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Integrin $\alpha 3 \beta 1$ as a breast cancer target

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Abstract

INTRODUCTION—Integrin receptors for cell adhesion to the extracellular matrix have important roles in all stages of cancer progression and metastasis. Since the integrin family was discovered in the early 1980's, many studies have identified critical adhesion and signaling functions for integrins expressed on tumor cells, endothelial cells, and other cell types of the tumor microenvironment, in controlling proliferation, survival, migration, and angiogenesis. In recent years, the laminin-binding integrin $\alpha 3 \beta 1$ has emerged as a potentially promising anti-cancer target on breast cancer cells.

AREAS COVERED—This review covers studies from the past decade that implicate integrins as promising anti-cancer targets and discusses the development of integrin antagonists as anti-cancer therapeutics. In particular, this paper discusses recent preclinical studies that have identified the laminin-binding integrin $\alpha 3 \beta 1$ as an appealing anti-cancer target, and considers the knowledge gaps that must be closed to fully exploit this integrin as a therapeutic target for breast cancer.

EXPERT OPINION—Although the tumor-promoting functions of $\alpha 3 \beta 1$ implicate this integrin as a promising therapeutic target on breast cancer cells, successful exploitation of this integrin as an anti-cancer target will require a better understanding of the molecular mechanisms whereby it regulates specific tumor cell behaviors, and the identification of the most appropriate $\alpha 3 \beta 1$ functions to antagonize on breast cancer cells.

Keywords

breast cancer; cell adhesion; cyclooxygenase-2 (Cox-2); extracellular matrix; integrin $\alpha 3 \beta 1$; laminin; matrix metalloproteinase-9 (MMP-9); tetraspanin CD151

1.1. Introduction

Current primary treatment options for breast cancer include chemotherapeutic strategies with cytotoxic drugs, such as anthracyclines and taxanes, often in combination with monoclonal antibody-based therapies [1]. Unconjugated monoclonal antibodies, which are generally safe and effective, are now available against a number of clinically validated targets on tumor cells or in the tumor microenvironment, including certain growth factors or their receptors that regulate tumor growth or angiogenesis [2]. Examples include trastuzumab/Herceptin™ against the human epidermal growth factor receptor (Her2/ErbB2), and bevacizumab against vascular endothelial growth factor (VEGF), each of which has been used either alone or in combination with chemotherapeutics to treat breast cancer in the clinic [3,4]. Despite these advances, breast cancer remains a leading cause of death in women, and progression to metastasis is the most significant cause of mortality [5]. Indeed, in recent years the average 5-year overall survival rate in patients with metastatic breast

cancer was only 12% (data compiled from 14 clinical trials spanning the years 1999 to 2009) [6], and there remains a critical need to identify more effective therapeutic targets to inhibit breast cancer in the clinic. Future developments in breast cancer therapy will depend in large part on the identification of novel functional targets for monoclonal antibodies or other agents to perturb the most relevant functions in tumor cells, or other cells in the tumor microenvironment, and to adapt suitable approaches and combination therapies for specific cancer types [2]. A major barrier to achieving this goal is our incomplete understanding of the molecular pathways that drive malignant progression and metastasis.

As the major receptors for cell adhesion to the extracellular matrix (ECM), integrins hold much promise as therapeutic targets to inhibit breast cancer [7,8]. Indeed, both normal and pathological functions of mammary tissue are regulated through integrin-mediated adhesion of the constituent cells to the ECM [9]. All members of the integrin family are heterodimeric, transmembrane glycoproteins that consist of one α and one β subunit. Eight different β subunits can dimerize in limited combinations with eighteen α subunits to form 24 different integrins with distinct, though often overlapping, ligand-binding specificities [7]. Integrins bind to ECM proteins, or other extracellular ligands, through their large extracellular domains, while their cytoplasmic domains can interact with cytoskeleton-associated proteins to mediate transmembrane ECM-cytoskeletal connections that regulate cell shape, polarized function, and motility [7,10,11].

Several characteristics of integrins make them attractive targets for strategies to inhibit breast cancer progression and metastasis, either as primary targets or as additional targets in combination therapies. First, integrins are universally important for controlling a number of essential cell functions during both early tumor growth and later stages of cancer progression, including tumor cell proliferation and survival, angiogenesis, invasion, and metastasis [8,12,13]. In addition, as cell surface proteins, integrins are relatively accessible to inhibitory agents. Finally, integrin-mediated signal transduction often controls multiple tumor cell functions or genes, suggesting that targeting a single integrin might produce the effect of a multi-combinatorial inhibitor treatment.

The general concept of targeting integrins in cancer is supported by an extensive literature showing that suppressing or blocking certain integrins can inhibit tumor growth, progression, or metastasis in a wide variety of preclinical cancer models [8,12,13]. These findings have led to the clinical testing of peptide antagonists (e.g. cilengitide, an RGD-mimetic that targets $\alpha v \beta 3$ and $\alpha v \beta 5$) and humanized monoclonal antibodies that target certain integrins (e.g. volociximab against $\alpha 5 \beta 1$; AbegrinTM against $\alpha v \beta 3$), although evidence suggests that such agents may work best in combination with other agents [8]. However, most such antagonists inhibit angiogenesis by targeting integrins that are expressed on endothelial cells of the tumor vasculature [14], and additional work is required to determine which integrins expressed on tumor cells are the best targets for inhibiting cancer progression. This task is complicated by the facts that tumor cells often express several distinct integrins, and that the repertoire of integrin expression varies among different cancers. Therefore, continued progress in the development of anti-integrin therapies for breast cancer will depend on elucidation of distinct roles that individual integrins play in disease progression, and identification of the most appropriate integrins to target on tumor cells. In the following sections, we will begin by reviewing roles that integrins play in cancer progression. We will then discuss the prospects of exploiting the laminin-binding integrin, $\alpha 3 \beta 1$, as a therapeutic target for breast cancer.

