Review

Involvement of $\alpha_6\beta_4$ integrin in the mechanisms that regulate breast cancer progression

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Abstract

Integrin $\alpha_6\beta_4$ is mostly expressed in epithelial tissues and endothelial and Schwann cells. Expression of $\alpha_6\beta_4$ is increased in many epithelial tumours, implicating its involvement in tumour malignancy. Moreover, this integrin activates several key signalling molecules in carcinoma cells, but its ability to activate the phosphatidylinositol 3-kinase/Akt pathway is among the mechanisms by which $\alpha_6\beta_4$ integrin regulates tumour behaviour. In this review we discuss the biological and clinical features of $\alpha_6\beta_4$ integrin that allow it to promote tumour survival and progression of mammary tumours.

Introduction

Integrins belong to a family of heterodimer transmembrane receptors whose major function is to mediate adhesion and migration through extracellular matrix components [1,2]. They also regulate other processes such as cell proliferation, growth and differentiation [3]. Studies conducted during the past 10 years have provided evidence that integrins are involved in mechanisms that influence tumour progression by activating various intracellular signalling pathways [4].

Among the integrin family of receptors, $\alpha_6\beta_4$ integrin was initially identified as tumour-specific antigen-180 [5]. A subsequent study [6] demonstrated the true identity of tumour-specific antigen-180 to be $\alpha_6\beta_4$ integrin. In most epithelial tissues, including mammary epithelium, the distribution of $\alpha_6\beta_4$ integrin is restricted to the basal layer [7,8], where it participates in the formation and stabilization of hemidesmosomes [9]. Most epithelial tumours lack hemidesmosomes, and $\alpha_6\beta_4$ integrin is distributed diffusely over the cell surface; the markedly increased expression of $\alpha_6\beta_4$ integrin in this setting suggests that it is involved in tumour progression [10,11]. Direct involvement of this integrin in tumour progression was first demonstrated by the finding that *de novo* expression of the β_4 integrin subunit increases the invasive capacity of β_4-negative colon carcinoma cells [12]. In mammary tumour cells it has been demonstrated that $\alpha_6\beta_4$ integrin, cooperating with Erb family members, plays an important role in regulating cancer behaviour [10].

Breast cancer is one of the most heterogeneous carcinomas in terms of metastatic capacity, expression of hormone receptors and responsiveness to treatment. In women it is the most common form of cancer and it is the second leading cause of cancer mortality (after lung cancer). It has been demonstrated that in many breast cancers the effect of therapy can be abrogated by high levels of ErbB-2 and vigorous activation of the phosphatidylinositol 3-kinase (PI3K) pathway [13]. Many breast cancer cell lines also exhibit high levels of expression of $\alpha_6\beta_4$ integrin; in these cell lines it has been observed that overexpression of this integrin results in potent activation of specific signalling pathways, especially the PI3K/Akt pathway [14]. These studies have revealed a specific function of $\alpha_6\beta_4$ integrin in tumours and have elucidated the mechanisms by which this integrin promotes the survival and progression of mammary tumours.

Role of $\alpha_6\beta_4$ integrin in cell migration

The altered expression of $\alpha_6\beta_4$ integrin in tumour cell lines of epithelial origin suggests that this integrin promotes tumour progression and spread [14]. Only during the past few years has it become clear how $\alpha_6\beta_4$ integrin contributes to these tumour behaviours. The large cytoplasmic tail of the β_4 subunit, which comprises more than 1,000 amino acids, is unique among the integrin family members [15].

Much progress has been made in identifying specific domains that mediate functions such as adhesion and migration in normal and tumour cells [16,17]. Chemotactic migration of carcinoma cells on laminin-1 requires not only the formation of F-actin-rich cell protrusions, which mediate $\alpha_6\beta_4$-dependent cell migration, but also disruption of

EGFR = epidermal growth factor receptor; IRS = insulin receptor substrate; PI3K = phosphatidylinositol 3-kinase; VEGF = vascular endothelial growth factor.

