serine-threonine kinases, phospholipid kinases, phosphatases, Ras superfamily proteins, and various adapter proteins (17–19).

Bidirectional signals of Intβ1, together with cross-talk with other cellular receptors (18), have been shown to play a crucial role in cell adhesion, survival, differentiation, and proliferation. Furthermore, several studies have underscored the important role of Intβ1 in tumor initiation (20, 21), reversion (22), survival (23), tumor progression, and metastasis (20, 24, 25).

We and others have shown that Intβ1 activation is a key regulator in the switch from cellular dormancy to metastatic growth *in vitro* and *in vivo* (5, 6, 26, 27). *In vitro* studies used a 3-dimensional (3D) culture system, constituted from growth factor–reduced basement membrane to model dormancy, and found that dormant versus proliferative behavior in this model mimicked the dormant versus metastatic behavior of multiple cell lines *in vivo* (5). By using this 3D system, it was shown that supplementation of the basement membrane with either fibronectin or type I collagen induces Intβ1 downstream signaling (5, 26), leading to activation of focal adhesion kinase (FAK) by Src. This activation results in downstream activation of the extracellular signal–regulated kinase (ERK), a key regulator in cell-cycle and cytoskeletal reorganization. ERK, in turn, induces phosphorylation of myosin light chain (MLC) by MLC kinase (MLCK), culminating in f-actin stress fiber organization (26), followed by translocation of cyclin-dependent kinase inhibitor p27 to the cytoplasm (5). The following induced cascade culminated in the transition from dormancy (quiescence) to proliferation. Inhibition of Intβ1, or its downstream signaling molecules Src, *p*-FAK, *p*-ERK, and MLCK, culminates in reduced MLC phosphorylation, cortical f-actin and in maintaining the cells in a dormant state. Additionally, previous studies in head and neck and breast cancer cells showed the importance of cross-talk between α5β1 integrins, urokinase receptor (uPAR), and epidermal growth factor receptor (EGFR) in cellular dormancy *in vivo* (7, 27). Downregulation of uPAR led to reduced cross-talk with α5β1 integrins and, in turn, reduced FAK and ERK activity and high cell division cycle 42 (CDC42)–p38 activity. The reduced ratio of ERK/P-$p38^{SAPK}$ culminated in induction of cellular dormancy. In contrast, high uPAR expression induced α5β1 integrin, and, in turn, this complex recruited EGFR and FAK, which in a fibronectin-dependent manner induced sustained ERK activation.

Hence, Intβ1 plays an important role in the cross-talk between disseminated tumor cells and their microenvironment, thus dictating the fate of the tumor cells. Fig. 1 summarizes the intracellular functions of Intβ1 in cellular dormancy and their potential role in the switch to metastatic growth.

β1-integrin and resistance to adjuvant and ionizing radiation therapy

Intβ1 may also play an important role in resistance of tumor cells to chemotherapy and ionizing radiation. Resistance of dormant solitary cells to chemotherapy has been shown previously *in vivo* (3, 8, 28) and in the 3D model system (D. Barkan; unpublished data). This resistance is due to the quiescent nature of the dormant cells. Resistance of dormant tumor cells to radiotherapy and or chemotherapy may lead to persistence of the cells and recurrence of the cancer following treatment. Indeed, low expression and/or function of Intβ1, as was shown in dormant tumors cells, have been reported in tumor cells that have acquired multidrug resistance (29). On the other hand, several lines of evidence show that Intβ1 signaling plays a significant role in mediating resistance to cytotoxic chemotherapies by enhancing the cell survival pathway mediated by phosphoinositide 3-kinase (PI3K) and the serine-threonine kinase (Akt) pathway (30, 31). Intβ1 has also been implicated in mediating resistance to ionizing radiation through activation of the PI3K/AKT pathway (32, 33), and it was shown to be upregulated upon exposure to clinical doses of ionizing radiation (33). Importantly, clinical evidence shows that increased Intβ1 expression, which is also linked to fibronectin levels, is associated with decreased survival in invasive breast cancer (34).

