The diverse roles of integrin α3β1 in cancer: Lessons learned from skin and breast carcinogenesis

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THE OPPOSING ROLES OF LAMININ-BINDING INTEGRINS IN CANCER

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ABSTRACT

Integrins play an important role in cell adhesion by linking the cytoskeleton of cells to components in the extracellular matrix. In this capacity, integrins cooperate with different cell surface receptors, including growth factor receptors and G-protein coupled receptors, to regulate intracellular signaling pathways that control cell polarization, spreading, migration, survival, and gene expression. A distinct subfamily of molecules in the integrin family of adhesion receptors is formed by receptors that mediate cell adhesion to laminins, major components of the basement membrane that lie under clusters of cells or surround them, separating them from other cells and/or adjacent connective tissue. During the past decades, many studies have provided evidence for a role of laminin-binding integrins in tumorigenesis, and both tumor-promoting and suppressive activities have been identified. In this review we discuss the dual role of the laminin-binding integrins α3β1 and α6β4 in tumor development and progression, and examine the factors and mechanisms involved in these opposing effects.

LAMININ-BINDING INTEGRINS, WHAT THEY ARE AND WHAT THEY DO

Laminins are large heterotrimeric extracellular matrix (ECM) glycoproteins that contain an α, a β, and a γ chain. They are major components of the basement membrane (BM) that separates the nervous system, epithelial, endothelial, fat and muscle cells from adjacent connective tissue [1]. The BM, however, is not just a physical barrier; it also contributes to the adhesion, proliferation, migration and survival of cells. Integrins are heterodimeric transmembrane glycoproteins that function as adhesion receptors for ligands in the extracellular matrix (ECM) and transduce mechanical signals from the ECM into biochemical signals within the cell. Four integrins recognize laminins as their extracellular ligands: α3β1, α6β1, α7β1 and α6β4 (reviewed in [2]). Their specificity and affinity for binding to various laminin isoforms differ considerably [3–5] (**Table 1**). Alternative mRNAs splicing of the α3, α6 and α7 subunits further increases the functional diversity of these laminin-binding integrins by generating evolutionary conserved isoforms with different affinities for ligand binding and signaling activities [6]. The α6 and α7 subunits have distinct isoforms that differ in both their extracellular (X1 and X2) and cytoplasmic domains (A and B), while the α3 subunit only exists as two distinct cytoplasmic variants [7–14]. The expression of these isoforms is tissue specific and developmentally regulated [15–18], however a full understanding of their role is still lacking.

Integrin α6β4 is expressed at the base of most epithelial cells, but also by a subset of endothelial cells [19] and by perineural fibroblasts and Schwann cells in peripheral nerves [20,21]. It mediates cell adhesion to laminins and plays a crucial role in the formation of specific cell-matrix complexes, *i.e.* hemidesmosomes (HDs) [22]. Hemidesmosomal dysfunction is associated with a group of inherited disorders called epidermolysis bullosa, symptoms of which are severe blistering of the skin and mucosal membranes [23]. Mice lacking either the integrin α6 or β4 subunit display very similar defects in skin and mucosal membranes, and die perinatally [24–26].

Despite sharing the common β1 subunit, the integrins α3β1, α7β1 and α6β1 have unique functions and distinct distribution patterns. Integrin α3β1 is most abundant in skin, kidneys, lungs, intestine, bladder and stomach. In these tissues, it mediates adhesion of epithelial cells to laminin-332 and -511 in the BM, and plays a role in the maintenance of cell-cell contacts. Recently, mutations in the gene encoding the α3 subunit (*ITGA3*) have been identified in patients suffering from a congenital nephrotic syndrome, interstitial lung disease and a mild form of epidermolysis bullosa [27–29]. Similar symptoms have been previously described in genetically engineered mice lacking α3β1 [30]. Notably, the skin defects observed in the absence of α3β1 occur

early in life and are associated with micro-blisters and a disorganized BM. Later in life, these defects are no longer observed [31,32].

LAMININ ISOFORM SPECIFICITY		GENE	MOUSE PHENOTYPE		HUMAN DISEASE
-332 -511/521	α6β 4	***Itgb4***	LETHAL, Perinatal	Severe skin blistering	Epidermolysis bullosa
-111, -332, -511/521 -211/221, -411	α6β1	***Itga6***	LETHAL Birth	Severe skin blistering, defects in cerebral cortex and retina	Epidermolysis bullosa
-511/521, -332 -211/221	α3β1	***Itgb1***	LETHAL E 5.5	Inner cell mass deterioration	Lethal
		Itga3	LETHAL Birth	Defects in kidneys, lungs, skin, and cerebral cortex. Disorganization of the BM	Congenital nephrotic syndrome, interstitial lung disease, and epidermolysis bullosa
-211/221 -111, -511/521	α7β1	***Itga7***	VIABLE Fertile	Muscular dystrophy	Congenital myopathy

Table 1: The ligand-binding specificity of the laminin-binding integrins (bold printed – laminin isoforms reported to bind with the highest affinity) and reported phenotypes of mice and human diseases linked to non-functional integrins

Integrin α7β1 is most prominently expressed in cardiac and skeletal muscles, where it connects muscle fibers to laminin-211/221 in the BM of the myotendinous junction. In line with its function, patients with a loss-of-function mutation in the gene encoding the α7 subunit (*ITGA7*) suffer from congenital myopathy [33], and mice lacking α7β1 develop muscular dystrophy [34].

Finally, integrin α6β1 is predominantly expressed on platelets, leukocytes, gametes and some epithelia. It binds to a wide range of laminin isoforms, with the highest affinity to laminin-111, -511 and -332 [5]. Apart from a defect in laminar organization of the developing cerebral cortex and retina, seen in the α6-deficient mice (but not in β4-deficient mice), no other defects are associated with the absence of this integrin α subunit in mice [26,35]. The β1 subunit is ubiquitously expressed and can bind to as many as 12 different α subunits (reviewed in [2]). Therefore, it is not surprising that its depletion causes a failure of embryonic development [36].

Laminin-binding integrins can be found in two different adhesion complexes, focal adhesions (FAs) and HDs. FAs are dynamic protein complexes that form mechanical links between the ECM and the actomyosin cytoskeleton [37]. The dynamic regulation of FAs and the reorganization of the associated actin cytoskeleton are important determinants for cell migration. HDs are more stable adhesion structures that act as

anchoring sites for intermediate filaments (reviewed in [38–41]). These adhesions need to be disassembled during migration and several mechanisms have been suggested to contribute to the disassembly of HDs, including endocytosis of HD proteins [42,43], laminin chain processing [44], cleavage of the β4 subunit by calpain or caspases [45,46], and phosphorylation of HD proteins [47–52]. Upon dissociation of HDs, α6β4 has been reported to be redistributed to actin-rich filopodia and lamellae [53,54], where it plays a role in the regulation of cell migration. However, the mechanism responsible is poorly understood.

In addition to their role in maintaining structural integrity of tissues, the laminin-binding β1 integrins also function as bidirectional signaling molecules. "Inside-out" signaling regulates the binding affinity and/or avidity of the integrin to its ECM ligand, while "outside-in" signaling is triggered upon adhesion and results in the transduction of signals into the cell (reviewed in [55–58]). As integrins lack intrinsic enzymatic activity, they signal through direct or indirect interactions of their cytoplasmic domains with numerous intracellular effector molecules (reviewed in [59–61]). Classical integrin outside-in signaling triggers autophosphorylation of focal adhesion kinase (FAK) [62]. Consequently, the FAK/Src complex is activated, resulting in the stimulation of multiple downstream signaling pathways, leading to the activation of effectors such as mitogen-activated protein kinases (MAPKs) ERK1/2 and JNK, as well as the Rho-family of small GTPases Cdc42 and Rac1. Through these effector molecules, the laminin-binding β1 integrins regulate cell polarization, spreading, migration, survival, and gene expression of cells [59]. Interestingly, compared to the β1 integrins that bind to fibronectin, the laminin-binding integrins support strong activation of Rac1 and Cdc42, and a minimal activation of RhoA. It has recently been pointed out by Stipp in his expert review [63] that this particular signaling results in the formation of smaller focal contacts on a laminin matrix as well as in dynamic actin cytoskeleton remodeling and rapid cell migration. Although α6β4 is reported to be involved in the activation of many of the kinases mentioned above, α6β4 and β1-integrins use different signaling mechanisms and the current understanding is that α6β4 needs to be dissociated from HDs to fulfill its role in signaling [64]. Whether α6β4 needs to adhere to laminin-332 in order to signal is unclear, since both adhesion-dependent and adhesion-independent signaling have been reported [65–68]. Data suggests that in transformed cells the β4 cytoplasmic domain is phosphorylated on specific tyrosine residues that serve as a docking platform for various signaling molecules to amplify the signaling output of growth factor receptors [69–71].

Integrin-mediated signaling can be additionally enhanced or modulated through interaction of integrins with integrin-associated proteins (IAPs), e.g. tetraspanins [72],

urokinase-type plasminogen activator receptor (uPAR) [73] and several growth factor receptors [74]. Therefore, extensive crosstalk takes place between pathways activated by integrins and other receptors, especially receptor tyrosine kinases (RTKs).

