Chapter 2
Roles of Integrins in the Development and Progression of Squamous Cell Carcinomas

John Lamar and C. Michael DiPersio

Abstract The identification of therapeutic targets for inhibiting malignant progression and metastasis remains a critically important step in combating cancer mortality in the clinic. Integrins, the major cell surface receptors for cell adhesion to the extracellular matrix, are involved in all stages of carcinogenesis and are promising targets for anti-cancer therapies. Indeed, roles for integrins in cancer have been the focus of intense investigation since this family of cell adhesion receptors was first discovered in the early 1980s, and many studies during the past three decades have described critical functions for integrins expressed on carcinoma cells in controlling proliferation, survival, migration, and angiogenesis. In addition to mediating cell adhesion, integrins serve as conduits of signal transduction across the plasma membrane, thereby mediating information flow between the interior of the tumor cell and the extracellular microenvironment that promotes angiogenesis and drives malignant growth and metastasis. Although a number of integrin antagonists are currently in pre-clinical and clinical development, the repertoire of integrins that is expressed by tumor cells varies considerably among different types of cancer. Therefore, the most effective combination of integrins to target will vary among cancer types and must be determined in each case. In this chapter, we will provide an overview of current knowledge regarding tumor-promoting functions of integrins that are expressed in squamous cell carcinoma (SCC), and we will consider the prospect of exploiting these integrins as therapeutic targets for inhibiting SCC in the clinic.

C.M. DiPersio (✉)
Center for Cell Biology & Cancer Research, Albany Medical College,
47 New Scotland Avenue, MC 165, Albany, NY 12208, USA
e-mail: dipersm@mail.amc.edu

A.B. Glick and C. Van Waes (eds.), *Signaling Pathways in Squamous Cancer*,
DOI 10.1007/978-1-4419-7203-3_2,

2.1 Introduction

Normal structure, function, and repair of stratified epithelial tissues are regulated by adhesive interactions of individual cells with both neighboring cells and the extracellular matrix (ECM), and abnormal changes in cell adhesion contribute to the development of squamous cell carcinoma (SCC) (Janes and Watt 2006). Integrins are the major receptors for cell adhesion to the ECM (Hynes 2002), while epithelial cell-cell interactions are controlled largely through cadherins, although there is considerable crosstalk between these two receptor families, as reviewed elsewhere (Chen and Gumbiner 2006; DiPersio 2008). While integrins are well known for their roles in cell adhesion, they can also modulate signal transduction pathways that control a variety of cell functions important in normal and pathological tissue remodeling, including proliferation, survival, motility, cytoskeletal dynamics, and gene expression (Hynes 2002; Giancotti and Ruoslahti 1999; Ridley et al. 2003). Indeed, integrins are important at every stage of carcinogenesis (Janes and Watt 2006; Kramer et al. 2005; Ziober et al. 2001), and they are potential therapeutic targets for inhibiting cancer progression (Rust et al., 2002; Stupp and Ruegg 2007).

This chapter provides an overview of current knowledge regarding the roles that integrins play in the development and malignant progression of SCC. Initial sections offer a brief review of known integrin functions in normal stratified epithelia, which provides the foundation for subsequent sections that are focused on integrin functions in SCC. The latter sections are structured to emphasize key concepts regarding various mechanisms that are used by different integrins to regulate SCC cell functions, and they draw on specific examples to illustrate these concepts. As space limitations preclude a complete discussion of the numerous published studies that have contributed to this field, the reader is directed to several excellent reviews for further coverage of relevant topics (Janes and Watt 2006; Kramer et al. 2005; Ziober et al. 2001).

2.2 Integrins as Potential Targets for Anticancer Therapies

All members of the integrin family are heterodimeric, transmembrane glycoproteins consisting of an α and a β subunit (Hynes 2002). Eighteen α subunits and eight β subunits can dimerize in various combinations to form at least 24 different integrins with distinct, though often overlapping, ligand-binding specificities (Hynes 2002). As a group, integrins bind to a wide variety of extracellular ligands, many of which are associated with the ECM. Simultaneously, integrin cytoplasmic domains can interact with cytoskeletal proteins to mediate a transmembrane linkage of the ECM to the cytoskeleton, which is critical for controlling cell shape, polarization, and motility (Chen and Gumbiner 2006; Delon and Brown 2007; Litjens et al. 2006; Liu et al. 2000; Ridley et al. 2003). In addition, although integrins lack intrinsic enzymatic activity, they are conduits of bidirectional signal transduction across the plasma membrane (Hynes 2002; Schwartz and Ginsberg 2002). Indeed,

through interactions of their cytoplasmic domains with a wide variety of signaling effectors inside the cell (Legate and Fassler 2009; Liu et al. 2000), integrins regulate intracellular pathways in response to extracellular cues (i.e., "outside-in" signal transduction). In addition, some cytoplasmic interactions can regulate the activation state of an integrin, thereby modulating its binding affinity for extracellular ligands (i.e., "inside-out" signal transduction) (Askari et al. 2009; Hynes 2002). Signaling functions of some integrins can be modulated by lateral interactions with other cell surface proteins, such as tetraspanins, urokinase receptor (uPAR), or caveolin, at sites of cell adhesion or from within specialized membrane microdomains (reviewed in Berditchevski 2001; Chapman et al. 1999; Del Pozo and Schwartz 2007; Hemler 2005; Porter and Hogg 1998). As discussed later in Sect. 2.4.3, some integrins signal through cooperative interactions with cell surface receptors for growth factors or cytokines (reviewed in Comoglio et al. 2003; French-Constant and Colognato 2004; Giancotti and Ruoslahti 1999; Guo and Giancotti 2004).

Integrins regulate many cell functions associated with epithelial-to-mesenchymal transition (EMT), and they have important roles in the development and malignant progression of SCC and other carcinomas (Brakebusch et al. 2002; Janes and Watt 2006; White et al. 2004). In their capacity as bidirectional signaling receptors, integrins regulate both tumor cell-mediated changes to the microenvironment that promote cancer progression, and tumor cell responses to such changes, implicating them as potential targets for antagonistic agents in anti-cancer therapies (Mulgrew et al. 2006; Rust et al. 2002; Stupp and Ruegg 2007; Wu et al. 1998). However, most integrin inhibitors in clinical development are thought to alter angiogenesis by targeting integrins on endothelial cells of the tumor vasculature (Alghisi and Ruegg 2006; Stupp and Ruegg 2007), and there remains a critical need to identify and validate specific integrin targets on tumor cells. As will be discussed, several integrins have been shown to regulate skin tumorigenesis, malignant progression, and metastasis, identifying them as possible therapeutic targets for SCC (Felding-Habermann 2003; Janes and Watt 2006; Ziober et al. 2001).

2.3 Roles of Integrins in Stratified Epithelia

Expression patterns of individual integrins in normal epidermis and other epithelia are well documented, and several integrins are known to have critical roles in regulating epithelial growth, differentiation, and wound repair (Watt 2002). Importantly, some integrin functions that are involved in maintenance of the stem cell compartment, or that promote epithelial regeneration during wound healing, also contribute to SCC (Janes and Watt 2006; Ziober et al. 2001). Indeed, it has long been recognized that wound healing and carcinogenesis share intriguing similarities regarding epithelial cell behaviors and microenvironmental factors that drive each process (Dvorak 1986). We will briefly review the expression and functions of specific integrins in normal stratified epithelia, and how they change during wound healing, to provide a foundation for our discussions in later sections on integrin functions in SCC.

2.3.1 Integrin Functions in Normal Stratified Epithelia

Stratified epithelia are continually renewed by stem cells that give rise to committed progenitor cells, or transit-amplifying cells, which in turn give rise to differentiated keratinocytes (Fuchs 2008; Owens and Watt 2003; Watt 2002). Proliferating keratinocytes, including stem cells and transit-amplifying cells, are normally restricted to the basal cell layer where they are adhered through integrins to the underlying basement membrane (BM), a specialized ECM that separates epithelial cell layers from adjacent connective tissue. In the epidermis, integrin expression is normally restricted to cells of the basal layer and outer root sheath of the hair follicle (Hertle et al. 1991; Watt 2002). Differentiating keratinocytes down-regulate integrin expression as they detach from the BM and are displaced into the suprabasal layers (Watt 2002).

Several integrins are expressed constitutively in normal, unwounded epidermis and oral squamous epithelium, including α3β1 and α6β4 (both laminin-332 receptors), α2β1 (a collagen receptor), α9β1 (a fibronectin and tenascin receptor) and αvβ5 (a vitronectin receptor) (Thomas et al. 2006; Watt 2002). Integrin α6β4 is an essential component of hemidesmosomes, which are adhesion structures on the basal surfaces of keratinocytes that anchor the epidermis to the dermis (Litjens et al. 2006). Consistently, deletion of α6β4 (through null mutation of either the *Itga6* or *Itgb4* gene, encoding the α6 or β4 subunit, respectively) leads to extensive epidermal blistering (Dowling et al. 1996; Georges-Labouesse et al. 1996; van der Neut et al. 1996). Deletion of α3β1 (through null mutation of the *Itga3* gene encoding the α3 subunit) causes minor perinatal blistering at the epidermal-dermal junction, but this is caused by rupture of the BM, which is disorganized in α3-null mice (DiPersio et al. 1997). Interestingly, mice that lack α3β1 and α6β4, either alone or in combination, show essentially normal epidermal stratification (DiPersio et al. 1997; Dowling et al. 1996; Georges-Labouesse et al. 1996; van der Neut et al. 1996; DiPersio et al., 2000a). Similarly, individual deletion of integrin α2β1, α9β1, or αvβ5 does not substantially alter epidermal differentiation (Grenache et al. 2007; Huang et al. 2000; Singh et al. 2009; Zweers et al. 2007). In contrast, ablation of all β1 integrins from epidermis (through null mutation of the *Itgb1* gene encoding the β1 subunit) leads to proliferation defects, loss of hair follicles and sebaceous glands and, depending on the genetic model, a modest increase in terminally differentiating keratinocytes (Brakebusch et al. 2000; Grose et al. 2002; Raghavan et al. 2000). Thus, there appears to be overlap in the roles of different integrins in maintaining epidermal homeostasis.

The level of integrin expression in keratinocytes is thought to control the balance between stem cell renewal and terminal differentiation, which is important for maintaining tissue homeostasis (Fuchs 2008; Jones et al. 1995; Watt 2002; Zhu et al. 1999). Indeed, β1 integrins and α6β4 are expressed at relatively high levels in epidermal stem cells (Janes and Watt 2006; Jones and Watt 1993; Jones et al. 1995; Terunuma et al. 2007), and some integrin signaling pathways have been linked to maintenance of the epidermal stem cell compartment, such as those

involving mitogen-activated protein kinases (MAPKs), or the Rho family guanosine triphosphatase (GTPase), RAC1 (Benitah et al. 2005; Haase et al. 2001; Zhu et al. 1999). Presumably, it is these resident stem cells that accumulate mutations in oncogenes and tumor suppressor genes that lead to tumorigenesis, since differentiated keratinocytes are eventually shed from the outer layer of stratified epithelia (Owens and Watt 2003; Watt 2002). Therefore, changes in integrins that disrupt the balance between stem cell renewal and differentiation are likely to greatly influence SCC development and progression.