Therefore, given that Intβ1 plays an important role in the transition from cellular dormancy to metastatic growth and its role in adjuvant and ionizing radiation resistance, Intβ1 may offer an attractive therapeutic target to inhibit the emergence of metastatic disease.

Clinical–Translational Advances

Several experimental models have shown the great potential in targeting Intβ1 as a means to prevent breast cancer recurrence and metastatic disease. Furthermore, new inhibitors for Intβ1 are already in clinical trials for several cancers as antiangiogenic therapy. Here, we discuss experimental models supporting the potential use of Intβ1 inhibitors in prevention of cancer recurrence. We discuss the progress already made in the use of Intβ1 inhibitors in several clinical trials that are ongoing for cancer patients, and we speculate on potential combinational therapies, including Intβ1 inhibitors, in the prevention of cancer recurrence.

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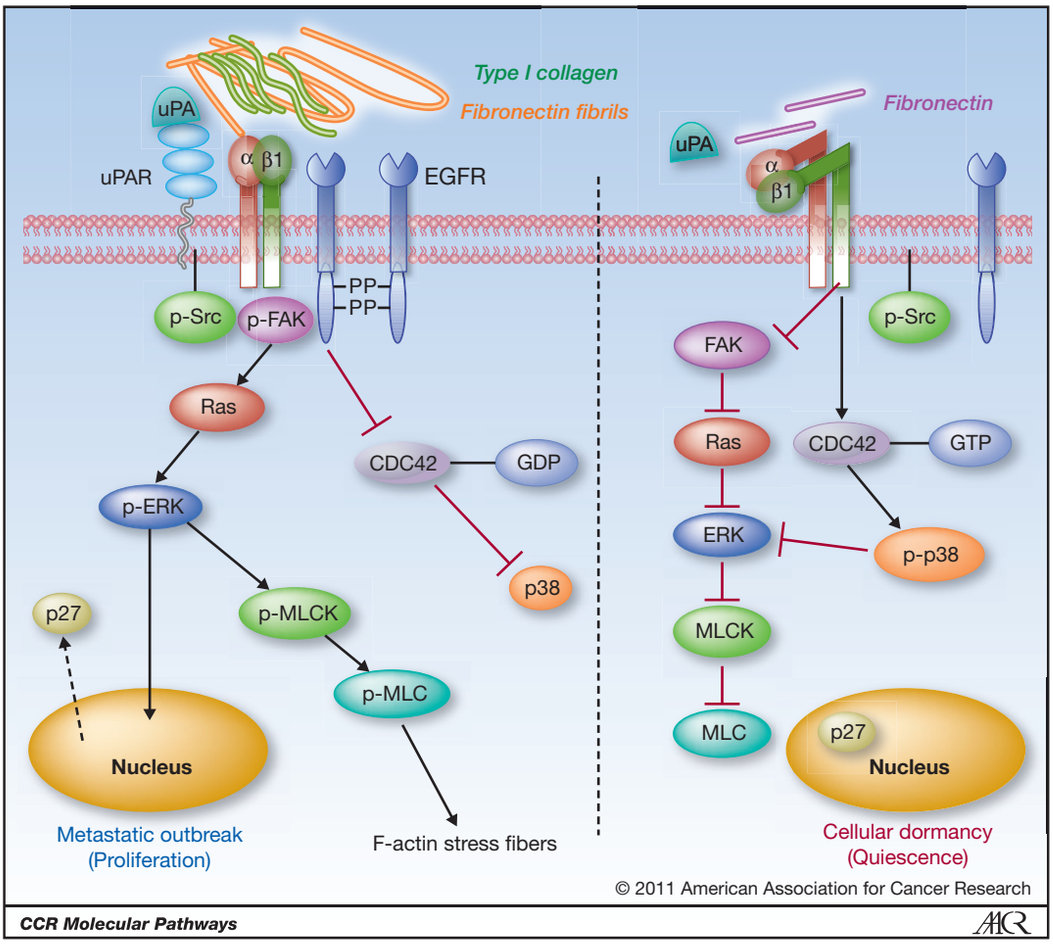