LAMININ-BINDING INTEGRINS AND CANCER

Over the last decades evidence for a role of laminins in cancer has accumulated and been addressed in several excellent reviews [75–77]. Laminin-332, -511 and -111 are reported to be particularly important in carcinogenesis and the motility of tumor cells [77]. Accordingly, α3β1, α6β1 and α6β4 have all been implicated in the development and progression of cancer, but there is little evidence for such role of α7β1 in tumorigenesis and cancer progression [78–81]. In the limited amount of available literature its tumor suppressing function in a variety of tumor cell types, as well as in a reduction of metastatic potential in melanoma cells, is described (reviewed in [63]). Recently it was reported that α7β1 is upregulated in biopsies of hepatocellular carcinoma, while *in vitro* its downregulation caused decreased invasion and migration, indicating that α7β1 can also act as a tumor promoter [82]. Such dual role in cancer is not restricted to α7β1; α6β4 and especially α3β1 can have both, disease suppressive and promoting roles. This does not seem to be the case for α6β1, which has been predominantly characterized as a tumor promoter, contributing to the spreading and invasion of tumors as well as mediating dissemination and the formation of metastases in areas rich in laminin, such as bone matrix and the space surrounding the nerve of the prostate gland. The role of α6β1 in cancer progression has been recently reviewed by others [63,83].

In this review we will focus on laminin-binding integrins with both an inhibitory and a promoting role in cancer, i.e. α3β1 and α6β4, and try to elucidate the factors and mechanisms involved in these opposing effects. Cancer is a disease with several different stages of development, which can be correlated to specific processes that are essential for its progress and development, i.e. hallmarks of cancer [84]. During primary tumorigenesis cancer cells exhibit sustained proliferation and avoidance of apoptosis. With growing tumor mass, a switch of metabolism and angiogenesis become important for the further development of the disease. During later stages of tumor progression, cancer cells acquire invasive properties in order to spread to distant tissues and form metastases. Integrins represent an important link between tumors and their environment as well as between different tumor cells within the tumor mass. Their role in each stage of tumorigenesis therefore will depend on external influences, for example, the molecular composition of the microenvironment and juxtacrine signaling from neighboring cells. Also oncogenic insults can have an effect on the function of integrins in different stages of cancer progression.

INETGRIN α3β1 AND CANCER

The opposing role of laminin-binding integrins in cancer is especially evident when considering α3β1-mediated tumorigenesis events (**Table 2**). From a number of studies it is clear that different stages of cancer can be influenced by the presence or absence of α3β1 and, conversely, that transformed cells can modulate the function of α3β1 by regulating its expression or post-translational modifications, through IAPs and via the induction of α3β1-mediated signaling. Furthermore, the expression of α3β1 in transformed cells can be influenced by oncogenic stimuli, such as the activation of K-Ras, and, vice versa, α3β1 can regulate the expression of a large number of genes in immortalized keratinocytes [85,86]. This suggests that transformed cells can be dependent on α3β1 for sustaining signaling pathways and cellular processes.

TISSUE	UPREGULATED/ CANCER PROMOTER		DOWNREGULATED/ CANCER SUPRESSOR	
	PRIMARY TUMORS	METASTASIS/ INVASION	PRIMARY TUMORS	METASTASIS/ INVASION
SKIN	[87–89]	[87]	[90]	[89]
BRAIN	[91,92]	[93,94]		[95]
ORAL CAVITY	[96]	[97–101]	[102]	[103]
HEAD AND NECK	[104]	[105]		
LUNG	[106,107]	[108,109]	[90,110]	[111]
BREAST	[112–118]	[117,119]	[118]	[118,120–122]
REPRODUCTIVE SYSTEM	[123]			[124–130]
STOMACH AND INTESTINE	[131]	[132–134]		[135,136]
PANCREAS	[137]			
LIVER	[138]	[138]		
BLADDER AND KIDNEYS	[139,140]			[141]
BONE			[142]	

Table 2: Summary of the studies on the role of α3β1 in cancer, including either biopsies of human diseased tissue or *in vivo* mammalian models. A role of α3β1 in both promoting and suppressing tumorigenesis and metastasis has been described.

Role of α3β1 in supporting sustained proliferation and avoidance of apoptosis

One of the most fundamental traits of cancer is the ability of tumor cells to maintain sustained proliferation. Integrins regulate cell proliferation through adhesion to the ECM [143]. Although the adhesion-dependent control of cell proliferation is generally downregulated in tumors, several studies have shown that proliferation of transformed cells can still be affected by integrin-mediated adhesion. Two recent studies, investigating the role of α3β1 in tumorigenesis of the epithelium of the skin and

mammary gland, showed that α3β1 is essential for the initiation of tumors and efficient proliferation of tumor cells [89,116]. The impaired proliferation in mammary epithelia was associated with the downregulation of activated FAK, resulting in a reduction of active Rac1 and its effector serine/threonine-protein kinase PAK1, and therefore in reduced activation of ERK1/2 and JNK [116]. This is consistent with the results of an earlier study, showing that the engagement of laminin-332 by α3β1 is essential for growth factor-stimulated cell proliferation, mediated through activation of the MAPK signaling pathway [144]. Both studies mentioned above observed that transformed cells deposit laminin into the matrix; therefore, their proliferation may still be dependent on signals, derived from integrin-mediated cell adhesion. In line with this, both α3β1 and laminin are required for an efficient proliferation of various types of tumors and the upregulation of laminin-511 together with α3β1 was shown to be a marker of poor prognosis in breast cancer [117,145,146].

It is therefore evident that α3β1 can promote proliferation of tumors that are adherent to the pre-existing or newly deposited laminin matrix. However, in later stages of carcinogenesis, when tumors rely less on adherent-mediated proliferation, loss of α3β1 may destabilize E-cadherin-mediated cell-cell adhesion, resulting in epithelial to mesenchymal transition (EMT)-like events and consequently increased tumor progression and metastatic growth at distant sites [128,147]. Loss of α3β1 can also contribute to metastatic growth through interactions of tumors with the metastatic environment. It was shown that *in vitro* the adhesion and proliferation of α3-deficient prostate carcinoma cells on laminin-332 was impaired, but the growth of the tumor was increased when injected into mice. Increased growth of α3-depleted tumor cells was also observed *in vitro* when these cells were co- cultured with stromal cells or grown in fibroblast-conditioned medium [129]. These observations further suggest that the role of α3β1 in modulating cancer cell proliferation is dual, depending on the stage of tumor progression (**Fig. 1**).

Integrins also contribute to tumorigenesis by regulating cell survival; ligated integrins can prevent pro- apoptotic signaling cascades initiated by anoikis (cell death by loss of adhesion) and relay survival signals. Studies of transformed cells depleted of α3β1 showed increased activation of caspase-3/7, reduced cell survival and increased radiosensitivity [116,148,149]. In all cases, α3β1 supported survival through adhesion to laminin and initiation of the FAK/ERK signaling pathway, indicating the importance of this mechanism.

Role of α3β1 in tumor-associated angiogenesis

The potential role of α3β1 in regulating angiogenesis has received relatively little attention and is not yet fully understood. In *Itga3* knockout mice the capillary loops in the kidneys are dilated and their number is reduced [30]. Furthermore, conditional deletion of *Itga3* in the epidermis of mice caused impaired cutaneous wound healing, due to a defect in angiogenesis and failure of α3-negative keratinocytes to promote the expression of the pro-angiogenic factor MRP3 (mitogen-regulated protein 3) [150]. In cancer-induced angiogenesis, α3β1 seems to act as both a promoter and suppressor of angiogenesis, and it influences vascular formation when expressed by tumor or endothelial cells (**Fig. 1**). Studies investigating the effect of α3β1 on endothelial cells mostly reported its suppressive function in angiogenesis, due to the inhibition of cyclooxygenase-2 (COX-2)-dependent angiogenic signaling, the regulation of vascular endothelial growth factor (VEGF), or the inhibition of endothelial cell proliferation, migration, and tubule formation [90,110,151,152]. In contrast, when expressed on tumor cells, α3β1 is predominantly associated with the promotion of angiogenesis. The expression of COX-2 and α3β1 is positively correlated in invasive ductal carcinoma, resulting in higher blood vessel density [115]. In MDA-MB-231 breast cancer cells, α3β1 controls the expression of COX-2 and influences endothelial cell function and invasion of tumor cells [112]. A possible explanation for the role of α3β1 in COX-2-mediated angiogenesis and stimulation of the tumor's microenvironment was recently provided by Subbram *et al.* [153], who showed that α3β1 can directly influence COX-2 expression by stabilizing its mRNA. Furthermore, there is data suggesting that the association of α3β1 with non-conventional ligands, such as the noncollagenous domain of the α3 chain of type IV collagen [α3(IV)NC1] [110], a tissue inhibitor of metalloproteinases (TIMP-2) [151,152,154] and thrombospondin-1 (TSP-1) [155,156], has an impact on tumor-associated angiogenesis.

