

$\beta 1$ and $\beta 3$ integrins in breast, prostate and pancreatic cancer: A novel implication (Review)

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Abstract. Integrins are transmembrane glycoproteins that consist of an α and a β subunit. Specific integrin heterodimers preferentially bind to distinct extracellular matrix (ECM) proteins to affect the characteristics of cells or the components of the ECM. Among the different integrins, $\beta 1$ and $\beta 3$ integrins serve essential roles in the progression of different cancer-associated processes, including the initiation, proliferation, survival, migration and invasion. Furthermore, previous studies have revealed a ratio between these two integrins in cancer cells, which also demonstrated that the functions of these two integrins are paradoxical. This indicated that the proliferation and metastasis of cancer cells are not always parallel and may be considered independently maintained. Additionally, the present review may assist in understanding certain aspects of cancer, and in making clinical decisions in a novel and more comprehensive manner.

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1. Introduction

Integrins are transmembrane glycoproteins that consist of an α subunit and a β subunit. A total of eight different β subunits may dimerize, in limited combinations, with 18α subunits to form ≥ 24 distinct integrins (1,2). Specific integrin heterodimers preferentially bind to distinct extracellular matrix (ECM) proteins. Integrins may bind the ligands in ECM directly, including fibronectin and laminin, to affect the characteristics of cells or the components of ECM. Regarding cancer cells, integrins serve roles in numerous aspects, including proliferation, survival, migration and invasion (1).

Integrins primarily affect cells in two ways, the first is through binding with proteins directly, including talin, vinculin and filamin, which may regulate the actin cytoskeleton of cells (3). The other is by phosphorylating the relative kinases, including focal adhesion kinases (FAKs), proto-oncogene tyrosine-protein kinase (Src)-family kinases (SFKs) and integrin-linked kinase (ILK), to activate or cooperate with the other cell signaling pathways (1,4). Additionally, integrin clustering on the cell surface and trafficking from the endosomes may affect the ligand affinity and quantity of the protein on cell surface (5-7).

Among the different integrins, $\beta 1$ and $\beta 3$ integrins serve essential roles in the progression of different types of cancer (1,2). Furthermore, previous studies investigating the association between these two integrins have demonstrated many different perspectives (8-11), together providing a novel and more comprehensive understanding of cancer.

2. Functions of $\beta 1$ integrin in cancer

In tumors, the $\beta 1$ subunit of integrin may combine with different α subunits, including $\alpha 4$, $\alpha 5$ and $\alpha 2$, to affect the characteristics of cancer cells, and the progression of tumors (1). The primary function of $\beta 1$ integrin is to form focal adhesion between cancer cells and ECM. This adhesion is the basis for the survival of cancer cells and is also associated with their migratory and metastatic capabilities (2). There are series of proteins in the cytoplasm, including talin, kindlin and ILK, which can affect the ligand affinity and activation of integrin, subsequently regulating focal adhesion and various characteristics of cancer cells, including invasion and metastasis (1,3,4). Simultaneously, $\beta 1$ integrin binding with

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variant ligands in ECM, including laminin-1 and fibronectin, may induce the secretion of certain cytokines and the progression of tumor (12). Furthermore, a previous study demonstrated that $\beta 1$ integrin may also affect cell-cell junctions (11). $\beta 1$ integrin may also affect the function of transforming growth factor- β (TGF- β) and regulate microRNA-200/zinc finger E-box-binding homeobox 2 to facilitate the expression of epithelial (E)-cadherin, which forms cell-cell junctions (9,11).

Proliferation and survival. Regarding numerous different types of cancer cells, the expression of $\beta 1$ integrin may facilitate the growth of tumors. $\beta 1$ integrin on the surface of the cells, which does not bind with the ECM, induces integrin-mediated death (IMD) of cells (1). However, when combined with their ligands, this integrin promotes the survival of cancer cells by activating different cell signaling proteins, including phosphoinositide 3-kinase/RAC- α serine/threonine protein kinase (AKT), FAKs and SFKs (1,13). While in certain tumors, $\beta 1$ integrin may also induce anoikis resistance of cancer cells in suspension by phosphorylating FAKs and AKT (14,15). Additionally, $\beta 1$ integrin may promote the proliferation of cells by phosphorylating FAKs and regulating SRC/mitogen-activated protein kinase (MAPK) to facilitate the expression of v-myc avian myelocytomatosis viral oncogene homolog (c-Myc) and cyclin D1 in cancer cells (16,17). Additionally, although the characteristics of the association between $\beta 1$ integrin and cancer stem cells are unclear, a previous study has identified that the expression of $\beta 1$ integrin in cancer stem cells is upregulated (18).