Figure 1. β1-integrin signaling mediating the switch from tumor dormancy to metastatic growth. Transition from dormancy to metastatic growth is induced by Intβ1 activation through fibronectin-fibrils/type I collagen and/or uPAR activation, which initiates downstream signaling via Src and FAK, inducing a high ERK-to-p38 ratio, which in turn activates MLCK, leading to cytoskeletal reorganization and metastatic growth. Inactivation of Intβ1 or downstream signaling, such as Src, FAK, or MLCK, or reducing the ERK-to-p38 ratio, will retain the cells in a dormant state.

Therapeutic targeting of Intβ1

Several experimental models have shown the efficacy of Intβ1 inhibitors in treatment of refractory tumors and advanced metastatic disease. Inhibitory antibodies to Intβ1 (e.g., AIIB2) have been previously shown to effectively synergize with ionizing radiation to modify Akt-mediated ionizing radiation resistance in breast cancer cell lines and were shown to dramatically enhance radiotherapy efficacy in human breast cancer xenografts (32, 33). We have reported that targeting Intβ1, by either an inhibitory antibody or short hairpin RNA, or its downstream-signaling mediator MLCK prevented the transition of dormant tumor cells to metastatic growth and maintained the tumor cells in a quiescent state, both in a 3D *in vitro* system as well as *in vivo* (5, 26).

Flavopiridol, a synthetic flavone that can inhibit cyclin-dependent kinases, was shown to cause a decrease in FGF-2–induced expression of integrins, including α5β1 integrin, and, in turn, decreased the survival of well-differentiated tumor cells *in vitro* (35). Importantly, a recent study by Chaurasia and colleagues (36) identified small molecules capable of specifically disrupting the uPAR–integrin $\alpha_5\beta1$ interaction and, thus, profoundly inhibited metastasis.

To date, 3 Intβ1-1 inhibitors have been or are being evaluated in clinical trials: ATN-161, volociximab (M200), and JSM6427. ATN-161 is an antagonist of α5β1. ATN-161 is a 5–amino acid peptide derived from the sequence of the integrin's ligand fibronectin, PHSRN, which acts in synergy with the RGD-containing binding site to strengthen the α5β1–fibronectin interaction (37). ATN-161 was shown to inhibit tumor growth and metastasis and extend survival in multiple animal tumor models, either when given as a single agent or when combined with chemotherapy and radiotherapy (38–40). A phase I clinical trial showed a very good safety profile for the use of ATN-161 in patients with advanced solid tumors (41). All of the treatment-related adverse events were grade 2 or lower, and no dose-limiting toxicities occurred. Furthermore, one third of the patients manifested prolonged stable disease. These findings led to preparation of a phase II trial

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in head and neck cancer in which ATN-161 will be used in combination with radiation and chemotherapy.

Volociximab, originally known as Eos200-4 and now M200, is a humanized monoclonal antibody against α5β1. It was developed as an antiangiogenic agent for the treatment of solid tumors and age-related macular degeneration (37). In a phase I trial, patients with advanced solid tumors were given 223 escalating i.v. infusions of volociximab. Treatment was well tolerated, and no dose-limiting toxicities occurred over the range examined. Mild (grade 1 or 2), reversible fatigue was the principal toxicity of volociximab at the highest dose levels. Nausea, fever, anorexia, headache, vomiting, and myalgias were mild and infrequent, and there was no hematologic toxicity. Approximately one quarter of the patients with advanced disease before study entry displayed stable disease as a result of treatment (42).