Integrin α3β1-dependent regulation of angiogenesis can be also mediated via its lateral association with tetraspanin CD151, an established IAP (see below). An increased expression of CD151 is correlated with increased vascularity in breast cancer, and *in vitro* experiments in three-dimensional (3D) extracellular matrices showed that CD151 modulates the response of endothelial cells to cancer cells through its association with both α3β1 and α6β4 [157].

Role of α3β1 in invasion and metastasis

The literature describing the role of α3β1 in later stages of tumor progression pays almost equal amount of attention to its cancer promoting and suppressing functions. While in numerous clinical studies a positive correlation between α3β1 expression and tumor invasiveness or poor prognosis has been observed, opposite findings have also

been reported (**Table 2**). A similar trend was observed in *in vitro* studies investigating the invasive and migratory phenotype of cells from transformed cell lines. While an increased expression of α3β1 in a head and neck carcinoma cell line is correlated with a more invasive phenotype [105], a low expression of α3β1 has been associated with reduced migration and invasiveness of many different types of tumor cells [158–160]. On the contrary, loss or inhibition of α3β1 function can result in enhanced migration and invasion of tumor cells [89,124,135,161].

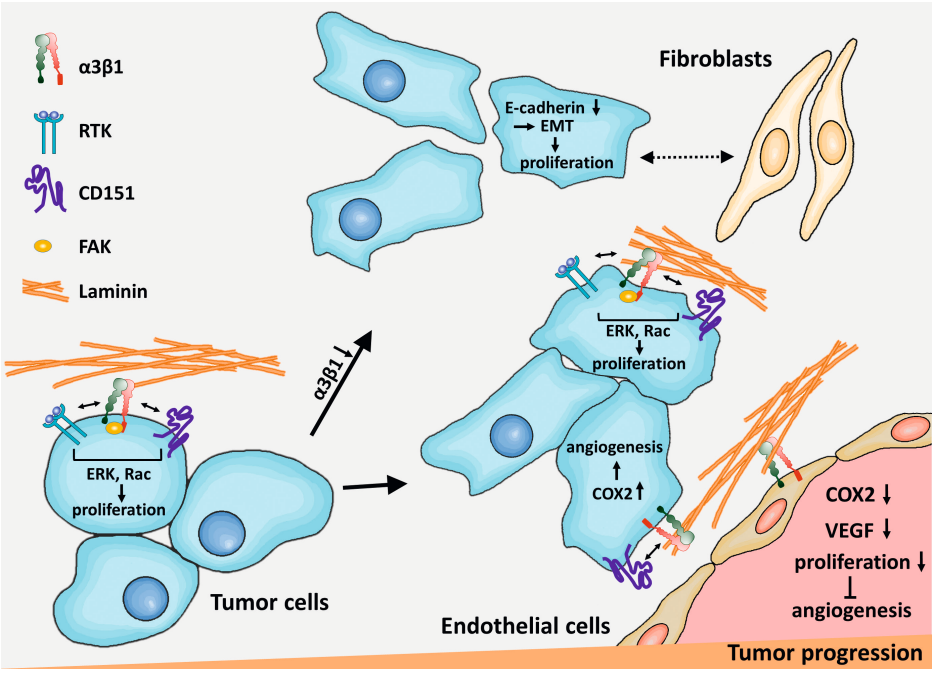

Figure 1: The role of α3β1 in tumor cell proliferation and angiogenesis. Ligation of α3β1 by laminins can result in the initiation of survival and growth signals via activation of FAK signaling, leading to the activation of the MAPK signaling pathway, which can additionally be supported through crosstalk with GFRs or upon association of α3β1 with the tetraspanin CD151. In later stages of tumor progression, when tumor cells rely less on adherent-mediated survival signaling, loss of α3β1 can destabilize adherent junctions, promote EMT and proliferation. Loss of α3β1 can promote metastatic growth also through interaction of tumor cells with other cells (*e.g.* fibroblasts) in a metastatic environment. When expressed on tumor cells, α3β1 can promote angiogenesis through stabilization of COX2 and via its lateral association with CD151. However, when present on endothelial cells, α3β1 downregulates proliferation and tubule formation and inhibits angiogenesis via inhibition of COX2-mediated signaling and regulation of VEGF signaling. GFR, growth factor receptor; EMT, epithelial to mesenchymal transition.

Different transcription factors have been reported that can either positively or negatively regulate the expression of α3β1 in tumor cells in order to acquire a more aggressive phenotype [142,162]. This suggests that the presence of α3β1 can have either beneficial or unfavorable effect on tumor cell invasion, and that it is important enough for tumor cells to develop mechanisms for regulating its expression. A remaining question is: what determines whether tumor cells will require either the presence or absence of α3β1 for successful invasion and the formation of metastases?

Laminin-dependent ligation of α3β1

Ligation of α3β1 by laminin-511 or -332 is one of the major events through which this integrin mediates cell adhesion and migration. This makes laminins of key importance for α3β1-mediated effects on cancer progression and invasion. Even more so since, as already discussed, laminins are implicated in the progression and spreading of cancer. In an early study it was shown that α3β1 is essential for the migration of keratinocytes on laminin-332 during wound healing [163]. A decade later Choma *et al*. [164] demonstrated that persistent keratinocyte migration is driven via the interaction of α3β1 with laminin-332, which induces FAK/Src kinase activity, thereby promoting Rac1 activation and polarized lamellipodium extension.

There is a strong positive correlation between the degree of invasiveness of glioma cells and α3β1-mediated migration. As it has been pointed out in a recent review, the attachment of the glioma cells to the ECM must be transient for them to be able to invade [165]. Furthermore, ECM rich in laminin-332 and -511 contributes strongly to the migration of highly invasive gliomas [93,166,167], while downregulation of α3β1 in glioma cells led to decreased migration and invasiveness [93], which was correlated with decreased phosphorylation of ERK1/2 [94]. In invasive protrusions of glioblastomas, α3β1 was found to be co-localized with the Ephrin A2 (EphA2), a known promoter of cancer invasiveness, making it plausible that the cross-talk between EphA2 and α3β1 additionally contributes to the adhesion-dependent signaling that leads to a more invasive phenotype [168,169]. Integrin α3β1-mediated cell adhesion in areas of the brain that are rich in laminin not only drives the invasion of glioma cells, but also plays a role in the formation of brain metastases of non-small cell lung carcinoma [108].

A pattern is now emerging of how laminin-332 and -511 promote the spreading of cancer cells via α3β1. Firstly, they facilitate α3β1-mediated tumor cell migration and invasion from the primary tumor site, which, in addition to the cases mentioned above, was observed in numerous other types of cancers [79,170–176]. Secondly, ligation of α3β1 by laminin-332 can increase the secretion of matrix metalloproteinase-9 (MMP-9), which then further promotes the invasion and migration through the dense ECM

[119,173,177]. Thirdly, laminins deposited by endothelial cells, can mediate α3β1-driven migration of tumor cells and stimulate trans-endothelial tumor cell invasion, thereby promoting tumor cell dissemination through the vasculature [178,179]. Fourthly, α3β1 expressed by endothelial cells may strengthen the adhesion of circulating tumor cells to the endothelium by stabilizing the binding of endothelium-expressed galectin-3 and cancer-associated carbohydrate Thomsen-Friedenreich antigen (TF-Ag) [180]. Lastly, α3β1 can mediate the initiation of new metastases in laminin-rich environment. Several studies have established a role of α3β1 in haptotatic migration and invasion toward laminin-511, suggesting that α3β1 plays an active role in the colonization of laminin-rich tissues by tumor cells [119,181–183]. This was confirmed in *in vivo* mouse studies, observing that α3β1 drives the formation of metastasis to the lung, lymph nodes and peritoneum [109,117,133,177,184].

Ligation of α3β1 by laminin, however, does not always clearly promote the spreading and invasion of cancer cells. For example, in highly invasive and metastatic prostate carcinoma cells the expression of α3β1 was decreased and they failed to spread when grown *in vitro* [124]. Furthermore, a recent study of patient samples of squamous cell carcinomas of the lower lip showed the absence of α3β1 at the invasive front, where the expression of laminin-332 was often detected [102]. One possible explanation for the anti-invasive-effect of ligated α3β1 is that the integrin suppresses the formation of invadopodia, actin-linked structures with putative adhesion properties, which are frequently observed to mediate BM degradation in epithelial tumors. It was proposed that a balance of focal contacts and invadopodia is necessary for cells to migrate and invade the BM [185]. In fact, Liu *et al*. [186] recently showed that depletion of either laminin-332 or α3β1 resulted in an increased number of invadopodia in bladder carcinoma cells. They proposed a mechanism, by which laminin-332-α3β1 interaction acts as a potent upstream inhibitor of cell invasion via mediating focal contacts that in turn limit the availability of active Src, necessary for inducing the formation of invadopodia.