Metastasis. Regarding metastasis, the effect of $\beta 1$ integrin is controversial. A previous study suggested that mutant cellular tumor antigen p53 promoted $\beta 1$ integrin-dependent cell motility and invasion by reusing $\alpha 5\beta 1$ integrin, and epidermal growth factor receptor (EGFR) through recycling endosomes to the tumor cell surface, facilitating the metastasis of cancer cells (19,20). However, this metastasis induced by $\beta 1$ integrin depends on the expression of EGFR and the phosphorylation of AKT, which is a downstream signaling protein of EGFR (20). Furthermore, in certain types of cancer, the data demonstrated that $\beta 1$ integrin may activate Src or phosphorylate p38 and AKT to affect urokinase-type plasminogen activator (uPA), and matrix metalloproteinase (MMP)-2, promoting the metastasis of cancer cells (21,22). Additionally, due to the lack of vasculature, cancer cells enhance $\beta 1$ integrin activity to induce vessel cooption by adhering to the vascular basement membrane, thus providing immediate vasculature structures for newly metastatic or locally invasive of cancer cells (23).

In contrast, $\beta 1$ integrin may cooperate with TGF- β to enhance the expression of E-cadherin and inhibit metastasis in breast cancer (11). Additionally, downregulation of $\beta 1$ integrin induces not only epithelial-to-mesenchymal transition (EMT) and anoikis resistance in cancer cells, but also the expression of MMP-9, and vascular endothelial growth factor (VEGF), promoting migration and invasion (10).

Prognosis and clinical features. Similar to the controversy concerning metastasis, the associations between $\beta 1$ integrin and the clinical features of patients are unclear. In certain types of cancer, $\beta 1$ integrin is associated with poor prognosis or metastasis, including in prostatic cancer (15,24),

melanoma (25), gastric carcinoma (26) and hypopharyngeal squamous cell carcinoma (27). However, in other types of cancer, including breast cancer, studies have reported different or contradictory conclusions (28-30). This suggests that additional clinical observations and studies are required to understand this association.

3. Functions of $\beta 3$ integrin in cancer

Regarding $\beta 3$ integrin in tumors, the subtype that exhibits the widest range of functions is $\alpha v\beta 3$ integrin (1). It is associated with the growth, survival, invasion and metastasis of different cancer cells (10,31-35). Furthermore, in certain types of cancer, it is an indicator of increased lymph node or bone metastasis and decreased patient survival (36-38).

Similar to $\beta 1$ integrin, $\beta 3$ integrin may also bind with the components of ECM to form focal adhesions between cancer cells and the ECM. Concomitantly, in suspension, $\beta 3$ integrin prevents cancer cells from IMD by activating a non-canonical FAK-independent signaling pathway (31). Additionally, cancer cells as well as somatic cells, including endothelial cells, have been demonstrated to affect the growth of tumors by regulating angiogenesis (33).

Tumor growth and initiation. Regarding tumor growth, $\beta 3$ integrin serves roles in cancer cell survival, tumor initiation and tumor stemness, primarily by regulating cytokines (31,34).

A previous study demonstrated that $\beta 3$ integrin was associated with cancer stem cells (39). An additional study identified that, mechanistically, $\alpha v\beta 3$ integrin in the unbound state recruits GTPase KRas and Ras-related protein Ral-B to the tumor cell plasma membrane, leading to the activation of TANK binding kinase 1 and nuclear factor- κB (34). These two proteins are necessary and sufficient for tumor initiation, anchorage independence, and self-renewal (34). Additionally, in the $\beta 3$ signaling pathway, the receptor tyrosine kinase (RTK) is unnecessary for the survival of cancer cells; therefore, cancer cells may survive using $\beta 3$ integrin, without RTK, which will induce resistance to RTK inhibition therapy (34). Furthermore, in a suspension of pancreatic cancer cells, $\beta 3$ integrin was revealed to activate Src directly without phosphorylating FAKs, to facilitate the survival of tumor cells (31). Simultaneously, $\beta 3$ integrin in endothelial cells can affect the growth of tumors by regulating angiogenesis (33). A study reported that $\beta 3$ integrin decreases the expression of VEGF receptor 2 (VEGFR2), thus inhibiting VEGF/VEGFR-induced angiogenesis and tumor growth (33). These results suggest that $\beta 3$ integrin exhibits the ability to regulate RTK; however, the features of the association remain unclear (40).