1.2. Integrin signaling in cancer cells

In addition to their well known roles in cell adhesion, integrins can transmit bidirectional signal transduction across the plasma membrane that regulates diverse cell processes, including proliferation, survival, and gene expression [7,15]. In general, this regulation occurs through direct or indirect interactions of the integrin cytoplasmic domain with a variety of signaling effectors inside the cell [7,15], as well as through lateral interactions of the integrin with other cell surface proteins (see below). Integrin signaling can occur as either “inside-out” signal transduction that modulates binding affinity of an integrin for its extracellular ligand, or “outside-in” signal transduction in response to extracellular cues [7].

A number of signaling proteins can mediate the initial events of outside-in integrin signaling, as reviewed in detail elsewhere [15]. Among the most extensively studied effectors of integrin signaling in cancer cells are the non-receptor tyrosine kinases, focal adhesion kinase (FAK) and Src. FAK and Src are both elevated in many types of cancers, including breast cancer, where they contribute to tumor growth and malignant progression, and both have been investigated as therapeutic targets of small molecule inhibitors (reviewed in [16,17]). Moreover, recent studies suggest that integrin signaling through FAK may promote mammary tumorigenesis by maintaining the pool of breast cancer stem cells that serve as primary targets of oncogenic transformation [18]. Upon integrin-mediated cell adhesion, FAK is activated by autophosphorylation of Tyr397, creating a high-affinity binding site for the SH2 domain of Src. Once bound to this site, Src can phosphorylate additional FAK Tyr residues to create binding sites for other signaling and adaptor proteins. Thus, the activated FAK/Src complex serves as a scaffold to link integrins to downstream signaling proteins, such as the Rac1 GTPase or the mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase-2 (ERK-2), c-Jun N-terminal kinase (JNK), or p38 [16,17]. Of particular relevance to the current review, integrin $\alpha 3 \beta 1$ has been shown to activate the FAK/Src complex and stimulate FAK signaling pathways in mammary and other epithelial cells [19,20]. These pathways, in turn, lead to activation of downstream effectors such as Rac1 or MAPKs (i.e. ERK1/2, JNK, or p38) that can alter a variety of cell behaviors including polarization, migration, proliferation, survival, and gene expression [15–17]. Thus, $\alpha 3 \beta 1$ -mediated activation of these pathways in breast carcinoma cells may contribute to tumor growth and metastasis, as depicted in Figure 1 and discussed further in Section 2.4.

Although many activated integrins can signal autonomously, signaling by some integrins may be enhanced or otherwise modulated through their interactions with integrin-associated proteins (IAPs) that also reside on the cell surface. Examples of such IAPs include tetraspanin proteins, caveolin, urokinase-type plasminogen activator receptor (uPAR), and certain growth factor receptors (for general reviews or examples, see [13,21–24]). Some of these interactions may occur at sites of cell adhesion to ECM, while others may occur at cell-cell adhesions or within specialized membrane microdomains (see above mentioned reviews). It stands to reason that the signaling function of an integrin can be regulated by its subcellular localization, such that the same integrin may signal differently from distinct pools within a cell. As discussed later, this possibility raises important considerations in the design of therapeutic strategies to target specific integrins on tumor cells (see Section 4).

1.3. Integrins as targets for anti-cancer therapies

As bidirectional signaling receptors at the interface of the tumor cell and its microenvironment, integrins regulate both tumor cell-mediated changes to the microenvironment that promote cancer progression, and tumor cell responses to such changes. Thus, integrins expressed on tumor cells present as appealing targets for anti-

cancer therapies [8,14,25]. However, tumor cells frequently express several different integrins, each with distinct functions in tumor growth and malignant progression. In addition, integrins are also expressed on other cell types present in the tumor microenvironment, including endothelial cells, inflammatory cells, and stromal fibroblasts, from where they can also regulate tumor progression. Therefore, effective exploitation of integrins as anti-cancer targets may require combinatorial approaches that simultaneously target multiple integrins, while at the same time incorporating strategies to target individual integrins within the appropriate cellular compartment of the tumor.

As already mentioned, most integrin inhibitors in clinical development are thought to alter tumor angiogenesis in large part by targeting integrins that are expressed on endothelial cells [8,14], and there remains a need to identify and validate appropriate integrin targets on tumor cells. Many integrins have been reported to show increased expression and/or have pro-tumorigenic/pro-metastatic functions in various cancer cells, including the laminin-binding integrins $\alpha 3\beta 1$, $\alpha 6\beta 4$ and $\alpha 6\beta 1$ [26–30], as well as $\alpha 2\beta 1$, $\alpha 1\beta 1$, $\alpha 5\beta 1$, and αv integrins [8]. Interestingly, a recent study showed that $\alpha 2\beta 1$ is a suppressor of metastasis in breast cancer cells [31], which further emphasizes the need to focus on functions that individual integrins play in specific cancer types as we move forward in our attempts to exploit them as therapeutic targets.