Association of α3β1 with tetraspanins

The ability of α3β1 to interact with several IAPs offers further explanation for its dual role in cancer invasion and its progression in general. Tetraspanins, multispanning membrane proteins that cluster into tetraspanin-enriched microdomains (TEMs) on the plasma membrane, are one of the most prominent proteins that can interact with laminin-binding integrins, thereby influencing their localization and function [63,72]. Several tetraspanins, including CD9, CD81 and CD63 have been suggested to associate with α3β1 and to influence the migration and invasiveness of tumor cells. With a few exceptions, these complexes are mainly associated with reduced migration and low

metastatic potential, and thus a better prognosis [98,126,135,187–189]. Recently, the tetraspanin CO-029 was found to form a complex with α3β1 and rictor in malignant gliomas, and thus to mediate migration of glioma cells via mammalian target of rapamycin (mTOR) complex 2 (mTORC2), of which rictor is a key component [190]. However, a clear understanding of how these tetraspanins associate with α3β1 and regulate α3β1-mediated migration and invasiveness is still lacking.

A direct and stable association has only been shown for CD151 and α3β1 [191,192]. The interaction of CD151 and α3β1 influences the distribution of α3β1 and shifts it from FAs into TEMs [193]. Furthermore, it strengthens α3β1-mediated cell adhesion and promotes the proliferation and migration of different types of tumors cells on laminin-332 [194–196]. Two major mechanisms may account for the CD151-dependent regulation of tumor cell behavior by α3β1. Firstly, CD151, which contains a YXXφ endocytosis motif in its C-terminal cytoplasmic domain, may stimulate cell migration by facilitating α3β1 recycling [197]. Secondly, CD151 may contribute to pro-migratory signaling of α3β1 by suppressing RhoA activity and formation of stress fibers [63,164,198,199]. Additionally, the signaling properties of α3β1 may be influenced by phosphatidylinositol 4-kinase (PI4K) that is associated with CD151 [192] (**Fig. 2**).

Recent data suggests that CD151 can also control cell migration independently of its association with α3β1, and that the balance between integrin-free CD151 and CD151-α3β1 complexes is important with regard to tumor invasion [130,200,201]. Scales *et al.* [199] demonstrated that the ligation of α3β1 by laminin promoted the association between α3β1 and CD151 and that cells lacking α3β1 exhibited increased formation of CD151 homodimers. This suggests that α3β1-mediated cell adhesion to laminin skews the balance from CD151-CD151 homodimers towards CD151-α3β1 complexes. The balance can also be altered by changes in the expression of either α3β1 or CD151, which is not uncommon in cancer [63]. Alternatively, association of α3β1 with CD151 could be regulated via α3 or β1 glycosylation, as it was shown in highly metastatic melanoma cells [202].

In breast cancer, it was shown that the complex of CD151 and α3β1 mediates malignancy through interaction with ErbB-2 (HER2) [203,204]. In invasive ductal carcinomas, the CD151-α3β1 complex is a marker of poor outcome, and experiments with ErbB-2 overexpressing breast cancer cells indicated that CD151-α3β1 complexes promote dimerization of ErbB-2 by keeping Rho activity low [114]. In contrary to invasive ductal carcinomas, in invasive lobular carcinomas poor patient survival is connected to the lack of correlation between CD151 and α3β1 [118].

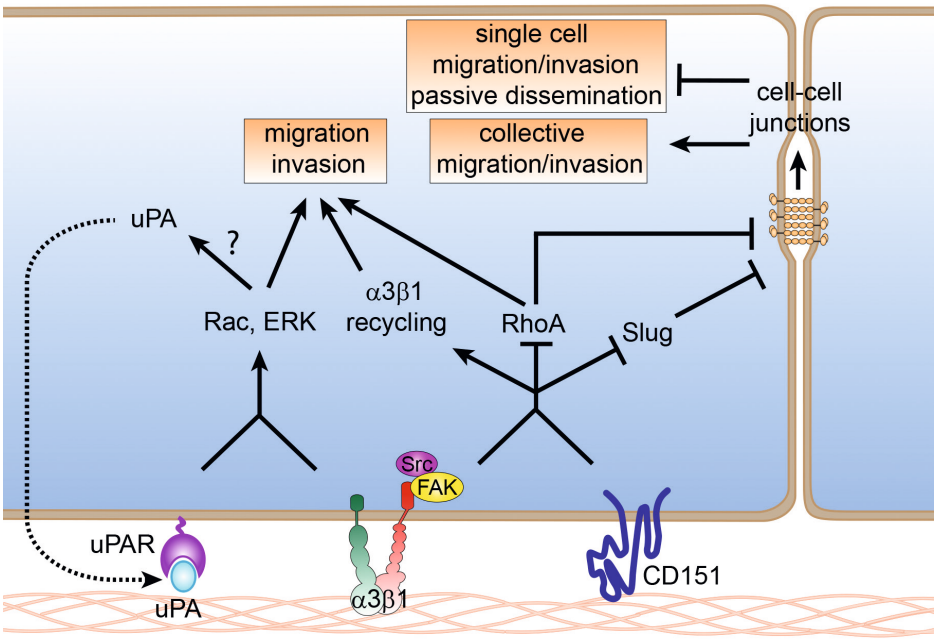

Figure 2: The interaction of integrin α3β1 with CD151 and uPAR can affect tumor cell migration and invasion. Integrin α3β1 can form complexes with several IAPs, which have an impact on the progression and development of tumors. The association of CD151 with α3β1 might be required to prevent the integrin from becoming linked to the actomyosin cytoskeleton and thus from supporting RhoA activity. The suppression of RhoA activity will lead to a shift of the Rho/Rac balance in favor of Rac1 and hence to the formation of smaller focal adhesion complexes and the activation of cytoskeleton remodeling. Additionally, the association of CD151 may promote tumor cell migration and invasion by facilitating the recycling of α3β1. Furthermore, α3β1-CD151-mediated suppression of RhoA activity and Slug expression may stabilize adherens junctions, thereby inhibiting tumor cell migration, invasion and passive shedding and dissemination of tumor cells. However, it may favor tumor spreading via collective cell migration. The association of α3β1 with CD151 may also skew the balance from CD151 homodimers, which can also have an impact on the migratory and invasive properties of tumor cells. The α3β1-uPAR complex can promote migration and invasion of tumor cells via activating the Src/ERK signaling pathway and/or upregulating uPA expression.

The biological differences between the two diseases were related to differences in cell-cell and cell-matrix interactions, the loss of E-cadherin being the most prominent characteristic of invasive lobular carcinoma [205]. As previously mentioned, α3β1 does not only mediate adhesion and migration on laminin substrates, but also plays a role in regulating the stability of cell-cell contacts. Although a precise mechanism has not yet been defined, it has been suggested that the CD151-α3β1 complex controls the stability of E-cadherin mediated cell-cell adhesion by regulating the expression of the membrane protein tyrosine phosphatase PTPm and its association with the E-cadherin-catenin complex in embryonic kidney cells [206]. Stipp and colleagues [207,208], however,

showed that this mechanism is not operative in A431 epidermoid carcinoma cells. In these cells, CD151 promotes the stability of cell-cell junctions by reducing α3β1-dependent activation of RhoA. In the absence of CD151, Rho activation is increased, which resulted in reduced collective migration in two-dimensional (2D) *in vitro* assay. However, in 3D matrices, the level of Rho activation, although being disruptive for junctional stability, did not prevent their formation and cells still invaded in a collective manner. Furthermore, there is evidence that the CD151-α3β1 complex plays a role in maintaining the integrity of ovarian carcinomas by repressing Slug-mediated EMT and canonical Wnt signaling [128]. Integrin α3β1-mediated cell-cell cohesion could hinder metastasis also in the context of passive tumor cell shedding to the blood stream. In line with this, tumor cells that have been released into the circulation of mice that contained induced (primary) renal tumors exhibited reduced levels of α3β1 [141]. Thus, the role of the CD151-α3β1 complex in carcinoma progression appears to be context-dependent and to depend on the mode of invasion and the phenotype of the tumor.

Association of α3β1 with uPAR

uPAR, the receptor for urokinase (uPA), is a glycosylphosphatidyl inositol-anchored protein expressed by many cell types. It forms complexes with several integrins, including α3β1, and has been implicated in tumor progression (**Fig. 2**). In oral squamous cell carcinomas, increased expression of α3β1 and uPAR correlates with a poor prognosis. *In vitro* and *in vivo* studies have shown that α3β1 clustering induces the recruitment of uPAR and the formation of α3β1-uPAR complexes that promote invasive cell behavior via Src and ERK1/2 signaling as well as via enhanced uPA expression [96,209]. In an independent study, it was shown that $p130^{Cas}$ is phosphorylated by Src in response to uPAR-α3β1-laminin-332 engagement, and that this led to enhanced cell motility through activation of Cdc42 and actin reorganization [210]. Complexes of uPAR and α3β1 have also been implicated in the fibroblast associated protein α (FAPα)-stimulated migration of ovarian cancer cells via activation of Rac1 [211]. In fact, an early study had already described that this complex can mediate binding to vitronectin [212]. Recently, an interesting novel mechanism was reported by Ferraris *et al*. [213], who showed that uPAR-mediated cell adhesion to vitronectin triggers integrin signaling independently of integrin-matrix engagement, by increasing the membrane tension. The same group also proposed that, in integrin ligand-independent conditions, the frictional membrane resistance participates in establishing adequate lamellipodial tension, which predominantly depends on coupling of the C-terminal talin-actin binding site to actomyosin-driven retrograde actin flow force [214]. This mechanism could provide an explanation for the role of uPAR-binding integrins, such as α3β1, in migration in an environment lacking conventional integrin ligands.