EMT and metastasis. EMT affects the metastasis of tumors in different ways, including through migration, invasion and adhesion. $\beta 3$ integrin has been demonstrated to be associated with EMT in cancer cells. The integrin cooperates with TGF- β to form $\beta 3$ integrin-TGF- β receptor (T β R) type II complexes, which may activate T β R-II through the $\beta 3$ integrin/SRC signaling pathway and induce EMT by activating MAPKs (32). Furthermore, $\beta 3$ integrin elevates the expression of MMP-9 and VEGF in cancer cells, contributing to autocrine TGF- β signaling, and activation of EMT processes (10). Additionally,

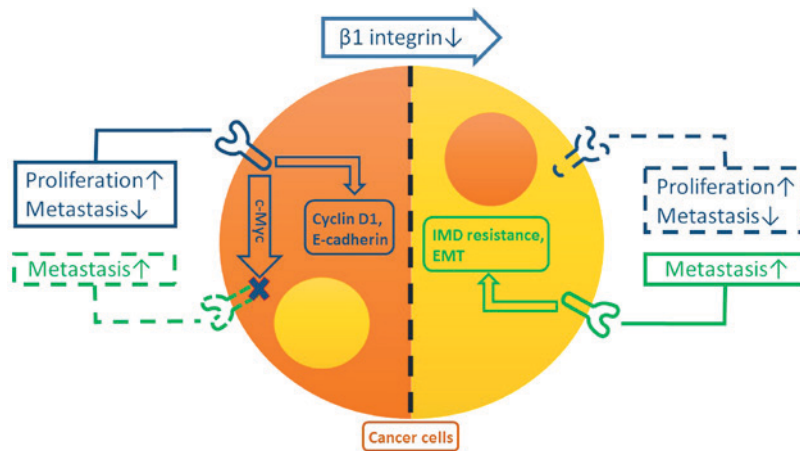


Figure 1. Functions of, and the association between, $\beta 1$ and $\beta 3$ integrins in cancer cells. $\beta 1$ integrin (blue) may facilitate cyclin D1 and E-cadherin in promoting proliferation and reducing the rate of metastasis in cancer cells, respectively. Concurrently, $\beta 1$ integrin inhibits the expression of $\beta 3$ integrin (green) in cancer cells, probably by the regulation of c-Myc. However, reductions in levels of $\beta 1$ integrin induce the compensatory expression of $\beta 3$ integrin, which promotes EMT and IMD resistance in cancer cells, resulting in metastasis. EMT, epithelial-mesenchymal transition; IMD, integrin-mediated death; E-cadherin, epithelial cadherin; c-Myc, v-myc avian myelocytomatosis viral oncogene homolog.

$\alpha v\beta 3$ integrin facilitates FAKs in regulating actin cytoskeleton remodeling and the induction of EMT (41). Concomitantly, $\beta 3$ integrin has the ability to activate canonical FAKs-dependent cytokines to affect cell migration and invasion (35). In addition, $\beta 3$ integrin is able to contribute to anchorage independence, thus facilitating cancer cell survival and increasing tumor malignancy, including lymph node metastasis (31). However, due to the co-expression of αv and $\beta 3$ subunits in cancer cells, future studies are warranted to identify which of these factors are essential for specific characteristics of cancer cells.

4. Ratio between $\beta 1$ and $\beta 3$ integrins in cancer cells

Regarding cancer cells, the expression levels of $\beta 1$ integrin and $\beta 3$ integrin are associated; and changes to either integrin exhibit significant effects on cancer cells (9-11) (Fig. 1). In breast cancer, the inactivation of $\beta 1$ integrin elicits the robust compensatory expression of $\beta 3$ integrin (10,11). However, the inhibition of $\beta 1$ integrin cannot induce the compensatory $\beta 3$ integrin expression in normal mammary epithelial cells (10). Furthermore, this compensatory $\beta 3$ integrin expression is essential for the growth and metastasis of tumors (10). A previous study demonstrated that when downregulating the expression of $\beta 1$ and $\beta 3$ integrins simultaneously, cancer cell survival was reduced (11). This suggests that, perhaps, when $\beta 1$ integrin is inactivated, the overexpression of $\beta 3$ integrin is necessary and important to maintain the survival, and characteristics of cancer cells.