The remainder of this review will focus on integrin $\alpha 3\beta 1$ and its potential value as a therapeutic target to inhibit breast cancer. Although $\alpha 3\beta 1$ has been reported to bind several ECM proteins with varying affinities, it binds primarily to certain isoforms of the laminin family, including laminin-332 and laminin-511 [32], both of which have been linked to invasion and metastasis in breast and other carcinomas [33–35]. In addition, as discussed more below, lateral interactions of $\alpha 3\beta 1$ with other cell surface proteins (e.g. uPAR, the tetraspanin CD151) play important roles in modulating a variety of normal and pathological cellular functions [32]. *In vivo* functions of $\alpha 3\beta 1$ have been described in several epithelial tissues, including the skin, kidney, and mammary gland [20,36–41]. In the skin, $\alpha 3\beta 1$ is expressed in the basal keratinocytes of the epidermis, where it has important roles in developmental organization and maintenance of the basement membrane at the epidermal-dermal junction [32,36], organization of hair follicles [37], and expression by wound keratinocytes of pro-angiogenic factors [38]. In the kidney, $\alpha 3\beta 1$ is expressed in the glomerular podocyte that provides a scaffold for the glomerular capillaries and is essential for effective filtration, and $\alpha 3$ -null mice show severe defects in branching morphogenesis in the developing kidney [39]. These kidney defects, and similar branching defects observed in the developing lung bronchi of $\alpha 3\beta 1$ -deficient mice, may be attributable in part to defective basement membrane organization during organogenesis [39], similar to that observed in the developing skin [32,36].

In the normal mammary gland, $\alpha 3\beta 1$ is expressed in both myoepithelial cells and luminal epithelial cells, where it binds to basement membrane laminins and co-operates with growth factor and hormonal signaling to maintain normal breast epithelial function [40,41]. Although $\beta 1$ integrins were shown to be required for normal development of secretory alveoli and essential to maintain regenerative potential of the mammary gland [42,43], the absence of $\alpha 3\beta 1$ alone did not alter branching morphogenesis following transplantation of embryonic mammary epithelium from $\alpha 3$ -null mice into cleared mammary fat pads [44]. Moreover, conditional deletion of $\alpha 3\beta 1$ from mammary epithelium did not alter mammary gland organogenesis or differentiation [20]. Interestingly, however, a recent study using conditional $\alpha 3$ -knockout mice showed that $\alpha 3\beta 1$ -deficiency in the mammary epithelium leads to lactational deficiencies caused by defects in myoepithelial cell contractility, which appear to involve changes in FAK signaling that lead to imbalanced Rho/Rac signaling [20]. These findings indicate an essential, post-developmental role for $\alpha 3\beta 1$ in the regulation of

myoepithelial cell contraction that is required for milk ejection in the mammary gland. In the following sections, we will focus our discussion on functions of $\alpha 3\beta 1$ in breast cancer cells, and we will consider prospects for exploiting this integrin as a therapeutic target.

2.1. Pro-tumorigenic functions of integrin $\alpha 3\beta 1$ in breast cancer cells

Enhanced expression of $\beta 1$ integrins has been associated with malignant breast cancer progression and correlates with decreased survival of breast cancer patients [45,46]. However, when interpreting these findings it is important to consider the broad functional heterogeneity of the $\beta 1$ integrin subfamily, since distinct $\alpha\beta 1$ heterodimers clearly have different functions [7]. Indeed, studies of clinical breast cancer samples have revealed different expression patterns for individual $\beta 1$ integrins, where expression of some (e.g. $\alpha 3\beta 1$) has been reported to persist or increase in breast carcinoma compared with normal tissue [47], while expression of others (e.g. $\alpha 2\beta 1$) has been reported to decrease [31]. Interestingly, recent findings in a spontaneous mouse model of breast cancer revealed a role for $\alpha 2\beta 1$ as a suppressor of metastasis [31], which is in contrast with the cancer-promoting functions that have been described in breast cancer cells for other $\beta 1$ integrins, such as $\alpha 3\beta 1$ and $\alpha 6\beta 1$ [27,29,30]. This finding, combined with the different expression patterns that have been observed among $\beta 1$ integrins in breast cancer, may indicate a role for integrin switching in breast cancer progression. Indeed, integrin switching occurs in squamous cell carcinoma (SCC), where transformed keratinocytes undergo a switch from $\alpha v\beta 5$ to $\alpha v\beta 6$ that facilitates carcinoma progression [48]. While integrin switches could be linked to specific stages of cancer progression, it remains to be determined whether such switches occur within tumor cells during progression, or reflect the clonal expansion of tumor cell subpopulations with different integrin expression profiles. In any case, a better understanding of integrin switches may be essential for the successful exploitation of individual $\beta 1$ integrins as therapeutic targets.

In the case of $\alpha 3\beta 1$, a positive correlation with metastasis in clinical samples was accompanied by pro-invasive roles for this integrin in human breast cancer cells [47]. It is possible that roles for $\alpha 3\beta 1$ in breast carcinoma are context-dependent, perhaps varying with stage or tumor type, since both positive and negative correlations have been reported between $\alpha 3\beta 1$ expression and metastatic potential (reviewed in [26]). However, preclinical studies have shown that $\alpha 3\beta 1$ promotes breast cancer cell functions that are associated with malignant progression and metastasis, including enhanced invasion [47], adhesion to cortical bone matrix or lymph node stroma [49,50], and pulmonary arrest of circulating cancer cells [29]. In addition, $\alpha 3\beta 1$ is pro-tumorigenic *in vivo*, as stable shRNA-mediated suppression of $\alpha 3\beta 1$ in the highly aggressive human breast cancer cell line, MDA-MB-231, caused reduced growth of ectopic or orthotopic tumors in nude mice [27].