Altered glycosylation of α3β1

The α3 and β1 subunits contain 14 and 12 potential N-glycosylation sites, respectively, and it has become increasingly clear that malignant transformation is associated with aberrant glycosylation of α3β1, which can modulate its function, signaling and lateral associations with IAPs [215,216]. In bladder carcinomas, the overexpression of aberrantly glycosylated α3β1 is correlated with poor clinical outcome, and a monoclonal antibody that recognizes the aberrantly glycosylated epitope on α3β1 has potent anti-tumor activity in bladder cancer *in vivo*. *In vitro* experiments revealed that aberrant glycosylation of α3β1, conferred by the glycosyltransferase GALNT1, initiates FAK signaling, resulting in c-Jun phosphorylation and increased cell cycle progression, and proliferation through upregulation of cyclin D1 and activation of CDK4 [139]. Aberrant N-glycosylation of α3β1 also influences the motility and invasiveness of cancer cells [217,218]. The presence of high mannose and sialylated tri- or tetra-antennary complex type N-glycans on α3β1 is associated with a reduced adhesion to laminin and an increased invasive behavior of bladder cancer cells [219,220]. Baldwin *et al.* [221] has shown that α3β1-mediated cell migration can also be influenced by N-glycosylation of α3β1 without a detectable loss of cell adhesion to laminin-332. They found that the changes to N-glycosylation of α3β1, induced by its binding to CD151 during biosynthesis, influenced tumor cell migration toward laminin-332 [221]. The exact mechanism underlying the effect of α3β1 glycosylation on cell migration is unknown, but may involve galectin-3-mediated clustering of α3β1 and subsequent activation of Rac1 signaling [222]. Recently, a study was published proposing a role of N-glycosylation modifications in the efficient translocation of α3β1 to the plasma membrane [223]. Glycosylation of α3β1 was observed to be suppressed by hypoxia, resulting in decreased levels of α3β1 at the plasma membrane, which facilitated the invasion of epidermoid carcinoma cell line A431. There is therefore strong evidence that glycosylation of α3β1 can play a role in promoting cell migration and invasiveness, as well as contribute to increased tumorigenesis.

Role of α3β1 in gene regulation

As already mentioned, in transformed cells the expression of α3β1 is often regulated to modulate its function. One of the examples of such regulation is mediated by transforming growth factor β (TGF-β). In invasive hepatocellular carcinoma cells, TGF-β stimulates the expression of α3β1 by transcriptional upregulation via Ets transcription factors, resulting in a pro-invasive phenotype on laminin-332 [138,162]. Similar observations were reported in bladder cancer and in oral squamous carcinoma cells [224,225]. However, there is also an increasing amount of evidence for the role of α3β1 in gene regulation and for the consequences this brings to the development and progression of tumors. α3β1-mediated gene regulation in the context of metastasis has

been recently reviewed [79] and will therefore only be briefly mentioned here. The most striking examples of the gene regulatory role of α3β1 were observed in immortalized keratinocytes. In these cells α3β1 was shown to induce expression of MMP-9 upon transformation of cells [226], which was mediated via α3β1-dependent stabilization of MMP-9 mRNA transcripts [227]. Furthermore, the production of MMP-9 in immortalized keratinocytes was potentiated by α3β1 in response to TGF-β stimulation [228]. The mechanism behind mRNA stabilization was recently proposed by Missan *et al.* [229], who observed that a shorter, more stable mRNA was preferentially generated in immortalized keratinocytes expressing α3β1. The presence of this short transcript was dependent on active ERK/MAPK signaling. Integrin α3β1 was also shown to influence the stability of COX-2 mRNA (discussed in chapter on proliferation and angiogenesis) and to regulate the expression of fibulin-2, a matrix-associated protein that binds laminin-332 and serves as a mediator of matrix remodeling and invasion [85]. In line with the latter, a recent study reported that α3β1 mediates the stability of the BM through fibulin-2 induction, indicating the importance of α3β1-mediated gene regulation not only in cancer progression, but also in maintenance of healthy tissue [230].

INTEGRIN α6β4 AND CANCER

Early studies have identified the integrin α6β4 as a tumor antigen [231,232], whose expression is increased in squamous cell carcinomas, as well as in other types of solid cancers (reviewed in [233]). Some controversy exists regarding the stage of cancer development and progression at which β4 overexpression becomes apparent, but most studies agree that it increases with tumor grade [234,235]. In addition to increased expression of β4, changes in its distribution have also been linked to the grade of tumors [236,237]. In normal epithelial tissues, β4 is concentrated at the basal membrane of basal epithelial cells, while in many tumors, it is diffusely expressed in multiple cell layers [238–240]. Although abnormal and high expression of α6β4 in cancer is generally associated with poor patient outcome and overall survival, in certain settings α6β4 suppresses tumorigenesis. Furthermore, in tumors such as prostate carcinomas and basal cell carcinomas, the expression of α6β4 is downregulated [241–245].

Different roles of α6β4 in tumor development and progression might derive in part from its ability to assemble HDs. Additionally, α6β4 may modulate oncogenic signaling by binding to its ligand laminin-332 in the ECM or through cooperative signaling with RTKs that stimulate or suppress proliferation. Finally, the role of α6β4 depends on the ability of tumor cells to remodel the ECM and on their oncogene mutational profile.

Role of α6β4 in tumor initiation

Although α6β4 cannot induce tumorigenesis on its own [246], it has been implicated in human papilloma virus (HPV)-mediated tumor initiation. HPV plays a role in the initiation of several cancers such as anal, cervical and oropharyngeal cancer. Once the virus enters a cell, its proteins interfere with the normal cell machinery, which results in uncontrolled cell growth and avoidance of cell death. In HPV16 infected cervical cancer cells, α6 expression levels were correlated to the binding of the virus particles to the cells [247]. And in fact, it recently became clear that β4 expression and α6 processing are important for HPV entry into the basal cells [248,249]. However, viral DNA replication occurs primarily in the differentiating suprabasal cells of the epidermis. The HPV E2 protein may trigger this differentiation step by downregulating β4 expression [250,251]. These data strongly suggest that α6β4 has a dual role in different stages of tumor initiation by HPV.

Role of α6β4 in sustained proliferation and avoidance of apoptosis

The unique function of α6β4 in potentiating growth factor receptor signaling is evident from its role in supporting sustained proliferation and avoidance of apoptosis during tumor development and progression. Integrin α6β4 has been implicated in the modulation of signal transduction pathways downstream of several RTKs, including the epidermal growth factor receptor (EGFR) family members EGFR [65] and ErbB-2 [252,253], the macrophage stimulating protein (MSP) receptor (also known as Ron) [254], the hepatocyte growth factor (HGF) receptor (also called c-Met) [71,255] and the insulin-like growth factor-1 receptor [256].

Many studies attribute the synergy between α6β4 and RTK-mediated signaling to the phosphorylation of specific tyrosine residues in the cytoplasmic domain of β4 and subsequent recruitment and activation of signaling intermediates to the phosphorylated subunit (reviewed in [257]). The C-terminal segment of the β4 cytoplasmic domain that harbors the tyrosine residues is also known as the β4 signaling domain. Tyrosine phosphorylation of β4 is typically mediated by the Src family of kinases (SFKs) downstream of RTKs [254,258,259], although direct tyrosine phosphorylation of β4 by the HGF receptor c-Met has also been demonstrated [260]. Additionally, clustering of the α6β4 molecules by itself can lead to tyrosine phosphorylation of the β4 subunit [261]. Recent data suggests that members of the syndecan family of cell-surface proteoglycans may play an important role in the phosphorylation of the β4 cytoplasmic domain by positioning this domain near the plasma membrane to be phosphorylated by the SFK member Fyn downstream of EGFR and ErbB-2. Syndecans can bind directly to the cytoplasmic domain of the β4 subunit [262,263].