It is important to point out, however, that altered integrin expression on differentiating cells of the suprabasal layers, as occurs in SCC and other hyperproliferative states such as wound healing and psoriasis, can also influence the stem cell compartment and, therefore, affect tumor growth and progression (reviewed in Janes and Watt 2006). Indeed, skin carcinogenesis studies performed in transgenic mice showed that forced integrin expression in suprabasal keratinocytes can influence both the clonal expansion of tumor progenitor cells and malignant progression of resulting tumors to SCC (Nguyen et al. 2000; Owens and Watt 2001; Owens et al. 2003, 2005). Interestingly, suprabasal expression of different integrins had distinct effects. For example, suprabasal α2β1 had no effect on SCC progression, while suprabasal α3β1 suppressed malignant conversion of papillomas (Owens and Watt 2001). In contrast, suprabasal α6β4 or α5β1 each increased tumor incidence and progression to SCC, although through distinct mechanisms (Owens and Watt 2003; Owens et al. 2005). Thus, new integrin signals that are turned on in suprabasal cells can influence nearby tumor progenitor/stem cells.

2.3.2 Integrin Functions in Wound Healing

As mentioned above, there are compelling similarities between wound healing and SCC progression (Dvorak 1986), and integrins regulate a number of epithelial functions important in both processes, including migration, proliferation, and the production of proangiogenic factors. Consistently, expression patterns of integrins in SCC often mirror those that occur in wound healing (Thomas et al. 2006; Watt 2002). During cutaneous wound healing, several integrins that are expressed in unwounded epidermis at high or moderate levels (i.e., α3β1, α9β1, α6β4) or low levels (i.e., α5β1) show sustained or increased expression, while αvβ5 is downregulated and replaced by αvβ6. As a group, these integrins can bind multiple ligands that are present in the provisional ECM of the wound, including fibronectin (α5β1, α9β1, αvβ6), vitronectin (αvβ6), and tenascin (α9β1, αvβ6), as well as laminin-332 (α3β1, α6β4) that is newly deposited by migrating keratinocytes (Nguyen et al. 2000; Thomas et al. 2006; Watt 2002). Furthermore, numerous studies in cultured cells have shown that these integrins regulate keratinocyte adhesion and migration on their respective ECM ligands [for example, (Grose et al. 2002; Carter et al. 1990a, b; Choma et al. 2004; Frank and Carter 2004; Pilcher et al. 1997;

Sehgal et al. 2006)]. Therefore, it is perhaps not surprising that wound healing studies in integrin knockout mice have indicated considerable overlap in the abilities of different integrins to mediate epidermal migration. Indeed, while mice with epidermis-specific deletion of all β1 integrins showed impaired wound reepithelialization (Grose et al. 2002), mice that lack certain β1 integrins individually (α2β1, α3β1, or α9β1) did not show such a defect (Grenache et al. 2007; Zweers et al. 2007); Singh et al. 2009; (Margadant et al. 2009). Similarly, absence of integrin αvβ6 did not cause impaired wound healing in young adult mice (although it caused delayed wound healing in old mice) (AlDahlawi et al. 2006).

On the other hand, epidermis-specific deletion of individual integrins has revealed important roles in regulating other aspects of wound healing. For example, deletion of α3β1 from epidermis was associated with reduced wound angiogenesis, indicating α3β1-dependent secretion of pro-angiogenic factors (Mitchell et al. 2009). In addition, deletion of α9β1 from epidermis caused proliferation defects in wound keratinocytes (Singh et al. 2009). Thus, the repertoire of distinct integrins expressed in wounded epidermis is important for coordinating diverse keratinocyte functions (migration, proliferation, ECM remodeling, secretion of pro-angiogenic factors) that collectively ensure efficient wound repair and epidermal regeneration. Importantly, these same integrin-mediated cell functions are also likely to contribute to SCC progression.

2.4 Roles of Integrins in SCC

Roles for integrins in promoting both early and late stages of SCC have been investigated extensively (reviewed in Janes and Watt 2006; Kramer et al. 2005; Marinkovich 2007; Thomas et al. 2006; Ziober et al. 2001). Integrins regulate a number of tumor cell functions that facilitate initial tumor growth, including proliferation, survival, and secretion of pro-angiogenic factors. In addition, integrin-mediated cell survival, migration, invasion, and ECM proteolysis are important for later stages of malignant tumor progression and metastasis (Brakebusch et al. 2002; Felding-Habermann 2003). Integrins can influence tumor cell behavior directly through their cell adhesion and signaling functions, or indirectly through effects on ECM remodeling. Indeed, there are many reports of integrins regulating expression or activities of extracellular proteases, such as matrix metalloproteinases (MMPs) or urokinase plasminogen activator (uPA), that can promote tumor angiogenesis and carcinoma progression [for example, (Brooks et al. 1996; Ellerbroek et al. 1999; Morini et al. 2000; Thomas et al. 2001a; Ghosh et al. 2000, 2006; Gu et al. 2002; Han et al. 2002; Iyer et al. 2005; Symowicz et al. 2007)]. In this section, we will review what is currently known about integrin expression and function in SCC. Although changes in relevant ECM ligands that occur in SCC will be mentioned where appropriate, the reader is directed to several excellent reviews for further details on this subject (Marinkovich 2007; Ziober et al. 2001). Because of space limitations, our discussion is concentrated on tumor cell-autonomous functions

of integrins on SCC cells and their potential value as therapeutic targets. However, integrins expressed on stromal cells, such as endothelial cells, macrophages, and fibroblasts, also regulate the abilities of these cells to alter the tumor microenvironment and influence carcinoma progression. Therefore, the importance of integrins on these nontumor cells as therapeutic targets should not be overlooked (Hofmeister et al. 2008).

2.4.1 Integrin Expression in SCC

There is evidence that the expression levels of certain integrins in SCC may serve as useful biomarkers for clinical outcome (Kurokawa et al. 2008). As already mentioned, altered integrin expression in SCC bears similarities to that which occurs during wound healing and includes sustained expression, increased expression, or loss of expression (Bagutti et al. 1998; Jones et al. 1993). For example, integrins $\alpha5\beta1$ and $\alpha v\beta6$ are expressed at low or negligible levels in normal epidermis but are increased in SCC (Gomez and Cano 1995; Shinohara et al. 1999), while $\alpha v\beta5$ is downregulated (Janes and Watt 2004, 2006). On the other hand, expression of $\alpha3\beta1$ and $\alpha6\beta4$ often persists in SCC (Janes and Watt 2006), although reduced expression has also been reported in some cases (Bagutti et al. 1998; Maragou et al. 1999). Colocalization of $\alpha9\beta1$ and its ligand, tenascin, has also been reported in SCC tumors, although inflamed areas often showed focal loss of both at the BM zone (Hakkinen et al. 1999). While some studies reported increased expression of $\alpha2\beta1$ in metastatic SCC cell lines and tumor biopsies (Shinohara et al. 1999), others reported that loss of $\alpha2\beta1$ and its collagen ligands is correlated with SCC progression (reviewed in (Ziober et al. 2001)). Importantly, there can also be considerable variation in expression of an individual integrin either within a tumor or between different SCC tumors, possibly reflecting differential expression in distinct cellular compartments of the tumor and/or at distinct stages of tumor progression (Janes and Watt 2006; Watt 2002).

However, while the expression pattern of an individual integrin might reflect its involvement in SCC, by itself it reveals no information about the functional role of the integrin at a particular stage of carcinogenesis. In fact, there is increasing evidence that some integrins that are already expressed on normal epithelial cells acquire new functions during SCC progression (see Sect. 4.5). As discussed in the following sections, numerous preclinical studies have identified key roles for specific integrins in SCC, and they also suggest that the malignant phenotype is influenced by the cumulative roles of several integrins, rather than by any particular integrin alone.

2.4.2 Integrin Signaling in SCC

Integrins expressed on tumor cells can relay signals bidirectionally across the plasma membrane that control basic cell functions important for cancer progression,

invasion, and metastasis, as reviewed in detail elsewhere (Brakebusch et al. 2002; Felding-Habermann 2003; Giancotti and Ruoslahti 1999; Gilcrease 2007; Guo and Giancotti 2004). As mentioned above and discussed in several reviews (Berditchevski 2001; Chapman et al. 1999; Del Pozo and Schwartz 2007; Hemler 2005; Porter and Hogg 1998; Salanueva et al. 2007), integrin signaling functions can be modulated through lateral associations with other cell surface proteins, including growth factor receptors (see Sect. 2.4.3). This discussion is focused on integrin-mediated outside-in signaling; however, changes in integrin activation state that are regulated by inside-out signals also control cell functions that promote carcinoma progression (Legate and Fassler 2009; Schwartz and Ginsberg 2002).

Focal adhesion kinase (FAK) has emerged in recent years as a particularly important effector of integrin-mediated signal transduction in tumor cells, and its regulation serves as a useful paradigm of outside-in integrin signaling that promotes malignant cell behavior (Brunton and Frame 2008; McLean et al. 2005; Mitra and Schlaepfer 2006; Zhao and Guan 2009). FAK is a nonreceptor tyrosine kinase that associates with several integrins at focal adhesions or other cell-matrix contacts, and its activation by cell adhesion is the initial enzymatic step in several integrin-dependent signaling pathways. Integrin-mediated FAK activation can contribute to many different tumor cell functions, including proliferation, survival, motility, and invasiveness, and it has been linked to the stimulation of various pathways involving the MAPKs, extracellular signal-regulated kinase (ERK) and Jun N-terminal kinase (JNK), certain Rho family GTPases (CDC42, Rho, RAC1), and the serine/threonine kinase AKT (Felding-Habermann 2003). FAK can also be activated by growth factor receptors, identifying it as a potential integrator of growth factor and integrin signaling (Brunton and Frame 2008; Sieg et al. 2000). Importantly, FAK expression is enhanced in invasive SCCs (Kornberg 1998), where it appears to regulate both early and late stages of cancer progression (reviewed in (Ziober et al. 2001)). Indeed, deletion of FAK from the epidermis suppresses carcinogen-induced skin tumorigenesis, as well as malignant progression of benign papillomas to carcinomas (McLean et al. 2004).