In summary, emerging evidence in the literature supports the potential use of Intβ1 inhibitors in preventing recurrence of breast cancer disease. Initial clinical trials using inhibitors for Intβ1, although used for already overt metastatic disease, show some encouraging results.

Future directions

The cross-talk between Intβ1 with ECM components and cellular receptors, such as uPAR and EGFR, induction of transmembrane links between the ECM and cell cytoskeleton proteins, and the ability of these interactions to regulate the switch from cellular dormancy to metastatic growth argues for the design of studies to assess inhibition of Intβ1 to either eradicate dormant tumor cells or to retain them in a dormant state. Inhibition of Intβ1 in combination with, for example, inhibitors of either EGFR or downstream effectors, such as Src or MLCK, should also be considered. Specific targeting of disseminated tumor cells is vital, but administering such inhibitors alone or in combination and for a long period may target normal cells, resulting in adverse side effects. However, recent findings showing high expression of HER2 and uPAR in some circulating tumor cells (43) make these receptors potential targets for delivery of the above inhibitors, using either trastuzumab or uPAR antagonists for drug delivery.

Intriguingly, it may even be possible to use selective small molecules, instead of combinational therapies, to achieve inhibition of multiple targets and prolong the dormant state of the disseminated tumor cells with no adverse side effects. For example, JSM6427 is a highly selective, small-molecule inhibitor of α5β1 integrin currently in a phase I clinical trial for the treatment of age-related macular degeneration. This drug was developed as an antiangiogenic drug to treat age-related macular degeneration, as was volociximab, and it is likely that this small molecule, like volociximab, could also be effective in maintaining stable disease in patients with metastases. JSM6427 was shown to inhibit attachment of human retinal pigment epithelium (RPE) cell to fibronectin, migration, and proliferation. This inhibition was followed by concomitant reorganization of the RPE cytoskeleton with distinctive features resembling a quiescent state of the cells (44). Given previous findings showing the role of fibronectin in regulating dormancy via Intβ1-mediated cytoskeletal reorganization (Fig. 1; ref. 5), further examination of the potential use of this small molecule in preventing recurrence of breast cancer disease is warranted.

Recent identification of small molecules capable of specifically disrupting uPAR–integrin $\alpha_5\beta1$ interaction and downstream signaling via ERK (36) may provide novel therapeutic strategies to specifically target disseminated dormant tumor cells with high expression of uPAR (43). Therefore, the use of such small molecules may have therapeutic advantage in long-term treatment of cancer patients who may harbor clinically undetectable residual disease. These small molecules may retain dormant tumor cells in a prolonged asymptomatic state. Notably, when considering giving an antimetastatic preventive therapy using anti-Inβ1 inhibitor, for example, in the setting of breast cancer, one must take into account whether the patient will benefit from such long-term treatment. It has been noted that long-term therapy for hormone-responsive breast cancer is effective in reducing metastatic recurrence, but large numbers of women may be treated for benefit to relatively few, and the balance between benefit and side effects must be weighed (11). Hence, future identification of markers predictive of response to anti-Intβ1 therapy will help establish a personalized medicine approach for the prevention of cancer recurrence.

Conclusions

Intβ1 has been shown experimentally to be a key regulator in the switch from tumor cell dormancy to active proliferation, both *in vitro* in a 3D dormancy model and *in vivo*. Inhibition of Intβ1 or its downstream signaling partners has been shown to inhibit metastasis and to maintain tumor cells in a dormant state. Clinical studies on the effect of direct or indirect Intβ1 inhibition suggest that this approach may be valid and feasible. More needs to be learned about the extent of dormant cells in cancer patients, and biomarkers of patients who might benefit from therapy designed to prevent awakening of dormant cells need to be identified. As more patients are surviving their cancers for many years, a better understanding of tumor dormancy and treatments designed to prevent metastatic recurrences after long latency periods is needed for the long-term health of patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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