The signaling intermediates that are recruited by tyrosine phosphorylated β4 include the adapter proteins Shc [260,264] and IRS-1/2 [70], and the protein-tyrosine phosphatase Shp2 (also known as PTPN11) [71]. Binding of Shc by tyrosine phosphorylated β4 has been shown in squamous carcinoma cells expressing the EGFR at high levels [260], but also upon EGF treatment of cells that express normal levels of the EGFR [258]. Shc links α6β4 to the MAPK signaling pathway, which is essential for inducing cellular proliferation and transformation [264]. On the other hand, c-Met-mediated tyrosine phosphorylation of β4 has been shown to recruit Shp2, which enhances the activation of Src. Subsequently, Src induces the phosphorylation of the multi-adapter Gab1, which leads to activation of the MAPK and phosphatidylinositol 3-kinase (PI3K) signaling pathways [71,255]. Activation of MAPK signaling can also be mediated by a fraction of α6β4 that is localized in lipid rafts and associated with palmitoylated SFKs [265]. Binding of IRS-1/2 by tyrosine-phosphorylated β4 has also been implicated in the activation of PI3K downstream of α6β4 clustering [70]. Furthermore, there is data suggesting that FAK can be recruited by tyrosine phosphorylated β4 and that the subsequent activation of FAK promotes malignancy by increasing the activity of p38MAPK and Akt [259]. Tyrosine phosphorylation of β4 and subsequent activation of PI3K signaling can also promote the survival of breast cancer cells through enhanced VEGF translation and stimulation of VEGFR-mediated autocrine signaling [266] (reviewed in [267]).

Most studies agree that α6β4 supports PI3K activation by different RTKs, although the details of the mechanisms may differ between cell types. Activation of PI3K by α6β4-mediated cell adhesion was first shown by Shaw *et al.* [268], and since then, numerous other studies have reported an association between α6β4-mediated adhesion and the requirement of PI3K activation for cell survival. In breast cancer cells, blocking α6β4 function with an antibody against β4 caused a reduction in PI3K signaling, which led to increased apoptosis [269]. The induced apoptosis could be rescued by the expression of constitutively active Akt, the downstream target of PI3K [269,270]. Integrin α6β4-mediated PI3K signaling can also support cell survival through activation of the transcription factors STAT3 and c-Jun, as was shown in an ErbB-2-driven breast cancer mouse model [252].

Intriguingly, it has been reported that α6β4 can also promote cell death. *In vitro*, treatment of cells with chemical or pharmacological agents induced apoptosis via elevating the levels of β4, while the depletion of β4 promoted survival [271–275]. Furthermore, in an immunocompromised SCID mouse model of human gastric cancer, the expression of β4 at high levels promoted apoptosis [276]. Bachelder *et al.* [277] suggested that the ability of α6β4 to either promote or suppress apoptosis depends on the p53 status of the cells. Integrin α6β4 stimulates p53-transactivating function

and promotes p53-dependent apoptosis in carcinoma cells that express wild-type p53, but not in p53-deficient carcinoma cells, in which it promotes survival in a PI3K/Akt dependent manner. Interestingly, in the same colon carcinoma cells depletion of p53 associates also with enhanced β4 transcription through the p53 family members p63 and p73, thereby further augmenting the survival function of α6β4 [278]. Although the inhibition of α6β4-mediated survival signaling by p53 activation has so far been only conclusively shown in RKO colon carcinoma cells [279], the fact that p53 mutations and overexpression of α6β4 are positively correlated in a number of human malignancies [233] suggests a general mechanism by which the activity of p53 in carcinoma cells is regulated by the signaling function of this integrin. Interestingly, p53 has also been suggested to regulate adhesion of cancer cells via α6β4 [280].

In addition to supporting cell proliferation and survival by providing an additional platform for RTK signaling, α6β4 may be needed to secure attachment during oncogenic transformation when the adhesive function of integrins that are linked to the actin cytoskeleton is compromised, while oncogenic signaling is still dependent on the structural integrity of the actin cytoskeleton. This might be responsible for the requirement of the presence of α6β4 and its ligand laminin-332 in squamous cell carcinomas, induced by oncogenic Ras and IκBα expression [281]. Similarly, the promotion of cell growth by α6β4, which was reported to be anchorage-independent [71,282], could still have been dependent on α6β4-mediated adhesion to autocrine-produced laminin. In support of this notion, in 3D culture of mammary spheroids, α6β4-mediated cell adhesion to autocrine produced laminin-332 conferred resistance to apoptosis by stimulating Rac1-Pak signaling and activation of NF-κB [283,284]. Moreover, Bertotti *et al*. [255] showed that the removal of the extracellular domain of β4 reduced anchorage-independent colony formation in soft agar.

Additionally, it has been suggested that suprabasal α6β4 contributes to cancer progression by enhancing proliferation of basal keratinocytes by relieving the growth inhibition of TGF-β [246]. TGF-β negatively regulates keratinocyte proliferation in the early stages of epidermal tumor promotion [285,286]. This growth inhibitory effect of TGF-β is dependent on cadherin-mediated cell-cell adhesion and PI3K, but not MAPK activity. Suprabasal α6β4 appears to perturb TGF-β signaling by blocking nuclear translocation of activated Smad2/3, resulting in increased cell proliferation and formation of skin papillomas and SCCs [246]. Surprisingly, tumorigenesis was further increased when mice expressed a mutant β4 subunit that lacked the cytoplasmic domain in the suprabasal layers of the epidermis, suggesting that α6, rather than β4 cytoplasmic domain might play a role in TGF-β signaling [246].

Role of α6β4 in angiogenesis

Within the vasculature, the expression of α6β4 in endothelial cells is dynamically regulated during angiogenesis and vessel maturation [287]. α6β4 is predominantly detected in small arterial vessels, where it may mediate strong endothelial cell adhesion, necessary to withstand the high shear rates in these vessels [19]. Contrary to β4, α6 is expressed in all vasculature, which suggests the presence of α6β1 in the absence of β4 [19,288]. Integrin α6β1 is known to promote angiogenesis; inhibition of α6 prevented endothelial cell migration and tube formation [289]. However, the role of β4 in angiogenesis is less clear. The exclusive presence of β4 in mature vessels suggests that it negatively regulates angiogenesis [287], and several studies report that α6β4 does not promote endothelial cell proliferation or growth of new vessels [19,287,290]. Furthermore, it has been recently suggested that downregulation of α6β4 is necessary for endothelial proliferation and tube formation during early stages of angiogenesis [288]. In line with this notion it was proposed that α6β4 can block angiogenesis by inducing endothelial cell death [291] (reviewed in [292]). On the other hand, experiments in mice in which the C-terminal domain of β4 was deleted, showed that α6β4 signaling is important for vascular remodeling and for a proficient angiogenic response to VEGF and basic fibroblast growth factor (bFGF) [290]. Furthermore, in mice lacking β4 in endothelial cells, hypoxia-induced arteriolar remodeling was defective, which was suggested to result from changed TGF-β signaling [19]. Alternatively, β4 can regulate angiogenesis via stimulation of translation and signaling of VEGF [266,293] (**Fig. 3**).

Although α6β4 seems to play a general regulatory role in angiogenesis, there is very little known about its role in tumor angiogenesis. In mice, carrying a deletion of the C-terminal domain of β4, vascularization in subcutaneously implanted tumors was impaired, suggesting that α6β4 promotes tumor angiogenesis [290]. However, the levels of tumor vascularization in a mammary gland tumor model were the same in mice carrying a similar β4 deletion as in β4 wild-type mice [252].

Role of α6β4 in invasion and metastasis

Unlike that of α3β1, the expression of α6β4 is positively correlated with tumor grade in most instances, indicating that this integrin promotes tumor progression and metastatic spread. The role of α6β4 in invasion and metastasis has been reviewed extensively over the last two decades, in articles primarily focusing on the mechanisms responsible for its tumor-promoting function [67,68,233,294,295]. However, there are certain cases in which α6β4 is negatively correlated with tumor invasion and formation of metastases. In order to elucidate the circumstances that determine the function of α6β4 in the final stages of cancer, it is important to understand under which conditions it contributes

to cellular migration and invasion, as well as to understand the differences between tumor settings, in which the role of α6β4 has been implicated.

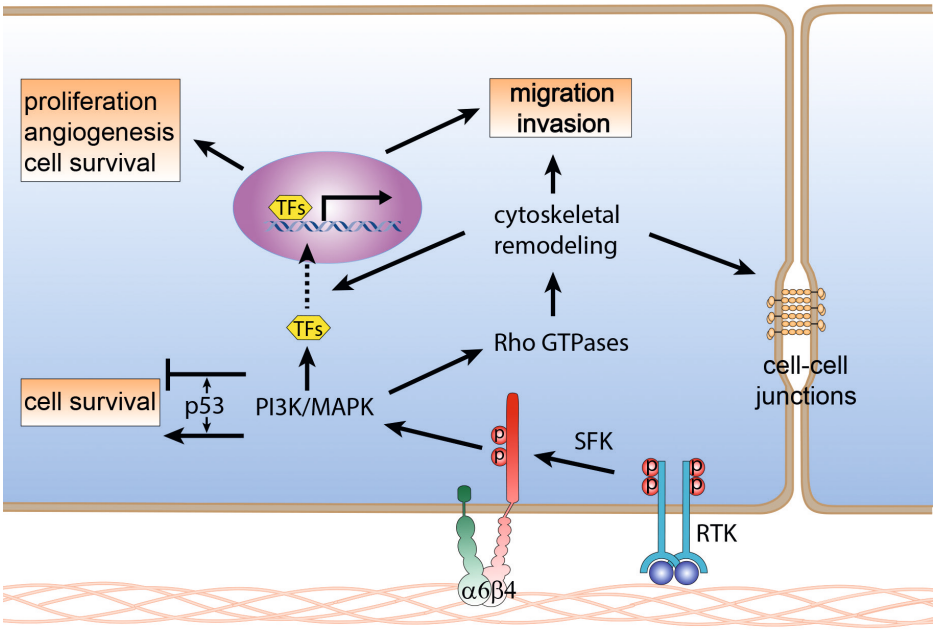

Figure 3: Integrin α6β4 regulates cell behavior by cooperating with RTKs. Integrin α6β4 amplifies intracellular signaling of RTKs. SFK that are activated by RTKs phosphorylate several tyrosine residues (red dots) in the signaling domain of the β4 cytoplasmic tail. These tyrosine residues act as docking site for adaptor proteins to activate the PI3K and MAPK signaling pathways. Activated PI3K and MAPK further regulate cell migration, proliferation, angiogenesis, apoptosis, invasion and survival via activation of downstream effectors, by regulating cell-cell adhesion or via regulation of gene expression by transcription factors. RTK, receptor tyrosine kinase; SFK, Src family kinase; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinases; TFs, transcription factors.