An early step in many integrin-FAK signaling pathways is the direct binding of a SRC-family kinase (SFK) to activated FAK at sites of cell adhesion (Schaller et al. 1999), as described in detail in several excellent reviews (Brunton and Frame 2008; Cary and Guan 1999; McLean et al. 2005; Mitra and Schlaepfer 2006). Briefly, integrin binding to ECM ligands leads to FAK clustering and auto-phosphorylation of Y397, creating a high-affinity binding site for the Src-homology 2 (SH2) domain of SRC (or another SFK) and leading to formation of a FAK/SRC complex. Subsequent phosphorylation of other FAK tyrosines by SRC creates binding sites for a number of signaling intermediates, such as GRB2, p130CAS, and phosphatidylinositol 3′-kinase (PI3-K). These intermediates link the FAK/SRC complex to different downstream effectors, including the RAS-to-ERK pathway, AKT, and JNK (Giancotti and Ruoslahti 1999; Grille et al. 2003; Mitra and Schlaepfer 2006), thereby activating several pathways that promote EMT by enhancing proliferation, survival, migration, invasion, and expression of ECM-degrading proteases and pro-angiogenic factors. As mentioned above, FAK/SRC

can also signal through Rho family GTPases (CDC42, Rho, and RAC1) to modulate cytoskeletal dynamics and cell migration (Felding-Habermann 2003). Furthermore, RAC1 plays important roles in keratinocyte proliferation and migration in vivo (Tscharntke et al. 2007), and it is critical for maintaining epidermal stem cell compartments (Benitah et al. 2005; Castilho et al. 2007; Chrostek et al. 2006), suggesting that enhanced FAK/SRC-to-RAC1 signaling may contribute to clonal expansion of tumor progenitor/stem cells. Consistently, mice that lack Tiam1, a guanine nucleotide-exchange factor (GEF) that activates RAC1, are resistant to RAS-induced skin tumors (Malliri et al. 2002).

Given the importance of the FAK/SRC complex as a major signaling nexus that links integrin-mediated adhesion to pathways that promote several cancer cell functions, it is not surprising that small molecule inhibitors of both FAK and SRC have been the focus of recent clinical studies to inhibit tumor progression (reviewed in (Brunton and Frame 2008; McLean et al. 2005; Mitra and Schlaepfer 2006)). However, integrins in epithelial cells can also signal through effectors other than FAK, such as integrin-linked kinase (ILK) and phospholipase C (PLC), as reviewed in detail elsewhere (Gilcrease 2007). Therefore, FAK-independent pathways should not be overlooked as potential therapeutic targets for SCC.

2.4.3 Functions of Individual Integrins in SCC

In the following subsections we will discuss tumor cell-autonomous functions of individual integrins that are expressed on SCC cells. This discussion is focused on integrins αvβ6, α3β1, and α6β4, since their roles have been studied most extensively. However, several other integrins with less-defined roles should also be mentioned briefly. For example, increased expression of integrin α9β1 and two of its ECM ligands, fibronectin and tenascin, has been reported in some SCCs (Hakkinen et al. 1999; Ziober et al. 2001). However, functional roles for α9β1 in SCC are poorly defined, in part because this integrin is down-regulated in cultured keratinocytes and has been largely overlooked in studies of integrin-mediated keratinocyte function. Although high expression of α2β1 (a receptor for certain laminins and collagens) and α5β1 (a receptor for fibronectin) has been reported in some SCC cell lines and tumor biopsies (Shinohara et al. 1999), expression patterns are quite variable and roles for these integrins in SCC require further study (Hakkinen et al. 1999; Ziober et al. 2001).

2.4.3.1 Integrin αvβ6

Regulatory roles for integrin αvβ6 in SCC have been studied quite extensively, as reviewed in (Thomas et al. 2006). Although not expressed constitutively by normal epithelium, αvβ6 is upregulated during wound healing and in many carcinomas (Breuss et al. 1995; Hamidi et al. 2000; Jones et al. 1997), and it has been correlated

with malignant progression of SCC (Hazelbag et al. 2007). Furthermore, numerous studies have demonstrated roles for this integrin in promoting SCC cell motility and invasion (for example, (Thomas et al. 2001a, b; Ramos et al. 2002)). αvβ6 binds to a tripeptide motif, arginine-glycine-aspartic acid (RGD), that occurs within several of its ECM ligands including fibronectin, tenascin, and vitronectin (Hynes 2002; Thomas et al. 2006). In addition to mediating cell migration on these ligands, αvβ6 may promote invasion by regulating expression of extracellular proteases that degrade or remodel ECM. For example, αvβ6 promotes invasion of oral keratinocytes through up-regulation of MMP-9 and, to a lesser extent, MMP-2 (Thomas et al. 2001a). Other invasion-promoting proteases that can be regulated by αvβ6 in carcinoma cells include MMP-3 (Ramos et al. 2002) and uPA (Ahmed et al. 2002). Signaling intermediates that have been implicated in αvβ6-mediated SCC cell invasion include cyclooxygenase-2 (COX-2) (Nystrom et al. 2006), RAC1 (Yap et al. 2009), and the SRC-family member FYN (Li et al. 2003). In addition to promoting an invasive phenotype, the de novo expression of αvβ6 has been shown to prevent oral SCC cells from undergoing differentiation, as well as protect them from anoikis (i.e., apoptosis caused by reduced or inappropriate cell adhesion) when they are deprived of normal attachments to BM (Janes and Watt 2004). The latter function involves αvβ6-mediated activation of an AKT survival pathway (Janes and Watt 2004).

One of the most important functions of αvβ6 in SCC cells may be its ability to activate the ECM-associated pool of latent TGFβ, thereby initiating TGFβ signaling pathways that influence tumor progression (Sheppard 2005; Thomas et al. 2006). As discussed further in Sect. 2.4.4.1, αvβ6 binds to an RGD motif within the latent TGFβ complex, thereby inducing a conformational change that activates TGFβ (Munger et al. 1999). Although this mechanism has been best characterized in colon cancer cells, it also occurs in keratinocytes and is likely to be important for regulating TGFβ-mediated signaling in SCC progression (Munger et al. 1999).

Finally, it is important to note that some studies have indicated that αvβ6 has tumor suppressing roles, rather than tumor promoting roles, in SCC. For example, mice that are doubly-deficient for αvβ6 and thrombospondin showed increased incidence of skin papillomas and SCCs, suggesting that αvβ6 suppresses tumor formation in this model (Ludlow et al. 2005). Similarly, genetic deletion of αv integrins in epithelial cells of the eyelid skin and conjunctiva lead to increased SCC (McCarty et al. 2008). In another study, increased expression of αvβ6 suppressed the invasive phenotype of transformed oral keratinocytes (Mogi et al. 2005). The paradoxical findings regarding roles for αvβ6 in SCC may, to some extent, be reflective of the well known biphasic roles of TGFβ, which suppresses early stages of skin tumorigenesis but promotes progression to malignancy at later stages (Wakefield and Roberts 2002; Wang 2001), such that effects of αvβ6-mediated TGFβ activation on tumor cells are dependent on the stage of cancer development at which this activation occurs (Thomas et al. 2006).

2.4.3.2 Laminin-332-Binding Integrins, α6β4 and α3β1

In recent years, a prominent role in SCC growth and invasion has emerged for laminin-332 (previously known as laminin-5, kalinin, nicein, or epiligrin) [for a

review, see (Marinkovich 2007)]. Laminin-332 expression is enhanced at the invasive fronts of SCCs (Pyke et al. 1995) and is correlated with poor prognosis in SCC patients (Ono et al. 1999). Laminin-332 also disrupts cell-cell adhesions and induces scattering in SCC and other carcinoma cells (Kawano et al. 2001; Miyazaki et al. 1993), suggesting that it can act as a pro-invasive autocrine factor (Marinkovich 2007). Laminin-332 can be cleaved by MMPs or other proteases (Ziober et al. 2001), and specific proteolytic events have been linked to carcinoma cell migration and invasion [for example, see (Gianelli et al. 1997; Goldfinger et al. 1998; Schenk et al. 2003)]. The effects of laminin-332 on behaviors of both normal keratinocytes and carcinoma cells are mediated largely through its main integrin receptors, α3β1 and α6β4 (Carter et al. 1991; Nguyen et al. 2000; Giannelli et al. 2002a; Dajee et al. 2003), although other receptors such as syndecan-1 also contribute (Okamoto et al. 2003). For simplicity, functions of α3β1 or α6β4 are discussed individually below, although as receptors for a common ECM ligand these two integrins are likely to function coordinately to regulate some aspects of SCC growth and invasion (Marinkovich 2007). There is also substantial evidence that some signaling functions of α3β1 or α6β4 occur independently of binding to laminin-332, and instead involve lateral interactions with other cell surface proteins (see below).

Integrin α6β4

Expression of integrin α6β4 is often high in SCCs and has been correlated with malignant conversion and poor prognosis (Jones et al. 1993; Rabinovitz and Mercurio 1996; Tennenbaum et al. 1993; Van Waes et al. 1991, 1995). Therefore, it is not surprising that roles for α6β4 in carcinogenesis have been studied extensively by several groups. These studies have revealed that α6β4 is critical for SCC formation (Dajee et al. 2003), and that it can promote survival and invasion of SCC and other carcinoma cells (Lipscomb and Mercurio 2005; Marinkovich 2007). α6β4 can also control organization of laminin-332 in the ECM, which is an important regulator of keratinocyte migration (Sehgal et al. 2006). However, α6β4 functions in carcinoma cells appear to be quite complex, and multiple mechanisms have been proposed for its effects on tumor cell behavior, as described below.

As already mentioned, α6β4 in normal keratinocytes mediates stable adhesion through its association with the intermediate filaments in hemidesmosomes (Carter et al. 1990a; Litjens et al. 2006). In contrast, α6β4 in invasive carcinoma cells is mobilized out of hemidesmosomes and associates instead with the actin cytoskeleton in membrane protrusions (Mercurio and Rabinovitz 2001; Mercurio et al. 2001), where it facilitates migration and invasion rather than stable adhesion. Signaling pathways through which α6β4 regulates cell behavior are complex and have been shown to involve several effectors, including PI3-K, RAC and Rho GTPases, and Shc/RAS-to-MAPK pathways (Lipscomb and Mercurio 2005; Mainiero et al. 1997; O'Connor et al. 2000; Russell et al. 2003). Adding further to this complexity, α6β4 often signals in collaboration with receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR) (Mariotti et al. 2001), the MET receptor for hepatocyte growth factor (HGF) (Trusolino et al. 2001), and the

Ron receptor for macrophage stimulating protein (MSP) (Santoro et al. 2003) (see Sect. 2.4.3).

Integrin α6β4 has also been implicated in the regulation of early stages of SCC progression, where it was shown to cooperate with RAS and IκBα to induce transformation of primary keratinocytes (Dajee et al. 2003). In this study, blocking antibodies against either α6β4 or laminin-332 blocked the formation of SCCs, and keratinocytes that lacked β4 were unable to form SCC after transformation with Ras. There is also evidence that α6β4 can regulate carcinoma cell survival (Chung et al. 2002; Zahir et al. 2003). While α6β4-mediated signaling pathways mentioned above are likely to contribute to this regulation, α6β4-mediated induction of VEGF protein translation in carcinoma cells can also regulate autocrine cell survival (Chung et al. 2002). The fact that α6β4 impacts SCC development and progression at multiple steps, and through multiple mechanisms, identifies this integrin as an attractive target for anticancer therapies, especially since at least some of these mechanisms are acquired by carcinoma cells (see Sect. 2.4.5.2).