At least some pro-tumorigenic functions of $\alpha 3\beta 1$ are likely to result from its ability to increase the expression of matrix metalloproteinase-9 (MMP-9) [47], as this extracellular protease is known to promote both cell invasion and tumor angiogenesis in preclinical models of breast cancer and other cancers [51–53]. MMP-9 can facilitate tumor progression by degrading ECM proteins, as well as by activating ECM-bound growth factors that promote cell growth, invasion and angiogenesis [52]. Although much of the MMP-9 in the tumor microenvironment is produced by stromal or inflammatory cells [52,54], tumor cell-derived MMP-9 may prime early tumor growth at stages that precede the induction of MMP-9 within stromal compartments, and it may also contribute at later stages of progression [53,55]. Transformed mouse keratinocytes or human SCC cells in which $\alpha 3\beta 1$ was genetically ablated or suppressed by RNAi, respectively, display reduced expression of MMP-9 mRNA [55–57]. Moreover, studies with function blocking antibodies have shown

that $\alpha 3\beta 1$ promotes MMP-9 expression in human breast cancer cells, although probably through a translational or post-translational mechanism [47].

To date, clinical trials of drugs that block MMP function have been unsuccessful, due in large part to their focus on patients with late-stage cancers where these inhibitors are now known to be ineffective [51,58]. In addition, MMP inhibitors often show broad specificity and/or produce side effects on normal tissue function [58]. Interestingly, $\alpha 3\beta 1$ -dependent induction of MMP-9 is a trait that has been shown to be acquired during keratinocyte immortalization [55,56]. This regulation shares similarity with other pathways of MMP-9 induction that are acquired by certain tumor cells in response to TGF β [59] or Ca^{2+} signaling [60]. Importantly, pathways of MMP-9 induction that are acquired by cancer cells would be attractive therapeutic targets, as targeting such pathways might avoid unwanted side effects on normal cells. While it is not yet known whether $\alpha 3\beta 1$ -dependent MMP-9 expression that has been described in breast cancer cells is an acquired phenotype [47], this question is worth exploring. Indeed, some of the above mentioned limitations of current MMP inhibitors might be circumvented through targeting of acquired, $\alpha 3\beta 1$ -dependent pathways of MMP-9 induction, if this can be done at appropriately early stages of cancer progression.

Pro-tumorigenic functions of $\alpha 3\beta 1$ in breast cancer cells also stem from its recently identified role in promoting expression of the cyclooxygenase-2 (Cox-2) gene. Indeed, Cox-2 mRNA expression was reduced dramatically in MDA-MB-231 cells in which $\alpha 3$ was stably suppressed using shRNA, which was accompanied by reduced invasive potential *in vitro* and reduced tumor growth in orthotopic or ectopic models [27]. This is a significant finding, since Cox-2 is expressed highly in breast cancer, where it mediates increased prostaglandin E(2) levels that promote tumor angiogenesis and metastasis. Preclinical studies in several xenograft or murine breast cancer models support a necessary and sufficient role for Cox-2 in promoting tumor growth and metastasis [61–63]. Moreover, Cox-2 has been the target of chemo-preventative drugs in breast cancer and other cancers (for reviews on this subject, see [64–66]). Indeed, Cox-2 has been targeted using non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin or Cox-2-specific inhibitors (coxibs) such as celecoxib (CelebrexTM), rofecoxib (VioxxTM), and valdecoxib (BextraTM), and clinical data suggest that treatment with Cox-2 inhibitors may improve survival in patients with colon cancer [67] or breast cancer [68]. However, significant side effects of some Cox-2 inhibitors include gastrointestinal, kidney and liver problems [69], which has lead to the withdrawal of some coxibs from the market [70]. Importantly, the finding that Cox-2 gene expression is reduced in breast cancer cells following suppression of $\alpha 3\beta 1$ [27] suggests that targeting this integrin on tumor cells may provide a means of suppressing Cox-2 in breast cancer without the adverse side effects that have been associated with some Cox-2 inhibitors.

2.2. Roles for laminin-binding activity and integrin-associated proteins in pro-tumorigenic functions of integrin $\alpha 3\beta 1$

Development of strategies to block $\alpha 3\beta 1$ function in breast cancer cells will require a thorough understanding of how these functions are regulated by intermolecular interactions between $\alpha 3\beta 1$ and its associated proteins. It is likely that many pro-tumorigenic and pro-metastatic functions of $\alpha 3\beta 1$ are attributable to its ability to bind to laminins in the ECM of the tumor microenvironment, as both laminin-332 and laminin-511 have roles in promoting invasion and metastasis of breast and other carcinomas [33–35]. Indeed, laminin-332 that is secreted by mammary epithelial cells can enhance motility and aggressive features of breast cancer cells [71], and $\alpha 3\beta 1$ -mediated adhesion to laminin-332 was implicated in the pulmonary arrest of circulating tumor cells in an experimental metastasis model [29].

Binding of $\alpha 3\beta 1$ to ECM may have a dichotomous role in modulating tumor cell invasion, as it not only directly facilitates cell motility and migration, but it can also regulate expression and/or function of MMPs (discussed above) and other extracellular proteases that enhance matrix proteolysis [47,55,56,72,73].