Migration and invasion

It is generally accepted that HDs have to be disassembled before cells can migrate (**Fig. 4**). Indeed, studies using primary keratinocytes have revealed that classical HDs (type I HDs), which contain α6β4, CD151, plectin, BP180 and BP230, prevent cell migration [296,297]. However, α6β4 does not necessarily impede cell migration as part of type II HDs, a less complex type of HDs that only contains α6β4 and plectin [298]. Type II HDs are found in simple epithelia and many cultured epithelial cells, and in contrast to type I HDs, their components have a turnover rate that is fast enough not to limit the migration of cells [50,52,299].

In many transformed cells the number of HDs is reduced and they are completely and/or partially disassembled. In these cells, α6β4 facilitates growth-factor stimulated migration and invasion via its cytoplasmic domain (reviewed in [47]). Induction of carcinoma cell migration by EGF is associated with a redistribution of α6β4 from HDs to the leading edge of the cell (reviewed in [67]), where it colocalizes with actin in lamellipodia and filopodia [53,54]. How α6β4 associates with actin and how this contributes to migration is not clear. Like α3β1, α6β4 has been implicated in actin cytoskeletal dynamics during migration through the regulation of the Rho family of GTPases [300,301]. Although RhoA plays a crucial role in the retraction of the tail of the cells, both Rac1 and RhoA are required for stimulating cell migration on 2D substrates by inducing the formation of actin-based protrusive structures [302]. Rac1, which is activated by α6β4-mediated cell adhesion, promotes the formation of lamellipodia and, interestingly, the localization of α3β1 in these structures [303]. Integrin α6β4 supports PI3K-Rac1 signaling [268] downstream of several pro-migratory factors (*e.g.* EGF [304], HGF [305], PTHrP (parathyroid hormone-related protein) [306] and LPA (lysophosphatidic acid) [307]) (**Fig. 3**). EGF-induced activation of Rac1 requires both the extracellular and the cytoplasmic domain of the β4 subunit [304]. On the other hand, when it is part of HDs, ligation of α6β4 by laminin activates Rac1 independently of the signaling domain of β4 [308,309]. In addition to stimulating migration by increasing the activity of Rac1 in tumor cells, α6β4 has also been implicated in augmenting the activity of RhoA by a mechanism that involves suppression of the intracellular cAMP concentration by activating a cAMP specific phosphodiesterase [261,310].

Several studies have shown that α6β4 influences migration and invasion of tumor cells through the NFAT (nuclear factor of activated T-cells) transcription factors [311] (**Fig. 3**), which are activated downstream of Src and PI3K/Akt signaling [312](reviewed in [67]). α6β4-mediated activation of NFAT1 induces the transcription of autotaxin [313], which promotes LPA-induced cell motility and invasiveness [314]. In line with this, α6β4-mediated cell motility was decreased in breast carcinoma cells that were depleted of autotaxin [313]. NFAT5, a transcription factor responsible for the upregulation of the calcium-binding protein S100A4, can also be activated by α6β4-mediated cell adhesion [315]. S100A4 is a metastasis-promoting protein implicated in the invasion of a number of tumor types including colon and breast carcinomas (reviewed in [316,317]). Another protein that plays a role in the calcium-dependent regulation of migration is the transient receptor potential vanilloid channel (TRPV1). In the absence of TRPV1, both directional migration and β4 expression are reduced [318].

Several studies suggested that α6β4 can influence ovarian and breast cancer cell migration and invasion through the activation of FAK [259,319]. α6β4-mediated FAK activation was

observed upon ligation of α6β4 to laminin-332, but also to alternative ligands, such as CLCA1 and MUC5Ac [320,321]. Recent findings have shown that FAK can directly bind to β4 and suggest that this association is regulated by tyrosine phosphorylation of the β4 subunit [259].

During invasion, the ECM is often remodeled, enabling tumor cells to efficiently migrate and disseminate. α6β4 has been implicated in ECM remodeling through its ability to contribute to the activation of PI3K and RhoA, and subsequent induction of traction forces generated by the actomyosin cytoskeleton [322,323]. Additionally, α6β4 plays a role in remodeling of the ECM by supporting signals that lead to the production of MMP1 and MMP2 [325,326]. MMP levels can also be induced by several of its interactors, such as CD151 (reviewed in [327–329]).

Metastasis – intravasation, extravasation and niche preparation

Many studies have demonstrated a critical role of α6β4 in promoting the formation of metastases (reviewed in [78,330,331]). Moreover, α6β4 serves as a marker to detect distant metastases in the early stages of specific malignancies [101,332,333]. However, the mechanism underlying its pro-metastatic role has received little attention. Metastases occur when cancer cells invade into the blood or lymph vessels, travel through these systems and subsequently extravasate into the stroma of the target organ. α6β4 contributes to intravasation and extravasation of tumor cells by upregulating VEGF expression (**Fig. 3**), which enhances transendothelial permeability and migration of malignant cells [334–337]. The effect of α6β4 on VEGF expression appeared to be dependent on the signaling domain of β4 [337].

Following extravasation, tumor cells need to adhere, proliferate and grow in the new environment (*i.e.* the metastatic niche) in order to form a metastasis. Cells from specific tumors tend to form metastasis in certain organs. Recently, Hoshino *et al.* [338] suggested that exosomes can contribute to the formation of a metastatic niche in specific organs. They showed that expression of α6β4 and α6β1 on exosomes was associated with lung metastases in mice, and that blocking of exosomal α6β4 decreased the formation of such metastases.

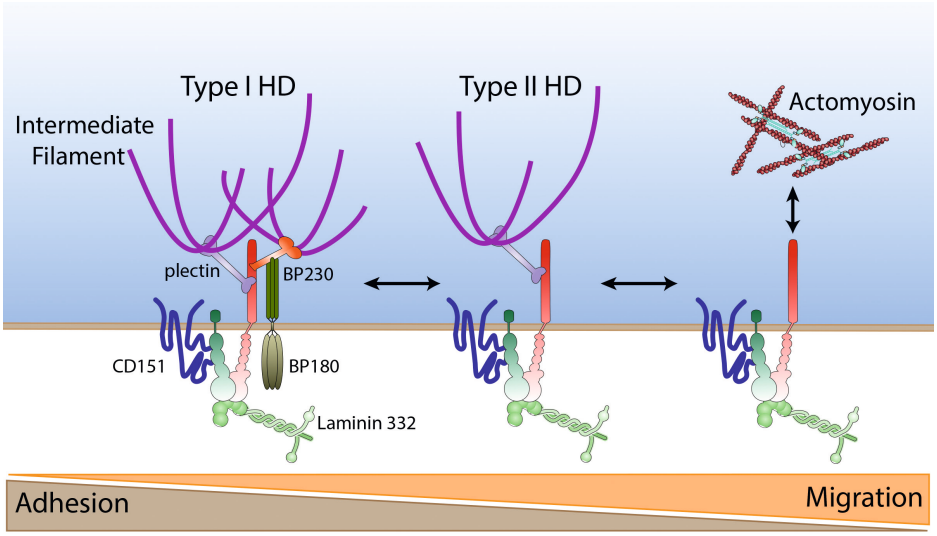

Figure 4: Integrin α6β4 regulates adhesion and migration by the formation of HDs. Type I HDs contribute to stable adhesion of basal epithelial cells to laminin-332 in the basement membrane and therefore inhibit cell migration. Although type II HDs contribute to adhesion as well, they are more dynamic and do not impede migration. In migrating cells, HDs are disassembled and α6β4 is suggested to be associated with the actin cytoskeleton.
HD, hemidesmosome.