hemidesmosomes by protein kinase C [18]. Moreover, stimulation of epidermal growth factor causes mobilization of $\alpha_6\beta_4$ integrin from the hemidesmosomes and increases formation of lamellipodia and membrane ruffles that contain $\alpha_6\beta_4$ integrin [18,19]. It has also been shown in keratinocytes that spreading on laminin-5 activates Ron, which results in a protein kinase C dependent translocation of $\alpha_6\beta_4$ integrin from hemidesmosome to lamellipodia [20]; this corroborates previous work in suggesting that $\alpha_6\beta_4$ integrin, by helping to stabilize dynamic structures, promotes migration. In addition, the ability of $\alpha_6\beta_4$ integrin to regulate the expression of genes such as the transcription factor NFAT [21] and the mitogen autotaxin/ENPP2 factor [22] could be among the mechanism through which the integrin can promote breast cancer cell motility.

Another mechanism by which $\alpha_6\beta_4$ integrin could be involved in breast cancer cell invasion is dependent on hypoxia [23]. Hypoxia causes a marked increase in surface expression of $\alpha_6\beta_4$ integrin in mammary tumour cells, which modulates their motility and ability to invade.

Role of $\alpha_6\beta_4$ integrin in PI3K-dependent tumour survival

As in keratinocytes, overexpression of $\alpha_6\beta_4$ integrin in breast cancer cells promotes motility by specifically activating PI3K [24]. In particular, regulation of PI3K by $\alpha_6\beta_4$ stimulation is required for the formation of motility structures and for activation of Rac to promote invasion. It has also been reported that $\alpha_6\beta_4$ integrin promotes survival by activating the PI3K/Akt pathway and that this function may be dependent on p53 status [25]. Specifically, it has been demonstrated that $\alpha_6\beta_4$ can promote PI3K/Akt-dependent survival of p53-deficent mammary tumour cells. Moreover, in response to $\alpha_6\beta_4$ ligation for the recruitment of PI3K on the plasma membrane are implicated two insulin receptor substrate (IRS) members, namely IRS-1 and IRS-2, as adaptor proteins, that mediate the $\alpha_6\beta_4$ -dependent PI3K activation [26].

A study conducted in our laboratory [27] provided the first evidence that in mammary tumour cells $\alpha_6\beta_4$ associates with ErbB-2, the orphan receptor of the epidermal growth factor receptor (EGFR) family, which is frequently found to be highly expressed in mammary tumours. A subsequent study conducted in a NIH3T3 cell model system [28] demonstrated that the β_4 cytoplasmic tail is required in this interaction and that both $\alpha_6\beta_4$ and ErbB-2 molecules are required for PI3K-dependent invasion. Both β_4 integrin subunit and ErbB-2 lack the consensus sequence to bind p85, the regulatory subunit of PI3K; this suggests that involvement of another EGFR family member is required to activate PI3K. Among EGFR family members, the ErbB-2/ErbB-3 heterodimer is the most potent activator of PI3K. $\alpha_6\beta_4$ Integrin and ErbB-2/ErbB-3 have been implicated in breast cancer progression and metastasis [29,30], findings that suggest a role for the ErbB-3 molecule in $\alpha_6\beta_4$/ErbB-2 cooperation. Indeed, $\alpha_6\beta_4$ regulates the translation of ErbB-3 protein in mammary cells, which results in significant induction of ErbB-2/ErbB-3 heterodimerization and consequent activation of the PI3K/Akt survival pathway [31]. Moreover, activation of PI3K/Akt pathway mediated by $\alpha_6\beta_4$ ligation is inhibited upon ErbB-3 depletion, indicating that the survival function of $\alpha_6\beta_4$ integrin is dependent on ErbB-3.

These data are apparently in contrast with the finding that clustering of $\alpha_6\beta_4$ under adherent conditions does not result in significantly increased PI3K activity [32]. However, these latter findings were obtained in a cell line that expresses high levels of $\alpha_6\beta_4$ integrin and that does not express ErbB-3 receptor. A probable explanation for the discrepant observations is that the cells used by Gilcrease and coworkers [32] express the Nrdp1 ubiquitin ligase, which promotes ErbB-3 degradation [33].