In addition to its laminin-binding activities, $\alpha 3\beta 1$ can undergo lateral interactions with other cell surface proteins that may regulate some of its functions in tumor cells. While this ability is not a unique property of $\alpha 3\beta 1$, this integrin appears to have a particularly strong propensity for such associations. Indeed, numerous studies have documented interactions of $\alpha 3\beta 1$ with several different cell surface proteins, including certain tetraspanin proteins and uPAR [26,32,74,75]. In particular, interactions with the tetraspanin protein, CD151, have been linked to several pro-tumorigenic functions of $\alpha 3\beta 1$ in breast cancer cells. CD151 forms stoichiometric complexes with a few integrins, but it binds most robustly to $\alpha 3\beta 1$ [26,74]. Through this interaction, CD151 can recruit $\alpha 3\beta 1$ into specialized tetraspanin-enriched microdomains (TEMs) on the cell surface, wherein its signaling functions may be influenced by other tetraspanins or TEM-associated proteins [23,26]. Like $\alpha 3\beta 1$, CD151 has been implicated at both early and late stages of cancer progression. Indeed, studies from several groups in different cancer models have shown that CD151 promotes tumor growth and metastasis, identifying the $\alpha 3\beta 1$:CD151 complex as a potential therapeutic target [26,30,76–78]. In breast cancer cells, RNAi-mediated suppression of CD151 reduces tumor growth in orthotopic or ectopic xenografts [30,77]. In addition, increased CD151 expression in breast cancer has been correlated with both higher tumor grade and estrogen receptor (ER)-negative status [30], and is associated with decreased overall survival, increased lymph node involvement, and high grade of ductal carcinoma *in situ* [76,77].

While the mechanisms whereby CD151 promotes tumor growth and metastasis are not yet known, some CD151 functions in breast cancer cells require binding to its integrin partners. These functions include mediating the response of breast cancer cells to endothelial cell-secreted factors [77], and mediating scattering or proliferative responses to TGF β [79]. Interestingly, CD151:integrin complexes have also been linked to ErbB2 activation and integrin-to-FAK signaling that occurs upon cell adhesion to laminin-332, and disruption of this signaling axis increases the sensitivity of breast cancer cells to drugs that antagonize ErbB2 [80]. CD151 can also regulate glycosylation of $\alpha 3\beta 1$ in epithelial cells, which is correlated with altered cell migration toward laminin-332 [81], indicating that CD151-mediated, post-translational modification of $\alpha 3\beta 1$ may affect tumor cell invasion. Importantly, the extent to which the CD151- $\alpha 3\beta 1$ complex regulates tumor cell functions independently of $\alpha 3\beta 1$ binding to its laminin ligands in the ECM is still not completely clear (Figure 1). Some studies support the idea that interactions with CD151 can regulate binding of $\alpha 3\beta 1$ or $\alpha 6$ integrins to their laminin ligands in the ECM [82–84]. On the other hand, $\alpha 3\beta 1$ association with CD151 was shown to promote cadherin-mediated cell-cell adhesion through a mechanism that did not involve integrin binding to laminin [85], suggesting that some functions of the CD151: $\alpha 3\beta 1$ complex may occur independently of integrin-ECM binding. Potential impact of these different models on development of $\alpha 3\beta 1$ -targeting strategies is discussed later in Section 4.

As reviewed elsewhere, interactions between some integrins and uPAR, a key regulator of the plasmin proteolytic cascade, may have important functional roles in some cancer cells [86]. Indeed, uPAR has been shown to regulate $\alpha 3\beta 1$ function in some cells [75], and uPAR: $\alpha 3\beta 1$ interactions have been linked to increased MAPK signaling and enhanced gene expression that promotes aggressive oral SCC [87]. Certain integrin-uPAR complexes may also regulate integrin signaling and migration in breast cancer cells, and they have been implicated in tumor progression and bone metastasis *in vivo* [88,89]. However, roles for the uPAR: $\alpha 3\beta 1$ complex have not been explored extensively in breast cancer cells.

2.3. Integrin $\alpha 3\beta 1$ regulates pro-angiogenic crosstalk to vascular endothelial cells

The ability of $\alpha 3\beta 1$ to promote the expression of MMP-9 [47] and Cox-2 [27] in breast cancer cells may reflect an important role for this integrin in crosstalk from tumor cells to endothelial cells that promotes tumor angiogenesis (Figure 2). Consistent with such a role, $\alpha 3\beta 1$ expression on epidermal keratinocytes has been shown to promote their secretion of pro-angiogenic factors that induce endothelial cell migration, and which may contribute to wound angiogenesis [38]. This regulation represents a novel mode of angiogenic induction by integrins that extends beyond their classical roles in directly regulating endothelial cell function. Given the similarities that exist between wound healing and tumorigenesis [90], $\alpha 3\beta 1$ may have a similar role in mediating crosstalk from tumor cells to endothelial cells that promotes angiogenesis. Consistent with this idea, expression of $\alpha 3\beta 1$ on MDA-MB-231 cells regulates the production of soluble factors that promote endothelial cell migration [27]. This regulation may be specific to $\alpha 3\beta 1$ (at least among integrins expressed by these cells), since $\alpha 3\beta 1$ -deficient cells remained adherent through other endogenous integrins [27]. The ability of $\alpha 3\beta 1$ to induce Cox-2 and MMP-9 expression in breast cancer cells strongly supports a pro-angiogenic role for this integrin, since both of these proteins are involved in the angiogenic switch during tumor progression [51,91]. The necessity of $\alpha 3\beta 1$ binding to laminin for these effects is not yet clear. However, it is worth pointing out that the interaction of $\alpha 3\beta 1$ with CD151 on breast cancer cells has been implicated in some aspects of crosstalk that occur between endothelial cells and tumor cells [77].