Crosstalk with growth factors and hormones

The crosstalk between α6β4 and growth factor receptors not only plays a role in tumor growth (see previous chapters), but also strongly contributes to the α6β4-mediated tumor invasion, metastasis formation and cell migration. The synergy between α6β4 and several RTKs (*e.g.* c-Met [260,268], Ron [254,339], ErbB-2 [340], EGFR [258] and ErbB-3 [341]) primarily promotes tumor spreading and invasion. This tumor promoting function of α6β4, like its promotion of tumor growth, often involves the disassembly of HDs and subsequent β4-mediated signaling (reviewed in [47,68,80,342,343]). Additionally, α6β4 can have an impact on invasion and metastasis through regulating cell-cell junctions [252] (**Fig. 3**). In ErbB-2 transformed mammary epithelial cells, β4 promotes invasion and metastasis by disorganizing cell-cell junctions via SFK-dependent ErbB-2 activation of STAT3. Accordingly, in these cells the loss of β4 signaling restores cell-cell adhesion, and as a consequence cell invasion is compromised. However, this negative effect of β4 on cell-cell contacts is only seen in the presence of receptors of the EGFR family, and blocking these receptors promotes reassembly of cell-cell junctions [252]. Like α3β1, α6β4 was reported to promote the formation of cadherin dependent cell-cell junctions, resulting in restrained cell migration [344,345]. Furthermore, upon induction of EMT by TGF-β a decrease in E-cadherin expression has been correlated

with a reduction of the levels of β4 [346]. Such a reduction has also been shown in carcinoma cells in which EMT was induced by overexpression of Snail [347]. In contrast, suppression of the EMT regulator Slug resulted in a reduction of the α6β4 levels [348]. In addition to the reduced levels of β4 in tumor cells, which have undergone an EMT, there is evidence that β4 is less sialylated during EMT, which may further decrease the tumor promoting capacity of this integrin [349,350].

Besides a signaling cooperation between α6β4 and growth factor receptors, there is also crosstalk between α6β4 and hormones during tumor progression. Estrogen and PTHrP signaling was shown to enhance the pro-tumorigenic effects of α6β4 [351,352]. On the other hand, the expression of β4 in prostate cancer is reduced by the androgen receptor and the absence of β4 in the androgen-sensitive tumors reduces their invasiveness [353,354].

Targeted disruption of the crosstalk between α6β4 and growth factor receptors or between α6β4 and hormone receptors has been recognized as a potential form of therapy in the treatment of cancer [252,341,355]. However, because of its dual role in tumor development and promotion, targeting β4 can only be beneficial under well-defined and specific circumstances. In certain cancers, such as gastric carcinomas, the degree of β4 expression is inversely correlated with invasive potential and blocking β4 function would likely increase the tumor burden [276]. Furthermore, the analysis of transformed keratinocytes suggests that blocking the function of β4 in the early-stages of tumorigenesis might promote the disease [356].

Regulation of β4 expression

As previously discussed, the expression of β4 is frequently upregulated in cancer. For example, hypoxia increases the surface expression of α6β4 by promoting Rab11-dependent trafficking, resulting in increased breast tumor cell invasion [43]. Other factors and proteins implicated in the expression of β4 in tumors include Rac1 [357], TR3/Nur77 [358], PTHrP [352,359,360], IL24 [361] and H-Ras [362], ARRDC3 [363] and ZEB1 [364]. Expression of α6β4 is also regulated by palmitoylation of the α6 and β4 subunits and ablation of the protein acyl transferase, responsible for their palmitoylation results in accelerated degradation of α6β4 [365]. miRNAs have emerged in the past decade as key regulators of gene expression. They repress gene expression by blocking mRNA translation or promoting mRNA degradation [366]. Several miRNAs have been reported to regulate expression of β4. Overexpression of miR-221 and miR-222 resulted in reduced β4 expression, which was partially responsible for impaired invasion of breast cancer cells [367], while in the absence of miR-21 a higher expression level of β4 was correlated with a reduction in the rate of colorectal cancer cell migration

[366]. Furthermore, loss of miR-205 in prostate cancer resulted in reduced secretion of laminin-332 and β4 *in vitro* [368]. Therefore, the different expression patterns of β4 in cancer might be explained, at least to some extent, by specific miRNAs present in the different tissues.

Role of CD151 and α6 in α6β4-regulated tumorigenesis

Most studies have focused on the role of α6β4 in cancer without considering the fact that two isoforms of the α6 cytoplasmic domain (i.e. A and B) can be generated by alternative splicing [13,16]. In colorectal carcinomas, in which both a relative decrease and increase of β4 expression was observed during malignant transformation [369,370], the tumorigenic outcome of β4 positive cancers was dependent on which isoform of the α6 subunit was associated with β4 [371]. A relationship between the expression of specific α6 isoforms and tumor malignancy has also been observed in skin tumorigenesis [372]. As well as forming dimers with the β4 subunit, the α6 subunit can also dimerize with β1 to form the α6β1 heterodimer, which has a tumor promoting role and is correlated with a poor prognosis (discussed in introduction) [373]. Similar to α6β4, the role of α6β1 in cancer can be dependent on α6 isoform expression [374,375]. α6β1 and α6β4 are co-expressed in numerous cell lines. However, the ratio of these complexes varies considerably from one cell line to another [21]. Since α6 preferentially binds to the β4 subunit [231,376], the absence of β4 might lead to a switch from α6β4 to α6β1, and thus to promoting carcinogenesis in an α6β1-dependent manner. A switch from α6β4 to α6β1 has been observed during prostate cancer progression, in which expression of the androgen receptor suppresses α6β4 expression [241].

We have already discussed the impact of CD151-α3β1 on tumor progression. However, CD151 can also bind α6 and the presence of CD151-α6β4 in breast cancer was associated with tumor progression [204,377]. CD151 may affect the function of α6β4 through its association with PI4K or by regulating α6β4 trafficking, its incorporation into TEMs and/or its ligand binding activity [192,194,378]. Recently, it has been shown that CD151 is also involved in the crosstalk between α6β4 and RTKs [204,379] and that deletion of CD151 reduces β4 phosphorylation at specific serine residues [377,380]. These serine residues have been previously implicated in the regulation of the interaction between α6β4 and plectin [50,381]. While the interaction between α6β4 and CD151 is well-established, there is data supporting that α6β4 can also form complexes with two other tetraspanins (D6.1A and CD9) and thus might also influence tumorigenesis by interacting with these molecules [382,383].

CONCLUSIONS

The importance of laminin-binding integrins in the development and progression of tumors has been demonstrated in many studies. However, the role they play during these processes is complex, and possibly determined by several intra- and extracellular factors. Among the factors that have been shown to impact the outcome of tumor cells expressing laminin-binding integrins are the oncogenic profile and the nature of the tumor cells (*e.g.* secretion of hormones, presence of different membrane receptors, hypoxia, etc.), the presence of different ECM components (especially laminins), and the regulation of posttranslational modifications of the integrins.

Integrins influence multiple aspects of tumorigenesis through their impact on adhesion and their ability to enhance signaling pathways downstream of RTKs. One of the features of laminin-binding integrins that strongly influences tumorigenesis and tumor progression is their ability to mediate bi-directional signaling with small GTPases and to promote cytoskeletal remodeling. Several decades ago it was already known that tension-dependent changes in cell shape are necessary for progression of the cell cycle [384], and since then numerous studies have shown that integrin-mediated adhesion and spreading of cells is essential for nuclear translocation of transcription factors [309,385,386]. Therefore, the activation of GTPases by either α3β1- or α6β4-mediated cell adhesion not only influences tumor cell migration and invasion, but may also enable nuclear translocation of transcription factors to promote proliferation and survival of tumor cells that have not yet acquired the ability to grow anchorage independent. Furthermore, adhesion mediated by laminin-binding integrins, especially α6β4, might be essential for tumor development and progression simply by promoting pro-oncogenic signaling pathways.

The pro-migratory role of laminin-binding integrins is often connected to their ability to support PI3K-Rac1 signaling, which might be due to a lack of association of these integrins with the actomyosin cytoskeleton. Integrin α6β4 is connected with the intermediate filament system in type I and type II HDs, while α3β1, when associated with CD151, is incorporated into TEMs. Activation of Rac1 by either α3β1- or α6β4-mediated cell adhesion most likely occurs through synergy with aberrantly expressed and activated RTKs. Additionally, two tyrosine phosphorylation sites in the third fibronectin type III repeat of the β4 cytoplasmic domain (*i.e.* Y1494 and Y1526) have been reported to be sufficient for the activation of Rac [69,387]. Although these residues are located in N*XX*pY motifs, their structural environments are not compatible with binding to the PTB and SH2 binding domains of Shp2 and Shc, respectively [388]. The relevance of this mode of signaling therefore remains debatable.

Finally, the crosstalk between laminin-binding integrins and RTKs, and their association with IAPs, are the key determinants of the role of integrins in modulating cell behavior. As discussed in length above, α3β1 and α6β4 can interact with several different proteins. Therefore, it is very likely that a crosstalk between integrins and several different RTKs occurs in individual cells, and that several different α3β1 or α6β4 integrin-containing complexes exist simultaneously. However, little is known about the localization of these complexes, or how these different complexes interact. Therefore, a better understanding of how the balance between these complexes is established and how they influence oncogenic signaling pathways in cells will be necessary to fully understand the role of laminin-binding integrins in the development and progression of tumors.

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