Integrin α3β1

Integrin α3β1 has also been implicated in invasion and metastasis of many cancer cell types (Morini et al. 2000; Tawil et al. 1996; Tsuji et al. 2002; Wang et al. 2004). In vivo and in vitro studies have identified roles for α3β1 in regulating several functions in epithelial cells that contribute to both wound healing and carcinogenesis, including ECM deposition and organization (deHart et al. 2003; Hamelers et al. 2005), cell polarization and migration (Choma et al. 2004; Frank and Carter 2004), adhesion-dependent survival (Manohar et al. 2004), proliferation (Gonzales et al. 1999), and secretion of ECM proteases and pro-angiogenic factors (Marinkovich 2007; Mitchell et al. 2009; Sugiura and Berditchevski 1999; DiPersio et al. 2000b). There is also solid evidence that some of these α3β1-mediated functions involve regulation of TGFβ signaling (see Sect. 2.4.2).

Integrin α3β1 in immortalized/transformed keratinocytes regulates the expression of MMP-9 (Iyer et al. 2005; Lamar et al. 2008a), a known promoter of both tumor angiogenesis and SCC invasion (Bergers et al. 2000; McCawley and Matrisian 2001). Using oncogenically-transformed keratinocytes generated from mice that either express or lack α3β1, we showed that α3β1 is required for MMP-9 gene expression, and also regulates tumor growth in vivo and cell invasion in vitro (Iyer et al. 2005; Lamar et al., 2008a). Although promigratory effects of α3β1-laminin binding probably contribute to invasion, RNAi and overexpression studies indicated that MMP-9 was largely responsible for α3β1-dependent invasion (Lamar et al. 2008a). α3β1 may also be involved in later stages of metastasis, as it was able to promote arrest of circulating carcinoma cells in the lungs (Wang et al. 2004).

Many functions of α3β1 are clearly dependent on its interactions with its laminin ligands in the ECM (Kreidberg 2000). However, some α3β1 functions have been reported to be mediated, or modulated, by direct or indirect interactions with other cell surface proteins, including tetraspanins (Berditchevski et al. 1996; Sugiura and

Berditchevski 1999), uPAR (Wei et al. 2001), and components of adherens junctions (Chattopadhyay et al. 2003; Kim et al. 2009). Thus, roles of α3β1 in tumor cells appear complex and may involve both ECM-dependent and ECM-independent signaling. In particular, α3β1 binds directly and robustly to the tetraspanin CD151 (Yauch et al. 2000), and this interaction has been shown to regulate both α3β1-mediated signaling (Yauch et al. 1998) and motility of epidermal carcinoma cells (Winterwood et al. 2006). Interestingly, recent studies have identified important roles for CD151-integrin interactions in several aspects of carcinoma progression and metastasis in vivo (Sadej et al. 2009; Yang et al. 2008; Zijlstra et al. 2008). Although the full extent to which CD151 modulates α3β1-dependent functions in tumor cells is still unclear, it seems likely that this interaction will prove to be important for SCC progression and metastasis.

2.4.4 Cooperative Functions of Integrins and Growth Factors in SCC

Growth factors influence cancer growth and progression through both autocrine and paracrine effects on tumor cells and stromal cells. Multiple studies in both normal and cancer cells have revealed significant signaling crosstalk and complex formation between integrins and growth factor receptors (French-Constant and Colognato 2004; Gilcrease 2007; Guo and Giancotti 2004). In the following sections, we will discuss several examples that serve to illustrate different mechanisms whereby integrins can collaborate with growth factors to promote tumor growth and progression, including forming complexes with growth factor receptors, regulating the expression of growth factors or their receptors, and activating ECM-bound growth factors. As described below, some of these mechanisms are best illustrated by roles that have been demonstrated for certain integrins in regulating cellular responses to TGFβ.

2.4.4.1 Integrin-Dependent Activation of Latent Growth Factors

In what is perhaps the best characterized example of direct activation of a latent growth factor by an integrin, αvβ6 plays a critical role in the activation of the latent TGFβ complex (Sheppard 2005). Each of the three mammalian TGFβ isoforms (TGFβ1, 2, and 3) is secreted as an inactive complex consisting of the latency-associated protein (LAP) and the latent TGFβ binding protein (LTBP). This latent complex is covalently linked through LTBP to certain ECM proteins (e.g., fibronectin) (Sheppard 2005; Taipale et al. 1994), and it must be activated either through proteolytic release of TGFβ from the LAP [for example, mediated by MMP-9 or plasmin (Lyons et al. 1990; Sato et al. 1990; Yu and Stamenkovic 2000)], or through a conformational change in the complex [for example, induced by thrombospondin-1 (Crawford et al. 1998; Schultz-Cherry et al. 1995)]. As already mentioned, αvβ6 can activate latent

TGFβ1 or TGFβ3 (but not TGFβ2) by binding to an RGD motif within the LAP and inducing a conformational change in the complex (Annes et al. 2004; Munger et al. 1999; Sheppard 2005). It is well known that TGFβ acts as a tumor suppressor at early stages of tumorigenesis, but switches to a promoter of EMT at later stages of progression (for several excellent reviews, see Derynck et al. 2001; He et al. 2001; Wakefield and Roberts 2002; Wang 2001; Zavadil et al. 2001). Given that αvβ6 is upregulated in SCC, its ability to activate latent TGFβ could play a role in these biphasic effects of TGFβ on cancer progression.

In addition to direct growth factor activation, there is evidence that some integrins can activate latent or ECM-sequestered growth factors through less direct mechanisms. For example, certain integrins, such as αvβ6 and α3β1, can induce the expression of MMP-9, uPA, or other extracellular proteases (Thomas et al. 2001a; Ghosh et al. 2000, 2006; Iyer et al. 2005), which can then degrade ECM and release reservoirs of ECM-associated growth factors (i.e., VEGF) that can promote tumor proliferation or angiogenesis (Bergers et al. 2000; McCawley and Matrisian 2001).

2.4.4.2 Integrin-Dependent Enhancement of Growth Factor Signaling

Once activated, TGFβ interacts with its type I and type II serine/threonine kinase receptors to initiate signaling pathways that modulate transcriptional or post-transcriptional gene regulation. Cellular responses to TGFβ can be mediated by the Smad family of transcription factors, or by Smad-independent pathways of TGFβ signaling, such as MAPK pathways (Derynck and Zhang 2003). Many studies have identified interactions between integrins and TGFβ signaling pathways that regulate motility or invasiveness of keratinocytes or carcinoma cells (Gailit et al. 1994; Zambruno et al. 1995; Giannelli et al. 2002b; Decline et al. 2003; Galliher and Schiemann 2007; Jeong and Kim 2004; Reynolds et al. 2008). We recently discovered that integrin α3β1 potentiates the ability of TGFβ to induce MMP-9 gene expression in immortalized keratinocytes through a mechanism that is independent of changes in the levels of TGFβ or its receptors (Lamar et al. 2008b). However, α3β1 did not enhance all TGFβ signaling pathways, since TGFβ-mediated Smad phosphorylation remained intact in α3β1-deficient (*Itga3*-/-) keratinocytes, suggesting that this integrin is a selective modulator of a subset of TGFβ signaling pathways (Lamar et al., 2008b). These findings raise the intriguing possibility that α3β1 is involved in the above-mentioned switch in TGFβ function from tumor suppressor to tumor promoter during SCC progression.

Although the mechanism whereby α3β1 enhances TGFβ signaling is not yet clear, it is unlikely that this integrin activates latent TGFβ as described above for αvβ6 (Sect. 2.4.1), since α3β1 does not bind RGD ligands efficiently, and such a mechanism was not indicated for β1 integrins (Munger et al. 1999). Rather, the ability of α3β1 to potentiate MMP-9 induction in response to exogenous pre-activated TGFβ, and the dependence of this regulation on SRC (Lamar et al. 2008b), suggests similarities to a previously described mechanism used by integrin αvβ3 to modulate

a subset of TGFβ signaling pathways in breast cancer cells (Galliher and Schiemann 2007). In the latter study, αvβ3 was shown to activate the TGFβ type II receptor in a SRC-dependent manner, which was required for TGFβ-mediated activation of p38 MAPK, but not for TGFβ-mediated stimulation of Smad2/3 (Galliher and Schiemann 2007). Further studies are required to determine if MMP-9 induction requires the formation of a α3β1/TGFβ receptor signaling complex, or results from distinct pathways that are initiated independently by TGFβ or α3β1 and converge on a common intermediate. In any case, it appears that different integrins may modulate TGFβ activation and signaling through different mechanisms, thereby cooperating to determine the overall response of the tumor cell to TGFβ.

Although TGFβ exerts its effects on tumor cells in large part through signaling pathways that ultimately regulate the transcription of target genes (Derynck et al. 2001; Derynck and Zhang 2003), it is well known that TGFβ can also regulate the expression of EMT-associated genes through post-transcriptional mRNA stability (Dibrov et al. 2006). Integrin α3β1 promotes *Mmp9* mRNA stability in immortalized mouse keratinocytes (Iyer et al. 2005), raising the intriguing possibility that TGFβ and α3β1 cooperate to stabilize mRNA transcripts of EMT genes. The MAPK p38 is a potential effector for this regulation, since it has been implicated in both EMT-promoting effects of TGFβ (Bakin et al. 2002; Zavadil and Bottinger 2005) and TGFβ-mediated mRNA stability (Dibrov et al. 2006), and it can be activated through cooperative interactions between β1 integrins and TGFβ (Bhowmick et al. 2001). The MAPK ERK is another potential intermediate in this regulation. Indeed, TGFβ activates ERK pathways in cell culture models of EMT (Zavadil and Bottinger 2005), and ERK is both activated by α3β1, and required for induction of *Mmp9* mRNA in immortalized keratinocytes (Iyer et al. 2005; Manohar et al. 2004). In addition, TGFβ signaling through the type I receptor, ALK5, leads to MEK/ERK-dependent induction of *MMP9* mRNA in human breast cancer cells (Safina et al. 2007).

2.4.4.3 Formation of Integrin-Growth Factor Receptor Signaling Complexes

Association of integrin α6β4 with the MET receptor provides a compelling example of an integrin-growth factor receptor interaction that regulates signal transduction in carcinoma cells, most likely in a manner that is independent of α6β4 binding to laminin-332 (Trusolino et al. 2001). Indeed, in a complex formed with activated MET, α6β4 acts as an essential adapter protein that facilitates HGF-mediated cell invasion through a signaling mechanism that involves Shc and PI3-K (Trusolino et al. 2001). α6β4 can also form a complex with the activated Ron receptor, dependent on 14-3-3 binding, which displaces α6β4 from hemidesmosomes and activates new signaling pathways that promote keratinocyte migration (Santoro et al. 2003). Other studies in carcinoma cells have revealed crosstalk between α6β4 and EGFR that leads to Rho activation (Gilcrease et al. 2009), as well as complex formation between α6β4 and ERBB2 (a binding partner of EGFR) that enhances activation of the transcription factors STAT3 and c-Jun (Guo et al. 2006). In a less direct

mechanism of enhanced growth factor signaling, α6β4 can also regulate translation of ERBB2 (Yoon et al. 2006) and VEGF (Chung et al. 2002).