2.4. $\alpha 3\beta 1$ -dependent mRNA stability: a possible mechanism for the regulation of cancer-promoting genes

MMP-9 expression is $\alpha 3\beta 1$ -dependent in murine keratinocytes that harbor a loss-of-function p53 mutation and express oncogenic RasV12, while it is independent of $\alpha 3\beta 1$ in primary keratinocytes, indicating that the pathway by which $\alpha 3\beta 1$ induces MMP-9 gene expression is acquired by tumor cells [55,56]. MMP-9 expression was similarly $\alpha 3\beta 1$ -dependent in immortalized human keratinocytes, and in certain SCC cells that harbor p53 mutations [55]. In immortalized cells, $\alpha 3\beta 1$ -dependent induction of MMP-9 occurs through enhanced mRNA stability [57]. Other studies have shown that MMP-9 mRNA stability is regulated in response to cytokines and growth factors through AU-rich elements (AREs) that reside in the 3'-untranslated region (3'-UTR) and control the rate of mRNA decay [59,92]. It seems likely that $\alpha 3\beta 1$ -mediated induction of MMP-9 also involves these 3'-UTR AREs, although other unidentified mRNA stability elements could also be involved. Interestingly, neoplastic transformation can stabilize ARE-containing mRNAs [93], and enhanced mRNA stability of growth- or invasion-promoting genes has been linked to human cancers, including breast cancer [94,95]. Post-transcriptional regulation of MMP-9 might be of particular importance during tumor growth or metastasis, when tumor cells may need to alter its production rapidly in response to changing microenvironmental cues. It remains to be determined whether $\alpha 3\beta 1$ -dependent mRNA stability that leads to MMP-9 induction extends to other cancer-associated genes, or whether this regulation is acquired in breast cancer cells as it is in some SCC models [55]. However, clear roles are beginning to emerge for $\alpha 3\beta 1$ in the regulation of pro-tumorigenic genes in breast cancer cells [27], and at least some of this regulation may occur through integrin-dependent changes in mRNA processing that could alter stability of mRNA transcripts [96].

Although pathways whereby $\alpha 3\beta 1$ regulates mRNA stability are not yet known, several MAPKs that are known to lie downstream of integrin signaling have been linked to mRNA stability, including p38, JNK, and ERK [97–99]. In particular, p38 has emerged as an

important regulator of ARE-mediated mRNA stability in several systems [97,100,101]. For example, α_v integrins may induce urokinase plasminogen activator (uPA) expression through ARE-mediated mRNA stability in response to Rac1-MKK3-p38 signaling [102]. Src family kinases, which are known effectors of integrin signaling in cancer cells (see Section 1.2), are also strong candidates for initiating signaling pathways that promote mRNA stability [103]. Given the roles that the FAK/Src signaling axis is likely to play in breast cancer growth and malignant progression (reviewed in [16,17], and discussed above in Section 1.2), it is significant that integrin $\alpha_3\beta_1$ can stimulate FAK in mammary epithelial cells or other epithelial cells [19,20,104], especially since FAK signaling can lead to the activation of downstream effectors such as Rac1 and/or the MAPKs, p38 and ERK. Indeed, the afore-mentioned involvement of these effectors in stabilizing mRNA transcripts implicates FAK activation as a candidate pathway through which $\alpha_3\beta_1$ enhances mRNA stability in tumor cells.

3. Conclusion

As described in the preceding section, preclinical studies have revealed that $\alpha_3\beta_1$ promotes pro-tumorigenic gene expression and function in breast cancer cells, which implicates this integrin as a promising therapeutic target. In addition to its established roles in tumor cell invasion, recent studies support an additional role for $\alpha_3\beta_1$ on tumor cells in the regulation of genes that promote crosstalk to endothelial cells and alter the tumor microenvironment in ways that promote angiogenesis and tumor growth [27,38,57] (Figure 2). Nevertheless, roles for $\alpha_3\beta_1$ in cancer are clearly complex, due to its ability to interact with both laminins present in the ECM of the tumor microenvironment and other cell surface proteins on tumor cells. Indeed, the ability of $\alpha_3\beta_1$ to associate with proteins such as CD151 or uPAR, perhaps in some cases independently of binding to ECM laminins, suggests the intriguing possibility that this integrin exists within functionally distinct and separable intracellular pools. In this case, $\alpha_3\beta_1$ adhesion or signaling functions within each pool might be determined by its interactions with other extracellular, cell surface, or cytoplasmic components that are also enriched in those pools. Therefore, attempting to block $\alpha_3\beta_1$ function using current strategies that exploit antagonists of ECM-binding may not be practical [14], and a better understanding of how $\alpha_3\beta_1$ interacts with its ECM ligands and/or IAPs, possibly within distinct subcellular pools, may be required prior to development of effective therapeutic strategies to target this particular integrin. Strategies to target $\alpha_3\beta_1$ will be further complicated by the opposite effects on angiogenesis that have been observed following suppression of this integrin in different cellular compartments (discussed below). In summary, exploitation of $\alpha_3\beta_1$ as an anti-cancer target will require a better understanding of how its signaling functions are regulated by ECM-dependent versus ECM-independent interactions, how these different interactions are linked to specific tumor cell functions, and how functions of this integrin differ between distinct cell types present in the tumor microenvironment.

4. Expert opinion

The ability of $\alpha_3\beta_1$ to regulate expression of multiple genes in breast cancer cells [27] suggests the intriguing concept that suppressing $\alpha_3\beta_1$ on tumor cells may inhibit multiple processes that promote tumor invasion and/or the angiogenic switch, thereby producing the effect of a combinatorial strategy (Figure 3). This concept is supported by $\alpha_3\beta_1$ -dependent regulation of Cox-2 and MMP-9, each of which has established roles in promoting breast cancer invasion and angiogenesis, and both of which have been targeted in clinical studies [58,64,65].