In addition, this ratio between $\beta 1$ and $\beta 3$ integrin activity is not only involved for maintaining the functions of cancer cells, but also for changing the survival and metastasis rates of tumors. In pancreatic cancer, $\beta 1$ integrin is able facilitate the growth of tumors, and its inhibition reduces the proliferation of cancer cells (11). Additionally, the inhibition of $\beta 1$ integrin may affect the function of TGF- β , therefore attenuating the expression of E-cadherin to reduce the activity of the cell-cell junctions and enhancing motility and migration (11). Nonetheless, whether $\beta 3$ integrin is involved in these processes is controversial (10,11). In contrast, $\beta 3$ integrin can induce

EMT (9-11) and activate a non-canonical FAKs-independent signaling pathway, thus preventing cancer cells from undergoing IMD (31), and promoting the metastasis of cancer cells. Therefore, according to these studies, the functions of $\beta 1$ integrin are the promotion of proliferation and inhibition of metastasis, and the functions of $\beta 3$ integrin are opposing. This indicates that proliferation and metastasis of cancer cells are not always parallel, and may be considered independently maintained. Furthermore, the association between clinical features, including prognosis, and these two integrins, is complicated and paradoxical.

5. Targeting therapies

The expression of $\beta 1$ and $\beta 3$ integrins in cancer is involved in tumor progression, and various other pathways, which suggests that they are potential therapeutic targets. In preclinical studies, the antagonists of $\beta 1$ or $\beta 3$ integrin effectively inhibited tumor growth by affecting tumor cells and tumor-associated host cells (33,40,42-45). These antagonists include monoclonal antibodies and arginylglycylaspartic acid (RGD) peptide mimetics, which mimic the structure of the RGD sequence in the ligands, and inhibit the binding of integrins with their ligands. Furthermore, certain antagonists have been demonstrated to be effective in clinical trials (1).

Cilengitide, a RGD peptide mimetic, inhibits the function of $\alpha v\beta 3$ integrin and lengthens the survival time of patients with certain types of cancer with minimal side effects in clinical trials (46,47). Nevertheless, *in vivo*, specific studies identified that the continuous infusion of low doses of RGD peptides stimulates tumor growth and angiogenesis by increasing VEGFR2 recycling to the endothelial cells membrane, and promoting VEGF-induced migration (33,40). The angiogenesis of tumors may increase the delivery of chemotherapeutic agents to the target areas, which may explain why the combination of cilengitide and chemotherapy is more effective compared with chemotherapy alone (1).

Regarding monoclonal antibodies, etaracizumab, a function-blocking monoclonal antibody of $\alpha v\beta 3$ integrin, has

demonstrated anti-angiogenic activity, direct inhibition of the tumor cell growth and a reduction in bone metastasis rates in preclinical studies (43,45). In clinical trials, etaracizumab also demonstrated antiangiogenic activity, low toxicity and disease stabilization in patients with certain types of cancer (48,49). In addition, in preclinical and clinical trials, volociximab, a function-blocking monoclonal antibody against integrin $\alpha 5\beta 1$, has exhibited efficacy in inhibiting angiogenesis and tumor growth (42,50).

In specific previous studies, variant peptide antagonists have been developed. For example, ATN-161 is a non-RGD-based peptide inhibitor of integrin $\alpha 5\beta 1$ that inhibits cancer growth and metastasis *in vivo* (44). It also prolongs disease stabilization in patients with advanced solid tumors (51).

6. Future perspectives

Certain previous studies have demonstrated that the ratio between $\beta 1$ and $\beta 3$ integrins activity is associated with specific important cytokines in cancer cells (8,10,17). A previous study has also suggested that bound $\beta 1$ integrin may activate Src and extracellular signal-related kinase 1/2 MAPK in mammary epithelial cells, which induces the overexpression of c-Myc (17). An additional previous study revealed that MYC repressed transcription of the two subunits of $\alpha v\beta 3$ integrin, thus suppressing cancer metastasis in breast cancer cells (8). However, the lack of definitive data makes identifying the association between MYC, and the ratio between $\beta 1$ and $\beta 3$ integrins in cancer cells difficult. The details of the association between these two integrins require additional study.

Regarding clinical features, due to the association between these two integrins, relying on one of them to evaluate the status of patient is not comprehensive. The combination of $\beta 1$ and $\beta 3$ integrins for prognosis and treatment is necessary. In addition, with reference to previous studies, targeted therapy also requires the combination of these two targets, or a focus on the common downstream cytokines, including FAKs and SFKs, to increase effectiveness.

7. Conclusion

$\beta 1$ and $\beta 3$ integrins are essential focal adhesion proteins in various cancer cell types, which may affect the initiation, proliferation, survival and metastasis of tumors. Previous studies have demonstrated a ratio between these two integrins in cancer cells, with contradictory functions. This indicates that perhaps the proliferation and metastasis of cancer cells are not always parallel; therefore, may be considered independently maintained. Furthermore, the association between clinical features and these integrins is more complicated than previously expected. Therefore, there is a requirement for additional clinical and experimental studies to elucidate the role of these notable proteins.

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