2.4.5 *Integrin Switches That Promote SCC*

As described in the following section, SCC cells can acquire new adhesion properties and signaling pathways either through changes in the expression of particular integrins, or through alterations in the signaling functions of integrins that were already expressed in normal epithelial cells. Elucidating the mechanisms that control these integrin switches may identify novel targets for therapeutic agents that inhibit cancer cell-specific integrin functions with minimal off-target effects on normal cells. Figures 2.1, 2.2, and 2.3 illustrate three different ways in which SCC cells can acquire new integrin functions: (1) expression of new integrins (Fig. 2.1), (2) changes in functions of pre-existing integrins (Fig. 2.2), and (3) integrin mutations (Fig. 2.3). The following sections will focus on examples of each mechanism from studies performed in keratinocytes or SCC cells. There are several points to keep in mind when considering these examples. First, as discussed below, there is evidence that some integrin switches may be linked to specific stages of carcinogenesis, and perhaps associated with specific oncogene or tumor suppressor mutations. Second, new integrin expression that is acquired during the clonal expansion of tumor progenitor cells could contribute to both heterogeneous expression patterns within a tumor, and variations in expression between different SCC samples (Janes and Watt 2006; Jones et al. 1993). Third, it is still not clear whether a "new" integrin function observed in SCC cells arises as a result of de novo activation of the function, or reflects the clonal expansion of a stem cell population within which the function pre-existed.

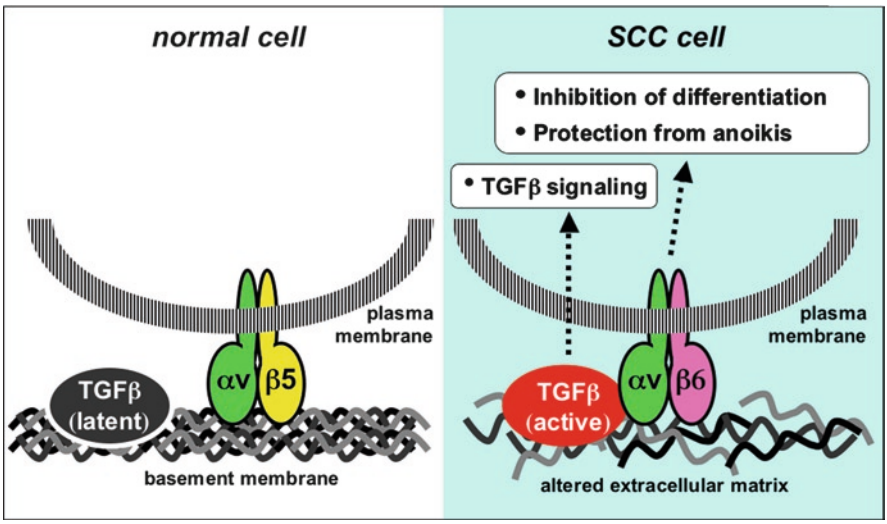

Fig. 2.1 Integrin switches that promote SCC: expression of new integrins.

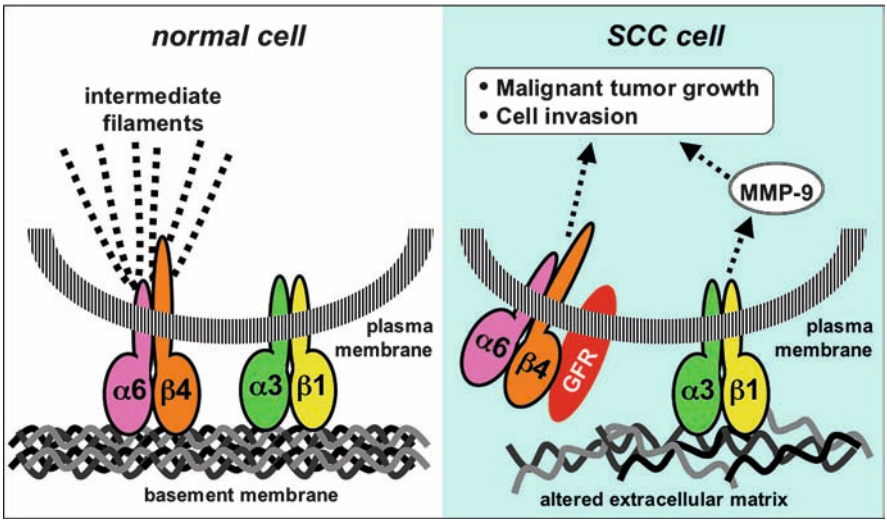

Fig. 2.2 Integrin switches that promote SCC: altered function of pre-existing integrins.

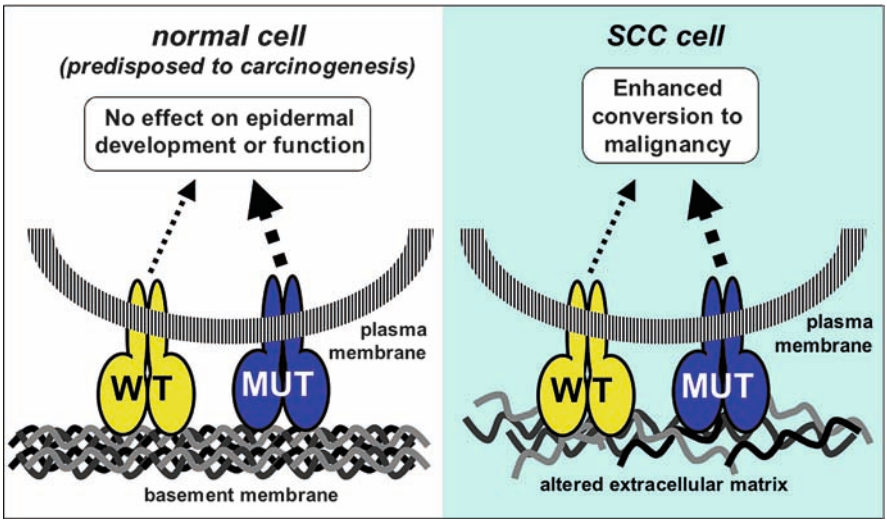

Fig. 2.3 Integrin switches that promote SCC: integrin mutations.

2.4.5.1 αv Integrin Switch

Upregulation of αvβ6 in SCC occurs at the expense of αvβ5 expression, probably due to higher affinity of the αv subunit for the β6 subunit (Janes and Watt 2004). Consequently, there is a switch from αvβ5 to αvβ6 as keratinocytes undergo malignant transformation, similar to that which has been described in wound healing (Clark et al. 1996). This switch in αv integrin expression from αvβ5 to αvβ6 provides a

clear example of new integrin expression that facilitates SCC progression (Fig. 2.1). Recent studies indicate that the switch from αvβ5 to αvβ6 protects SCC cells from undergoing differentiation or anoikis when they are deprived of normal attachments to BM, due to the very different effects that these two integrins have on both cell survival pathways and cell death pathways (Janes and Watt 2004). For example, protection of SCC cells from anoikis results in part from the ability of newly expressed αvβ6 to activate AKT survival pathways in cells that have lost adhesion to the BM and would otherwise undergo anoikis (Janes and Watt 2004). Loss of αvβ5 may also enhance cell survival, since this integrin had pro-apoptotic effects in its unligated form (Janes and Watt 2004). The switch from αvβ5 to αvβ6 may also provide temporal control of TGFβ activation by αvβ6 (see Sect. 2.4.1), since αvβ5 binds to the latent TGFβ complex with significantly lower avidity and probably does not support efficient TGFβ activation (Sheppard 2005). Although the mechanism that triggers the switch in αv integrins is not yet clear, possible effectors of αvβ6 induction include TNFα (Scott et al. 2004) and, interestingly, TGFβ itself (Zambruno et al. 1995).

2.4.5.2 Functional Switch in α6β4

In addition to de novo integrin expression described above, there is increasing evidence that some pre-existing integrins undergo functional changes during carcinoma progression, leading to the activation of new signaling pathways that promote tumorigenesis and invasion. Integrin α6β4 provides a paradigm for this sort of regulation, as during malignant conversion it switches from a predominantly adhesive receptor to a pro-invasive signaling protein that can form complexes with growth factor receptors (Lipscomb and Mercurio 2005; Mercurio et al. 2001) (Fig. 2.2). As already mentioned, α6β4 is associated with the intermediate filaments in hemidesmosomes of normal, undamaged epidermis (Litjens et al. 2006), but in invasive carcinoma cells this integrin relocates to actin-associated filopodia and lamelipodia through a mechanism that involves PKCα-mediated phosphorylation of the β4 cytoplasmic domain (Mercurio et al. 2001; Rabinovitz et al. 1999). There is also evidence that EGFR signaling through FYN kinase can disrupt α6β4 function in hemidesmosomes (Mariotti et al. 2001). This relocalization of α6β4 not only relieves tumor cells of stable adhesion that would presumably suppress invasive growth, but it also frees α6β4 to form new signaling complexes with growth factor receptors, such as those described above in Sect. 2.4.4.3, that promote tumor growth and malignant progression.

Interestingly, the SCC-associated switch in α6β4 function can be influenced by mutations in key oncogenes and tumor suppressor genes. Indeed, a recent study showed that α6β4 acts as either a tumor suppressor or tumor promoter depending on specific mutations that are acquired by keratinocytes (Raymond et al. 2007). Specifically, α6β4 inhibited tumor growth in tumorigenic keratinocytes that harbor loss-of-function mutations in the genes that encode p53 (*Trp53*) and Smad4 (*Smad4*), but it promoted tumor growth when these same cells were transformed by oncogenic RAS, indicating that RAS-mediated transformation induces a switch in α6β4 function (Raymond et al.

2007). Consistently, α6β4 was also shown to be essential for SCC formation caused by oncogenic RAS and the inhibitor of κBα (IκBα) (Dajee et al. 2003).

2.4.5.3 Functional Switch in α3β1

Integrin α3β1 provides another example of an integrin that can acquire novel signaling functions as keratinocytes accumulate cancer-promoting mutations (Fig. 2.2). We showed that α3β1-dependent *Mmp9* gene expression (discussed above in Sect. 2.3.2) was acquired in mouse keratinocytes as a result of immortalization caused by loss of p53, and was retained in RASV12-transformed versions of these cells where it promoted cell invasion (Lamar et al. 2008a). Importantly, α3β1-dependent MMP-9 expression was also observed in immortalized human keratinocytes and human SCC cell lines that harbor p53 mutations (Lamar et al. 2008a). Cancer-cell specific pathways whereby α3β1 induces expression of the *MMP9* gene or other EMT-promoting genes, would be attractive therapeutic targets. However, it is not yet known whether the acquisition of α3β1-dependent MMP-9 expression by immortalized cultures of keratinocytes represents a switch in α3β1 function that occurred de novo within tumor progenitor cells that have lost p53, or reflects the α3β1-dependent outgrowth of stem/tumor-progenitor cells that already possess this pathway. That α3β1 may promote the expansion of a tumor progenitor/stem cell compartment is an intriguing possibility, especially since α3β1 has been reported to be expressed at higher levels in epidermal stem cells (Jones et al. 1995). Consistent with such a role, α3β1 in keratinocytes is a known regulator of RAC1 signaling pathways (Choma et al. 2004), and RAC1 is essential for maintenance of the stem cell compartment in the epidermis (Benitah et al. 2005).