Nevertheless, several significant challenges remain to be overcome before $\alpha 3\beta 1$ can be exploited as a therapeutic target. For example, $\alpha 3\beta 1$ has important roles in the normal physiology of many tissues, so $\alpha 3\beta 1$ -blocking agents that fail to discriminate between tumor cells and normal cells might produce undesirable side-effects. A potential solution to this limitation is to focus the search for therapeutic targets on molecular components of $\alpha 3\beta 1$ -mediated pathways that are acquired specifically by cancer cells during malignant progression. We believe that $\alpha 3\beta 1$ -dependent pathways that control MMP-9 mRNA stability, and perhaps mRNA stability of other tumor-promoting genes, may represent such targets (see Section 2.4). For example, $\alpha 3\beta 1$ also regulates other pro-tumorigenic/pro-angiogenic genes that are already known to be regulated through mRNA stability, including Cox-2 and the proliferin family member, MRP3/PRL2C4 [27,38]. Indeed, Cox-2 mRNA stability is regulated through AREs within the 3'-UTR of the transcript in response to growth factors [105,106], and MRP3 mRNA stability is increased in some immortalized cells [107]. It is possible that $\alpha 3\beta 1$ regulates intracellular pathways of post-transcriptional mRNA stability, either directly through regulation of ARE-binding proteins or indirectly through altered mRNA processing that determines inclusion of mRNA stability elements in the target transcript [57,96]. Elucidating the mechanisms whereby $\alpha 3\beta 1$ controls mRNA stability of MMP-9 or other genes may identify pathways in tumor cells on which to focus the search for novel therapeutic targets. Indeed, if these pathways are acquired by tumor cells, as has been observed for $\alpha 3\beta 1$ -dependent induction of MMP-9 in tumorigenic keratinocytes [55], then determining the molecular nature of this switch in $\alpha 3\beta 1$ function might reveal a vulnerability that can be exploited as a cancer cell-specific therapeutic target.

A limitation of anti-integrin agents that are currently in clinical development is that they are not integrin-specific, instead targeting two or more integrins that bind to similar motifs (i.e. RGD) that occur within their ligands [8]. In contrast, targeting some of the unique binding interactions that have been identified for $\alpha 3\beta 1$, such as the $\alpha 3\beta 1$:CD151 complex, might represent an integrin-specific approach to inhibit certain breast cancer cell functions [77,79]. However, pro-tumorigenic/pro-metastatic functions of $\alpha 3\beta 1$ have also been linked to its interactions with laminins, and as already mentioned it remains unclear the extent to which interactions of $\alpha 3\beta 1$ with laminins and CD151 are functionally separate or may be intertwined (see Figure 1). Therefore, the exploitation of $\alpha 3\beta 1$ as an anti-breast cancer target will require a clearer understanding of whether these distinct binding interactions work synergistically, or sometimes separately, to drive certain aspects of cancer progression. Towards this goal, recent studies have begun to elucidate in greater molecular detail the nature of $\alpha 3\beta 1$ binding interactions with both CD151 [80,82,108] and its laminin ligands [109,110]. These studies have also led to the generation of engineered $\alpha 3\beta 1$ mutants that fail to bind to either laminins or CD151 [82,111,112], which may be useful reagents in preclinical studies to distinguish the individual importance of these interactions for $\alpha 3\beta 1$ -dependent tumor cell functions and may provide the basis for designing therapeutic agents that block specific $\alpha 3\beta 1$ -binding interactions to inhibit the corresponding cell functions that they control. For example, one $\alpha 3\beta 1$ -dependent step in tumor progression might be vulnerable to a conventional strategy of using an antagonist that blocks binding to laminin, while another step might require an alternative strategy that instead (or additionally) targets the interaction between $\alpha 3\beta 1$ and CD151.

Another limitation of some integrin antagonists is that their effects can vary depending on the treatment dose and cancer type being targeted. This important issue is highlighted by recent studies of RGD mimetics, which have produced mixed results in clinical and preclinical models of different cancer types [8]. For example, the RGD mimetic cilengitide, which targets integrins $\alpha v \beta 3$ and $\alpha v \beta 5$, showed some promise in clinical trials involving patients with recurrent glioma [113], while another study showed that low doses of cilengitide stimulated angiogenesis and tumor growth in preclinical models of melanoma

and Lewis lung carcinoma [114]. It seems likely that the paradoxical effects of cilengitide on angiogenesis were due to some extent to differences between the clinical and preclinical models that were used in these studies. Nevertheless, these dose-dependent and/or cancer-specific effects of cilengitide treatment highlight important limitations that may also extend to antagonists of other integrins, including $\alpha 3 \beta 1$.