Previous work [34] demonstrated that $\alpha_6\beta_4$, through the PI3K/Akt pathway, phosphorylates and inactivates 4E-BP1 (a translational repressor), which in turn stimulates production of vascular endothelial growth factor (VEGF) and promotes survival of breast cancer cells. The VEGF is an autocrine survival factor for breast carcinoma cells [34], and because $\alpha_6\beta_4$ cooperates with EGFR members to promote survival of breast cancer cells [31] we cannot exclude the possibility that $\alpha_6\beta_4$-mediated ErbB-2/ErbB-3 signalling promotes breast carcinoma survival by elevating VEGF expression. It is interesting to note that the crosstalk between $\alpha_6\beta_4$ integrin and EGFR family members is strong. For example, it was recently shown that $\alpha_6\beta_4$ integrin also regulates the translation of ErbB-2 protein and that expression of $\alpha_6\beta_4$ integrin is necessary to regulate Ras activation [35]. Moreover, H-Ras promotes carcinoma invasion by E2F-dependent regulation of $\alpha_6\beta_4$ integrin [36]. Overexpression of E2F family members increases levels of the β_4 subunit both at transcriptional and protein levels, resulting in markedly increased invasion.

Role of $\alpha_6\beta_4$ integrin in breast cancer progression

A specific role for $\alpha_6\beta_4$ integrin in breast cancer progression and tumourigenesis was recently demonstrated by the finding that depletion of $\alpha_6\beta_4$ integrin, by RNA interference, strongly reduces *in vitro* and *in vivo* tumourigenicity [37,38]. Interestingly, loss of $\alpha_6\beta_4$ integrin reduces significantly the tumourigenicity of mammary tumour cells, reducing the production of VEGF *in vivo*. This finding is in agreement with previous data indicating that $\alpha_6\beta_4$ integrin regulates VEGF translation [34], supporting the important role played by $\alpha_6\beta_4$ integrin in sustaining the survival of mammary tumour cells [25]. Loss of $\alpha_6\beta_4$ integrin also results in significant downregulation of PI3K/Akt activity [38].

It has been found that in the absence of hormone β_4-depleted cells exhibit a 17% rate of apoptosis, which increases to

45% with to hormone therapy [38]. This finding indicates that $\alpha_6\beta_4$ integrin plays a role in promoting survival in mammary tumour cells in the absence of hormone. Recently, it has been described that mice carrying a deletion of the c-terminal region of the β_4 tail evidenced that $\alpha_6\beta_4$ integrin promotes mammary tumourigenesis [39]. *In vivo*, cooperation between $\alpha_6\beta_4$ integrin and ErbB-2 enhances activation of the transcription factors STAT3 and c-Jun, which results in disrupted epithelial polarity and hyperproliferation, respectively [39].

The $\alpha_6\beta_4$ integrin cooperates with other tyrosine kinases such as c-met (a hepatocyte growth factor receptor) to promote invasion [40]. Stimulation with hepatocyte growth factor (c-met kinase) transphosphorylates β_4, which associates with Shc and PI3K, potentiating hepatocyte growth factor-triggered signalling on both Ras and PI3K dependent pathways. The same group [41] recently found that over-expression of β_4 subunit is sufficient to transform rodent fibroblasts, increases the *in vitro* growth of mammary tumour cells, and induces tumourigenicity in nude mice, whereas depletion of $\alpha_6\beta_4$ integrin abrogates the transformed phenotype.

Altogether, these studies demonstrate that the crosstalk between $\alpha_6\beta_4$ integrin and receptor tyrosine kinase signalling is strong and contributes to increased ability of mammary tumour cells to grow and invade.

In vivo expression and localization of $\alpha_6\beta_4$ integrin in breast cancer

Although expression of $\alpha_6\beta_4$ integrin *in vivo* has not been evaluated extensively, the *in vivo* data obtained in the following studies are in agreement with *in vitro* findings.

The first study to analyze the distribution of $\alpha_6\beta_4$ integrin in human carcinomas [42] identified high levels of expression in various epithelial tumours. Similar findings were reported from a study that analyzed the β_4 subunit in normal, hyperplastic and neoplastic breast cancers [43]. Among the tumours analyzed, immunohistochemical study found that mucinous carcinomas are highly positive for β_4 expression, whereas luminal cells of normal ducts and acini as well as fibroadenocystic tissue exhibit rare, weak reactivity.