2.4.5.4 Gain-of-Function Mutations in Integrins

Another potential mechanism whereby altered integrin function may contribute to SCC progression is through rare gain-of-function mutations in integrin genes that predispose keratinocytes to the transforming effects of oncogenes. To date, the best example of such a mutation is T188Iβ1, which was first identified as a heterozygous mutation in the β1 gene (*ITGB1*) of a human cell line derived from a poorly differentiated SCC of the tongue (Evans et al. 2003). This mutation, which occurs in a region of the β1 I-like domain that determines ligand-binding specificity, leads to constitutive activation of all αβ1 integrin heterodimers and causes enhanced cell spreading, sustained ERK signaling, and reduced differentiation (Evans et al. 2003; Ferreira et al. 2009). Nevertheless, transgenic expression of T188Iβ1 did not alter normal architecture or homeostasis of the epidermis (Ferreira et al. 2009), consistent with the notion that this mutation is a genetic polymorphism that has no deleterious effects on epidermal development or function (Evans et al. 2003). However, following chemical carcinogenesis to induce skin tumors, mice expressing T188Iβ1 in the epidermis showed an increase in the frequency and rate of papilloma conversion to

SCCs, and also formed more poorly differentiated SCCs, compared with mice expressing only wild type β1 (Ferreira et al. 2009). These intriguing findings suggest that the T188Iβ1 mutation both predisposes benign tumors to malignant conversion and promotes formation of less differentiated tumors, providing an example of an integrin mutation that may influence both susceptibility to SCC and disease progression. Although other polymorphisms in the genes that encode β integrin subunits have been reported to occur in SCCs or other human cancers (Evans et al. 2003, 2004), their effects on carcinogenesis are not yet known. It also remains to be determined whether activating mutations in other domains of the β1 subunit, or in other β or α integrin subunits, can similarly predispose epidermis to SCC.

2.5 Exploiting Integrins in the Clinic

As described in the preceding sections, preclinical studies using cell culture and in vivo models of SCC have identified critical roles for integrins in the regulation of tumor growth, invasion, and metastasis. These studies provide a solid foundation for the development of therapeutic strategies to inhibit SCC using agents that target integrins, particularly since the location of integrins on the cell surface make them readily accessible to therapeutic compounds. Indeed, several types of integrin antagonists are currently in preclinical and clinical development, including humanized monoclonal antibodies (i.e., volociximab against α5β1, and Vitaxin against αvβ3), RGD-containing peptides (i.e., cilengitide), and non-peptide antagonists (Mulgrew et al. 2006; Rust et al. 2002; Stupp and Ruegg 2007; Thomas et al. 2006; Van Waes et al. 2000; Wu et al. 1998). The majority of these compounds are intended for use as angiogenesis inhibitors with a demonstrated ability to target integrins expressed on endothelial cells in the tumor vasculature (reviewed in (Stupp and Ruegg 2007; Tucker 2006)). However, preclinical studies in mice suggest that these and other compounds also effectively target integrins on tumor cells to reduce tumor cell growth, survival and metastasis (Chen et al. 2008; Gramoun et al. 2007; Harms et al. 2004; Landen et al. 2008; Park et al. 2006; Stoeltzing et al. 2003). Importantly, investigators have also exploited the increased or newly acquired expression of integrins on tumor cells, or tumor vessels, to deliver chemotherapies specifically to tumors (Abraham et al. 2007; Arap et al. 1998; Hallahan et al. 2003). Integrin-targeted micelles or liposomes have also been utilized to specifically deliver genes and antisense oligonucleotides to tumors (Bachmann et al. 1998; Cemazar et al. 2002; Oba et al. 2007).

Despite the success of some integrin antagonists in preclinical studies, these compounds have had only minimal success in early clinical trials (reviewed in (Stupp and Ruegg 2007; Tucker 2006)). In addition, recent evidence suggests that at least some integrin antagonists may enhance, rather than inhibit, tumor growth and angiogenesis under certain circumstances. For example, the αvβ3/αvβ5-specific RGD-mimetic, cilengitide, was shown to have antitumor activity in preclinical and clinical studies of certain forms of glioblastoma (Reardon et al. 2008), but it was recently reported to stimulate tumor growth and angiogenesis when administered at low doses in a murine model of tumor growth (Reynolds et al. 2009). These

discordant findings could be due to dose-dependent effects of cilengitide, or they may reflect differences between cancer types in the roles that αv integrins play on tumor cells and endothelial cells (Weller et al. 2009). In any case, they highlight the importance of understanding the roles of the intended integrin targets within distinct cellular compartments of the tumor type being tested, in order to predict the overall effect of a particular integrin antagonist. Future preclinical studies using inducible and cell-specific transgenic/knockout models, in which candidate integrins and signaling proteins can be manipulated with temporal and spatial precision, should reveal roles of individual integrins within different cellular compartments of the tumor, and help develop effective strategies to inhibit SCC by targeting integrins.

Another potential challenge that must be overcome before integrins can be fully exploited as therapeutic targets is that most integrins expressed on SCC cells also perform essential functions in normal cells; therefore systemic delivery of integrin inhibitors may cause adverse side effects. This problem might be avoided by targeting integrins that are expressed at high levels on SCC cells but at low or negligible levels on normal cells, such as αvβ6 (Fig. 2.1). In addition, identifying mechanisms that trigger new functions of pre-existing integrins, such as α3β1 and α6β4 (Fig. 2.2), or determining how gain-of-function mutations in integrins predispose keratinocytes to SCC (Fig. 2.3), may reveal intermediate molecules or pathways that are activated specifically in cancer cells and can be targeted with minimal effects on normal cell function. Another challenge is that the malignant phenotype is probably influenced by the cumulative functions of the various integrins expressed on SCC cells, such that combinatorial targeting of more than one integrin may be necessary to effectively inhibit disease progression.

Integrin antagonists may prove to be most useful in combination with other types of therapeutics. For example, preclinical studies have already demonstrated that cilengitide can synergize with either chemotherapy or radiotherapy (Albert et al. 2006; Burke et al. 2002; Tentori et al. 2008), and other compounds targeting integrins α5β1 and αVβ3 were also demonstrated to enhance chemosensitivity (Menendez et al. 2005; Stoeltzing et al. 2003) and augment the effects of radiotherapy (Abdollahi et al. 2005). Whether administered alone or in combination with other therapies, the efficacy and specificity of integrin antagonists or inhibitors of integrin signaling pathways could be improved by exploiting newly developed strategies for targeted delivery of compounds to tumors and tumor stroma. It may also be advantageous to target integrin function in tumor cells by combining targeted delivery systems with antisense oligonucleotides or RNAi to inhibit specific integrin expression. In support of this approach, antisense oligonucleotides that target αvβ3 were found to be effective against hepatocellular and mammary carcinoma in preclinical studies (Li et al. 2007; Townsend et al. 2000).

In summary, integrins represent promising targets for therapeutic strategies to inhibit SCC development and progression. Although most studies to test integrin antagonists have focused on cancers other than SCC, one preclinical study demonstrated that a non-peptide antagonist of integrin αv, SM256, significantly inhibited the in vivo growth of a murine SCC (Van Waes et al. 2000), suggesting that integrin αv antagonists are likely to be effective inhibitors of SCC in the clinic, as well. Future clinical and preclinical studies in SCC model systems, using antagonists or RNAi

strategies developed against other integrins discussed in this chapter, should determine if these integrins will also serve as effective therapeutic targets to treat SCC.

Acknowledgments The authors are grateful to the members of the DiPersio laboratory, and colleagues at Albany Medical College, for valuable discussions and insights. Studies conducted by the authors were supported by grants from the NIH/NCI to C.M. DiPersio (R01CA84238, R01CA129637). In addition, J. Lamar was supported by a predoctoral training grant from the National Heart, Lung, and Blood Institute (NIH-T32-HL-07194) and a predoctoral fellowship from the National Cancer Center (06118). We offer our apologies to the many researchers whose valuable contributions to the field could not be cited due to space constraints.

References

Abdollahi A, Griggs DW, Zieher H et al (2005) Inhibition of alpha(v)beta3 integrin survival signaling enhances antiangiogenic and antitumor effects of radiotherapy. Clin Cancer Res 11:6270–6279

Abraham S, Guo F, Li LS, Rader C, Liu C, Barbas CF 3rd, Lerner RA, Sinha SC (2007) Synthesis of the next-generation therapeutic antibodies that combine cell targeting and antibody-catalyzed prodrug activation. Proc Natl Acad Sci USA 104:5584–5589

Ahmed N, Pansino F, Clyde R, Murthi P, Quinn MA, Rice GE, Agrez MV, Mok S, Baker MS (2002) Overexpression of alpha(v)beta6 integrin in serous epithelial ovarian cancer regulates extracellular matrix degradation via the plasminogen activation cascade. Carcinogenesis 23:237–244

Albert JM, Cao C, Geng L, Leavitt L, Hallahan DE, Lu B (2006) Integrin alpha v beta 3 antagonist Cilengitide enhances efficacy of radiotherapy in endothelial cell and non-small-cell lung cancer models. Int J Radiat Oncol Biol Phys 65:1536–1543

AlDahlawi S, Eslami A, Hakkinen L, Larjava HS (2006) The alphavbeta6 integrin plays a role in compromised epidermal wound healing. Wound Repair Regen 14:289–27

Alghisi GC, Ruegg C (2006) Vascular integrins in tumor angiogenesis: mediators and therapeutic targets. Endothelium 13:113–135

Annes JP, Chen Y, Munger JS, Rifkin DB (2004) Integrin alphaVbeta6-mediated activation of latent TGF-beta requires the latent TGF-beta binding protein-1. J Cell Biol 165:723–734

Arap W, Pasqualini R, Ruoslahti E (1998) Cancer treatment by targeted drug delivery to tumor vasculature in a mouse model. Science 279:377–380

Askari JA, Buckley PA, Mould AP, Humphries MJ (2009) Linking integrin conformation to function. J Cell Sci 122:165–170

Bachmann AS, Surovoy A, Jung G, Moelling K (1998) Integrin receptor-targeted transfer peptides for efficient delivery of antisense oligodeoxynucleotides. J Mol Med 76:126–132

Bagutti C, Speight PM, Watt FM (1998) Comparison of integrin, cadherin, and catenin expression in squamous cell carcinomas of the oral cavity. J Pathol 186:8–16

Bakin AV, Rinehart C, Tomlinson AK, Arteaga CL (2002) p38 mitogen-activated protein kinase is required for TGFbeta-mediated fibroblastic transdifferentiation and cell migration. J Cell Sci 115:3193–31206

Benitah SA, Frye M, Glogauer M, Watt FM (2005) Stem cell depletion through epidermal deletion of Rac1. Science 309:933–935

Berditchevski F (2001) Complexes of tetraspanins with integrins: more than meets the eye. J Cell Sci 114:4143–4151

Berditchevski F, Zutter MM, Hemler ME (1996) Characterization of novel complexes on the cell surface between integrins and proteins with 4 transmembrane domains (TM4 proteins). Mol Biol Cell 7:193–207