The efficacy of an integrin antagonist for treatment of a particular type of cancer may also be determined by different roles that the target integrin plays on tumor cells versus endothelial cells of the tumor vasculature, making it difficult or impossible to predict a clinical outcome upon inhibiting the integrin. In particular, a potential barrier to exploiting $\alpha 3 \beta 1$ as a therapeutic target may arise from the paradoxical roles that this integrin appears to play in the regulation of angiogenesis from within tumor cells versus endothelial cells, as revealed through both xenograft studies and genetic studies using conditional $\alpha 3$ -knockout mice. On one hand, deletion of $\alpha 3 \beta 1$ from epidermal keratinocytes was correlated with reduced wound angiogenesis and reduced expression of pro-angiogenic factors [38], and suppression of $\alpha 3 \beta 1$ in breast cancer cells was similarly linked to reduced expression of pro-angiogenic factors [27]. On the other hand, endothelial cell-specific deletion of $\alpha 3 \beta 1$ caused enhanced pathological angiogenesis through a mechanism that involves regulation of endothelial-produced VEGF [115]. These opposing angiogenic effects of deleting or suppressing $\alpha 3 \beta 1$ in different cellular compartments most likely reflects distinct signaling functions that this integrin has in epithelial/tumor cells versus endothelial cells. Perhaps most importantly, these findings indicate that successful exploitation of $\alpha 3 \beta 1$ as a therapeutic target may require that it be inhibited specifically within tumor cells, but not within the tumor vasculature, if an anti-angiogenic effect is to be achieved. Therefore, it may be necessary to couple development of $\alpha 3 \beta 1$ -targeting agents with other strategies to deliver such agents specifically to tumor cells [116].

In summary, further study of the mechanisms and signaling pathways whereby integrin $\alpha 3 \beta 1$ promotes pro-tumorigenic gene expression and tumor cell function should reveal novel therapeutic targets and open up new avenues of breast cancer treatment. Nevertheless, the complex modes of $\alpha 3 \beta 1$ regulation, combined with the opposing effects that this integrin may have on angiogenesis from within different cellular compartments of the tumor microenvironment, indicate that successful exploitation of $\alpha 3 \beta 1$ as a therapeutic target may require the development of agents that block individual $\alpha 3 \beta 1$ functions specifically in tumor cells. Adding to this complexity, other integrins can also contribute to breast cancer cell function [30,31], suggesting that the most successful strategies may require combinatorial approaches that target several integrins within the appropriate cellular compartments.

Information for the “Article Highlights” box

- As the major receptors for cell adhesion to the extracellular matrix, members of the integrin family hold considerable promise as therapeutic targets to inhibit breast cancer.
- In addition to regulating cell adhesion, integrins mediate bidirectional signal transduction across the cell membrane that regulates a variety of tumor cell functions.
- Most integrin antagonists currently in clinical development inhibit tumor angiogenesis by targeting endothelial cell integrins, and there remains a need to identify and validate integrin targets that are expressed on tumor cells.
- Preclinical studies with human breast cancer cells have revealed key roles for $\alpha 3 \beta 1$ in the regulation of cancer cell functions that promote malignant progression and metastasis.

- In addition to its laminin-binding activities, $\alpha 3\beta 1$ can undergo lateral interactions with other cell surface proteins, such as the tetraspanin CD151, which regulate some of its functions in tumor cells.
- $\alpha 3\beta 1$ in breast cancer cells promotes expression of at least two pro-angiogenic factors, MMP-9 and Cox-2, which may reflect an important role in crosstalk to endothelial cells that drives tumor angiogenesis.
- Roles are beginning to emerge for $\alpha 3\beta 1$ in the regulation of pro-tumorigenic/pro-angiogenic genes, some of which may occur through alterations of mRNA processing and stability.
- Preclinical studies have revealed important roles for $\alpha 3\beta 1$ on breast cancer cells in pro-angiogenic gene expression, tumor growth, and metastasis, identifying this integrin as an appealing future target of anti-cancer therapies.
- The ability of $\alpha 3\beta 1$ to regulate expression of multiple genes in breast cancer cells suggests that suppressing this integrin may inhibit multiple processes that promote tumor growth and invasion, thereby producing the effect of a combinatorial strategy.

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Declaration of interest

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Figure 1.

Some studies have shown that association of integrin $\alpha 3\beta 1$ with the tetraspanin protein CD151 can regulate its binding affinity for laminin ligands present in the extracellular matrix (ECM) and contribute to subsequent signaling functions. However, other studies have identified functions of the CD151: $\alpha 3\beta 1$ complex that appear independent of integrin-ECM binding. Interestingly, FAK has been shown to be activated by both the CD151: $\alpha 3\beta 1$ complex, and binding of $\alpha 3\beta 1$ to ECM, suggesting that some pro-tumorigenic functions of $\alpha 3\beta 1$ may occur via FAK/Src-to-MAPK signaling pathways, as depicted (see text and references [16,17] for details). As indicated by the question mark (?), the full extent of functional interactions between ECM-bound $\alpha 3\beta 1$ and CD151-bound $\alpha 3\beta 1$ is not yet clear, which leaves open the possibility that there may be functionally distinct pools of $\alpha 3\beta 1$ within the same cell. Other membrane bound proteins have also been shown to interact laterally with $\alpha 3\beta 1$, leading to both 'outside-in' and 'inside-out' signaling events (see text for details).

Figure 2.

The ability of $\alpha 3 \beta 1$ on breast cancer cells to promote expression of MMP-9, Cox-2, and possibly other genes that mediate ECM remodeling and/or crosstalk to endothelial cells points towards an important role for this integrin in regulating the ability of the cancer cell to alter the tumor microenvironment in ways that promote angiogenesis and malignant growth.

Figure 3.

Recent findings indicate that integrin $\alpha 3 \beta 1$ can regulate the expression of multiple genes in breast cancer cells (designated schematically as A–G), some of which have been implicated in different aspects of tumor growth, invasion, and/or the angiogenic switch, which suggests that antagonists of $\alpha 3 \beta 1$ function might produce the effect of a combinatorial strategy. ECM, extracellular matrix.