In contrast to previous findings, an analysis conducted in a limited number of breast cancers [44] demonstrated loss of $\alpha_6\beta_4$ integrin in grade III ductal carcinoma (7/11 cases) whereas most of grade I and II carcinomas analyzed were positive (6/8 cases). Even though this study is restricted to a small number of mammary tumours and the results obtained did not achieve statistical significance, it revealed marked de-regulation of integrin expression that correlated with loss of polarization, which is a characteristic feature of epithelial tumours. Similar results were obtained in an analysis of the expression of α_6 and β_4 subunits in primary and metastatic breast cancers [45]. Interestingly, the findings obtained indicate that, as expected, in normal mammary gland both subunits colocalize at the basolateral aspect of the epithelium, which remains unchanged in benign breast lesions; in contrast, in primary carcinomas expression of both chains is reduced and restricted over the cell surface. The same study revealed that $\alpha_6\beta_4$ integrin is present at lymphonodal foci, but that the level of expression is less in metastases to the pleural cavity and parenchymal tissues. Moreover, lack of laminin and collagen type IV correlates in these tumours with reduced $\alpha_6\beta_4$ expression [45].

More recently, a study conducted in 119 tumours from patients with invasive breast carcinoma [46] demonstrated that low levels of expression of α_6 subunit correlate with survival, whereas high levels of expression correlate with significantly reduced survival. Indeed, elevated expression of α_6 was present in 90% of cases with distant metastases, indicating that this integrin plays a role in tumour progression. In agreement with the findings of that study, an analysis of $\alpha_6\beta_4$ integrin in 80 patients with breast carcinoma [47] revealed that 36 of these tumours expressed high levels of β_4 subunit, with a significant association between expression of α_6 subunit and production of laminin by tumour cells. That study demonstrated, for the first time, that concomitant expression of $\alpha_6\beta_4$ integrin and laminin production has clear prognostic value, suggesting that these molecules mediate signalling events that are important for tumour progression.

An *in situ* hybridization study was recently conducted in which β_4 mRNA expression was evaluated in paraffin-embedded sections of tissue from 25 patients with invasive breast carcinoma, and compared with immunohistochemical findings from frozen sections derived from same tumours [48]. It revealed that all cases positive for β_4 protein also expressed β_4 mRNA; three cases in which β_4 mRNA was detected did not express β_4 at the protein level. Using *in situ* hybridization, the same group analyzed β_4 subunit mRNA expression in early breast cancer and correlated their findings with both tumour size and nuclear grade [49]. They also analyzed the expression of laminin-5 (the major substrate for $\alpha_6\beta_4$ integrin in epithelial tissue) in these tumours. They observed a strong correlation between β_4 mRNA expression and tumour size and nuclear grade, but correlation between β_4 and laminin-5 expression was not found to have prognostic significance [50].

All of these studies, in agreement with literature published during the past 2 years, strongly support a role for $\alpha_6\beta_4$ expression in promoting tumour progression. These studies also indicate that the biological role played by $\alpha_6\beta_4$ in mammary tumours is complex; studies should be extended to other molecules that may cooperate with $\alpha_6\beta_4$ integrin to render tumours more aggressive. These studies could help us to determine whether $\alpha_6\beta_4$ integrin should be considered an early marker of tumourigenicity and to evaluate tumour prognosis better.

Conclusion

Both experimental data and *in vivo* studies discussed in this review indicate that $\alpha_6\beta_4$ integrin plays a major role in mediating the aggressiveness of mammary tumours. Metastasis is a complex process that involves many molecules and many biochemical alterations in tumour cells. Integrin $\alpha_6\beta_4$ is a key molecule in this process, but much more needs to be learned about the contribution of this integrin to tumour progression. There is much cooperation between $\alpha_6\beta_4$ integrin and EGFR family members; furthermore, this integrin can modulate the expression of growth factors and growth factor receptors that are involved in tumour progression. Acknowledgement of the intimate relationships between these molecules could represent an aid in determining prognosis, could guide management decisions, and could facilitate development of drugs with novel targets.

Competing interests

The authors declare that they have no competing interests.

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