Bergers G, Brekken R, McMahon G et al (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744

Bhowmick NA, Zent R, Ghiassi M, McDonnell M, Moses HL (2001) Integrin beta 1 signaling is necessary for transforming growth factor-beta activation of p38MAPK and epithelial plasticity. J Biol Chem 276:46707–46713

Brakebusch C, Grose R, Quondamatteo F et al (2000) Skin and hair follicle integrity is crucially dependent on beta 1 integrin expression on keratinocytes. EMBO J 19:3990–4003

Brakebusch C, Bouvard D, Stanchi F, Sakai T, Fassler R (2002) Integrins in invasive growth. J Clin Invest 109:999–1006

Breuss JM, Gallo J, DeLisser HM et al (1995) Expression of the beta 6 integrin subunit in development, neoplasia and tissue repair suggests a role in epithelial remodeling. J Cell Sci 108(Pt 6):2241–2251

Brooks PC, Stromblad S, Sanders LC, von Schalscha TL, Aimes RT, Stetler-Stevenson WG, Quigley JP, Cheresh DA (1996) Localization of matrix metalloproteinase MMP-2 to the surface of invasive cells by interaction with integrin αvβ3. Cell 85:683–693

Brunton VG, Frame MC (2008) Src and focal adhesion kinase as therapeutic targets in cancer. Curr Opin Pharmacol 8:427–432

Burke PA, DeNardo SJ, Miers LA, Lamborn KR, Matzku S, DeNardo GL (2002) Cilengitide targeting of alpha(v)beta(3) integrin receptor synergizes with radioimmunotherapy to increase efficacy and apoptosis in breast cancer xenografts. Cancer Res 62:4263–4272

Carter WG, Kaur P, Gil SG, Gahr PJ, Wayner EA (1990b) Distinct functions for integrins α3β1 in focal adhesions and α6β4/bullous antigen in a new stable anchoring contact (SAC) of keratinocytes: relation to hemidesmosomes. J Cell Biol 111:3141–3154

Carter WG, Ryan MC, Gahr PJ (1991) Epiligrin, a new cell adhesion ligand for integrin α3β1 in epithelial basement membranes. Cell 65:599–610

Carter WG, Wayner EA, Bouchard TS, Kaur P (1990a) The role of integrins α2β1 and α3β1 in cell-cell and cell-substrate adhesion of human epidermal cells. J Cell Biol 110:1387–1404

Cary LA, Guan JL (1999) Focal adhesion kinase in integrin-mediated signaling. Front Biosci 4:D102–D113

Castilho RM, Squarize CH, Patel V, Millar SE, Zheng Y, Molinolo A, Gutkind JS (2007) Requirement of Rac1 distinguishes follicular from interfollicular epithelial stem cells. Oncogene 26:5078–5085

Cemazar M, Sersa G, Wilson J, Tozer GM, Hart SL, Grosel A, Dachs GU (2002) Effective gene transfer to solid tumors using different nonviral gene delivery techniques: electroporation, liposomes, and integrin-targeted vector. Cancer Gene Ther 9:399–406

Chapman HA, Wei Y, Simon DI, Waltz DA (1999) Role of urokinase receptor and caveolin in regulation of integrin signaling. Thromb Haemost 82:291–297

Chattopadhyay N, Wang Z, Ashman LK, Brady-Kalnay SM, Kreidberg JA (2003) alpha3beta1 integrin-CD151, a component of the cadherin-catenin complex, regulates PTPmu expression and cell-cell adhesion. J Cell Biol 163:1351–1362

Chen X, Gumbiner BM (2006) Crosstalk between different adhesion molecules. Curr Opin Cell Biol 18:572–578

Chen Q, Manning CD, Millar H, McCabe FL, Ferrante C, Sharp C, Shahied-Arruda L, Doshi P, Nakada MT, Anderson GM (2008) CNTO 95, a fully human anti alphav integrin antibody, inhibits cell signaling, migration, invasion, and spontaneous metastasis of human breast cancer cells. Clin Exp Metastasis 25:139–148

Choma DP, Pumiglia K, DiPersio CM (2004) Integrin α3β1 directs the stabilization of a polarized lamellipodium in epithelial cells through activation of Rac1. J Cell Sci 117:3947–3959

Chrostek A, W X, Quondamatteo F, Hu R, Sanecka A, Niemann C, Langbein L, Haase I, Brakebusch C (2006) Rac1 is crucial for hair follicle integrity but is not essential for maintenance of the epidermis. Mol Cell Biol 26:6957–6970

Chung J, Bachelder RE, Lipscomb EA, Shaw LM, Mercurio AM (2002) Integrin (alpha 6 beta 4) regulation of eIF-4E activity and VEGF translation: a survival mechanism for carcinoma cells. J Cell Biol 158:165–174

Clark RA, Ashcroft GS, Spencer MJ, Larjava H, Ferguson MW (1996) Re-epithelialization of normal human excisional wounds is associated with a switch from alpha v beta 5 to alpha v beta 6 integrins. Br J Dermatol 135:46–51

Comoglio PM, Boccaccio C, Trusolino L (2003) Interactions between growth factor receptors and adhesion molecules: breaking the rules. Curr Opin Cell Biol 15:565–571
Crawford SE, Stellmach V, Murphy-Ullrich JE, Ribeiro SM, Lawler J, Hynes RO, Boivin GP, Bouck N (1998) Thrombospondin-1 is a major activator of TGF-beta1 in vivo. Cell 93:1159–1170
Dajee M, Lazarov M, Zhang JY, Cai T, Green CL, Russell J, Marinkovich MP, Tao S, Lin Q, Kubo Y, Khavari PA (2003) NF-kappaB blockade and oncogenic Ras trigger invasive human epidermal neoplasia. Nature 421:639–643
Decline F, Okamoto O, Mallein-Gerin F, Helbert B, Bernaud J, Rigal D, Rousselle P (2003) Keratinocyte motility induced by TGF-beta1 is accompanied by dramatic changes in cellular interactions with laminin 5. Cell Motil Cytoskeleton 54:64–80
deHart GW, Healy KE, Jones JC (2003) The role of alpha3beta1 integrin in determining the supramolecular organization of laminin-5 in the extracellular matrix of keratinocytes. Exp Cell Res 283:67–79
Delon I, Brown NH (2007) Integrins and the actin cytoskeleton. Curr Opin Cell Biol 19:43–50
Del Pozo MA, Schwartz MA (2007) Rac, membrane heterogeneity, caveolin and regulation of growth by integrins. Trends Cell Biol 17:246–250
Derynck R, Akhurst RJ, Balmain A (2001) TGF-beta signaling in tumor suppression and cancer progression. Nat Genet 29:117–129
Derynck R, Zhang YE (2003) Smad-dependent and Smad-independent pathways in TGF-beta family signalling. Nature 425:577–584
Dibrov A, Kashour T, Amara FM (2006) The role of transforming growth factor beta signaling in messenger RNA stability. Growth Factors 24:1–11
DiPersio CM (2008) Crosstalk between cell-cell and cell-matrix adhesion. In: LaFlamme SE, Kowalczyk AP (eds) Cell Junctions. Wiley-VCH, Weinheim, Germany
DiPersio CM, Hodivala-Dilke KM, Jaenisch R, Kreidberg JA, Hynes RO (1997) $\alpha 3\beta 1$ integrin is required for normal development of the epidermal basement membrane. J Cell Biol 137:729–742
DiPersio CM, Shao M, Di Costanzo L, Kreidberg JA, Hynes RO (2000a) Mouse keratinocytes immortalized with large T antigen acquire $\alpha 3\beta 1$ integrin-dependent secretion of MMP-9/gelatinase B. J Cell Sci 113:2909–2921
DiPersio CM, van der Neut R, Georges-Labouesse E, Kreidberg JA, Sonnenberg A, Hynes RO (2000b) alpha3beta1 and alpha6beta4 integrin receptors for laminin-5 are not essential for epidermal morphogenesis and homeostasis during skin development. J Cell Sci 113:3051–3062
Dowling J, Yu QC, Fuchs E (1996) $\beta 4$ integrin is required for hemidesmosomal formation, cell adhesion and cell survival. J Cell Biol 134:559–572
Dvorak HF (1986) Tumors: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med 315:1650–1659
Ellerbroek SM, Fishman DA, Kearns AS, Bafetti LM, Stack MS (1999) Ovarian carcinoma regulation of matrix metalloproteinase-2 and membrane type 1 matrix metalloproteinase through beta1 integrin. Cancer Res 59:1635–1641
Evans RD, Jones J, Taylor C, Watt FM (2004) Sequence variation in the I-like domain of the beta1 integrin subunit in human oral squamous cell carcinomas. Cancer Lett 213:189–194
Evans RD, Perkins VC, Henry A, Stephens PE, Robinson MK, Watt FM (2003) A tumor-associated beta 1 integrin mutation that abrogates epithelial differentiation control. J Cell Biol 160:589–596
Felding-Habermann B (2003) Integrin adhesion receptors in tumor metastasis. Clin Exp Metastasis 20:203–213
Ferreira M, Fujiwara H, Morita K, Watt FM (2009) An activating beta1 integrin mutation increases the conversion of benign to malignant skin tumors. Cancer Res 69:1334–1342
Frank DE, Carter WG (2004) Laminin 5 deposition regulates keratinocyte polarization and persistent migration. J Cell Sci 117:1351–63
French-Constant C, Colognato H (2004) Integrins: versatile integrators of extracellular signals. Trends Cell Biol 14:678–686
Fuchs E (2008) Skin stem cells: rising to the surface. J Cell Biol 180:273–284
Gailit J, Welch MP, Clark RA (1994) TGF-beta 1 stimulates expression of keratinocyte integrins during re-epithelialization of cutaneous wounds. J Invest Dermatol 103:221–227

Galliher AJ, Schiemann WP (2007) Src phosphorylates Tyr284 in TGF-beta type II receptor and regulates TGF-beta stimulation of p38 MAPK during breast cancer cell proliferation and invasion. Cancer Res 67:3752–3758

Georges-Labouesse E, Messaddeq N, Yehia G, Cadalbert L, Dierich A, Le Meur M (1996) Absence of integrin α6 leads to epidermolysis bullosa and neonatal death in mice. Nat Genet 13:370–373

Ghosh S, Brown R, Jones JC, Ellerbroek SM, Stack MS (2000) Urinary-type plasminogen activator (uPA) expression and uPA receptor localization are regulated by alpha 3beta 1 integrin in oral keratinocytes. J Biol Chem 275:23869–23876

Ghosh S, Johnson JJ, Sen R, Mukhopadhyay S, Liu Y, Zhang F, Wei Y, Chapman HA, Stack MS (2006) Functional relevance of urinary-type plasminogen activator receptor-alpha3beta1 integrin association in proteinase regulatory pathways. J Biol Chem 281:13021–13029

Giancotti FG, Ruoslahti E (1999) Integrin signaling. Science 285:1028–1032

Gianelli G, Falk-Marzillier J, Schiraldi O, Stetler-Stevenson WG, Quaranta V (1997) Induction of cell migration by matrix metalloprotease-2 cleavage of laminin-5. Science 277:225–228

Giannelli G, Astigiano S, Antonaci S, Morini M, Barbieri O, Noonan DM, Albini A (2002a) Role of the alpha3beta1 and alpha6beta4 integrins in tumor invasion. Clin Exp Metastasis 19:217–223

Giannelli G, Fransvea E, Marinosci F, Bergamini C, Colucci S, Schiraldi O, Antonaci S (2002b) Transforming growth factor-beta1 triggers hepatocellular carcinoma invasiveness via alpha-3beta1 integrin. Am J Pathol 161:183–193

Gilcrease MZ (2007) Integrin signaling in epithelial cells. Cancer Lett 247:1–25

Gilcrease MZ, Zhou X, Lu X, Woodward WA, Hall BE, Morrissey PJ (2009) Alpha6beta4 integrin crosslinking induces EGFR clustering and promotes EGF-mediated Rho activation in breast cancer. J Exp Clin Cancer Res 28:67

Goldfinger LE, Stack MS, Jones JCR (1998) Processing of laminin-5 and its functional consequences: role of plasmin and tissue-type plasminogen activator. J Cell Biol 141:255–265

Gomez M, Cano A (1995) Expression of beta 1 integrin receptors in transformed mouse epidermal keratinocytes: upregulation of alpha 5 beta 1 in spindle carcinoma cells. Mol Carcinog 12:153–165

Gonzales M, Haan K, Baker SE, Fitchmun M, Todorov I, Weitzman S, Jones JCR (1999) A cell signal pathway involving laminin-5, α3β1 integrin, and mitogen-activated protein kinase can regulate epithelial cell proliferation. Mol Biol Cell 10:259–270

Gramoun A, Shorey S, Bashutski JD, Dixon SJ, Sims SM, Heersche JN, Manolson MF (2007) Effects of Vitaxin, a novel therapeutic in trial for metastatic bone tumors, on osteoclast functions in vitro. J Cell Biochem 102:341–352

Grenache DG, Zhang Z, Wells LE, Santoro SA, Davidson JM, Zutter MM (2007) Wound healing in the alpha2beta1 integrin-deficient mouse: altered keratinocyte biology and dysregulated matrix metalloproteinase expression. J Invest Dermatol 127:455–466

Grille SJ, Bellacosa A, Upson J, Klein-Szanto AJ, van Roy F, Lee-Kwon W, Donowitz M, Tsichlis PN, Larue L (2003) The protein kinase Akt induces epithelial mesenchymal transition and promotes enhanced motility and invasiveness of squamous cell carcinoma lines. Cancer Res 63:2172–2178

Grose R, Hutter C, Bloch W, Thorey I, Watt FM, Fassler R, Brakebusch C, Werner S (2002) A crucial role of beta 1 integrins for keratinocyte migration in vitro and during cutaneous wound repair. Development 129:2303–15

Gu X, Niu J, Dorahy DJ, Scott R, Agrez MV (2002) Integrin alpha(v)beta6-associated ERK2 mediates MMP-9 secretion in colon cancer cells. Br J Cancer 87:348–351

Guo W, Giancotti FG (2004) Integrin signalling during tumour progression. Nat Rev Mol Cell Biol 5:816–826

Guo W, Pylayeva Y, Pepe A, Yoshioka T, Muller WJ, Inghirami G, Giancotti FG (2006) Beta 4 integrin amplifies ErbB2 signaling to promote mammary tumorigenesis. Cell 126:489–502

Haase I, Hobbs RM, Romero MR, Broad S, Watt FM (2001) A role for mitogen-activated protein kinase activation by integrins in the pathogenesis of psoriasis. J Clin Invest 108:527–536

Hakkinen L, Kainulainen T, Salo T, Grenman R, Larjava H (1999) Expression of integrin alpha9 subunit and tenascin in oral leukoplakia, lichen planus, and squamous cell carcinoma. Oral Dis 5:210–217

Hallahan D, Geng L, Qu S, Scarfone C, Giorgio T, Donnelly E, Gao X, Clanton J (2003) Integrin-mediated targeting of drug delivery to irradiated tumor blood vessels. Cancer Cell 3:63–74

Hamelers IH, Olivo C, Mertens AE, Pegtel DM, van der Kammen RA, Sonnenberg A, Collard JG (2005) The Rac activator Tiam1 is required for α3β1-mediated laminin-5 deposition, cell spreading, and cell migration. J Cell Biol 171:871–881

Hamidi S, Salo T, Kainulainen T, Epstein J, Lerner K, Larjava H (2000) Expression of alpha(v) beta6 integrin in oral leukoplakia. Br J Cancer 82:1433–1440

Han Q, Leng J, Bian D, Mahanivong C, Carpenter KA, Pan ZK, Han J, Huang S (2002) Rac1-MKK3-p38-MAPKAPK2 pathway promotes urokinase plasminogen activator mRNA stability in invasive breast cancer cells. J Biol Chem 277:48379–48385

Harms JF, Welch DR, Samant RS et al (2004) A small molecule antagonist of the alpha(v)beta3 integrin suppresses MDA-MB-435 skeletal metastasis. Clin Exp Metastasis 21:119–128

Hazelbag S, Kenter GG, Gorter A, Dreef EJ, Koopman LA, Violette SM, Weinreb PH, Fleuren GJ (2007) Overexpression of the alpha v beta 6 integrin in cervical squamous cell carcinoma is a prognostic factor for decreased survival. J Pathol 212:316–324

He W, Cao T, Smith DA, Myers TE, Wang XJ (2001) Smads mediate signaling of the TGFbeta superfamily in normal keratinocytes but are lost during skin chemical carcinogenesis. Oncogene 20:471–483

Hemler ME (2005) Tetraspanin functions and associated microdomains. Nat Rev Mol Cell Biol 6:801–811

Hertle MD, Adams JC, Watt FM (1991) Integrin expression during human epidermal development *in vivo* and *in vitro*. Development 112:193–206

Hofmeister V, Schrama D, Becker JC (2008) Anti-cancer therapies targeting the tumor stroma. Cancer Immunol Immunother 57:1–17

Huang X, Griffiths M, Wu J, Farese RV Jr, Sheppard D (2000) Normal development, wound healing, and adenovirus susceptibility in beta5-deficient mice. Mol Cell Biol 20:755–759

Hynes RO (2002) Integrins: bidirectional, allosteric signaling machines. Cell 110:673–687

Iyer V, Pumiglia K, DiPersio CM (2005) α3β1 integrin regulates MMP-9 mRNA stability in immortalized keratinocytes: a novel mechanism of integrin-mediated MMP gene expression. J Cell Sci 118:1185–1195

Janes SM, Watt FM (2004) Switch from alphavbeta5 to alphavbeta6 integrin expression protects squamous cell carcinomas from anoikis. J Cell Biol 166:419–431

Janes SM, Watt FM (2006) New roles for integrins in squamous-cell carcinoma. Nat Rev Cancer 6:175–183

Jeong HW, Kim IS (2004) TGF-beta1 enhances betaig-h3-mediated keratinocyte cell migration through the alpha3beta1 integrin and PI3K. J Cell Biochem 92:770–780

Jones PH, Watt FM (1993) Separation of human epidermal stem cells from transit amplifying cells on the basis of differences in integrin function and expression. Cell 73:713–724

Jones J, Sugiyama M, Watt FM, Speight PM (1993) Integrin expression in normal, hyperplastic, dysplastic, and malignant oral epithelium. J Pathol 169:235–243

Jones PH, Harper S, Watt FM (1995) Stem cell patterning and fate in human epidermis. Cell 80:83–93

Jones J, Watt FM, Speight PM (1997) Changes in the expression of alpha v integrins in oral squamous cell carcinomas. J Oral Pathol Med 26:63–68

Kawano K, Kantak SS, Murai M, Yao CC, Kramer RH (2001) Integrin alpha3beta1 engagement disrupts intercellular adhesion. Exp Cell Res 262:180–196

Kim Y, Kugler MC, Wei Y, Kim KK, Li X, Brumwell AN, Chapman HA (2009) Integrin alpha-3beta1-dependent beta-catenin phosphorylation links epithelial Smad signaling to cell contacts. J Cell Biol 184:309–322

Kornberg LJ (1998) Focal adhesion kinase and its potential involvement in tumor invasion and metastasis. Head Neck 20:745–752

Kramer RH, Shen X, Zhou H (2005) Tumor cell invasion and survival in head and neck cancer. Cancer Metastasis Rev 24:35–45

Kreidberg JA (2000) Functions of α3β1 integrin. Curr Opin Cell Biol 12:548–553

Kurokawa A, Nagata M, Kitamura N, Noman AA, Ohnishi M, Ohyama T, Kobayashi T, Shingaki S, Takagi R (2008) Diagnostic value of integrin alpha3, beta4, and beta5 gene expression levels for the clinical outcome of tongue squamous cell carcinoma. Cancer 112:1272–1281

Lamar JM, Pumiglia KM, DiPersio CM (2008a) An immortalization-dependent switch in integrin function up-regulates MMP-9 to enhance tumor cell invasion. Cancer Res 68:7371–7379

Lamar JM, Iyer V, DiPersio CM (2008b) Integrin alpha3beta1 potentiates TGFbeta-mediated induction of MMP-9 in immortalized keratinocytes. J Invest Dermatol 128:575–586

Landen CN, Kim TJ, Lin YG et al (2008) Tumor-selective response to antibody-mediated targeting of alphavbeta3 integrin in ovarian cancer. Neoplasia 10:1259–1267

Legate KR, Fassler R (2009) Mechanisms that regulate adaptor binding to beta-integrin cytoplasmic tails. J Cell Sci 122:187–198

Li X, Yang Y, Hu Y, Dang D, Regezi J, Schmidt BL, Atakilit A, Chen B, Ellis D, Ramos DM (2003) Alphavbeta6-Fyn signaling promotes oral cancer progression. J Biol Chem 278:41646–41653

Li J, Tan H, Dong X, Xu Z, Shi C, Han X, Jiang H, Krissansen GW, Sun X (2007) Antisense integrin alphaV and beta3 gene therapy suppresses subcutaneously implanted hepatocellular carcinomas. Dig Liver Dis 39:557–565

Lipscomb EA, Mercurio AM (2005) Mobilization and activation of a signaling competent alpha-6beta4integrin underlies its contribution to carcinoma progression. Cancer Metastasis Rev 24:413–423

Litjens SH, de Pereda JM, Sonnenberg A (2006) Current insights into the formation and breakdown of hemidesmosomes. Trends Cell Biol 16:376–383

Liu S, Calderwood DA, Ginsberg MH (2000) Integrin cytoplasmic domain-binding proteins. J Cell Sci 113:3563–3571

Ludlow A, Yee KO, Lipman R, Bronson R, Weinreb P, Huang X, Sheppard D, Lawler J (2005) Characterization of integrin beta6 and thrombospondin-1 double-null mice. J Cell Mol Med 9:421–437

Lyons RM, Gentry LE, Purchio AF, Moses HL (1990) Mechanism of activation of latent recombinant transforming growth factor beta 1 by plasmin. J Cell Biol 110:1361–1367

Mainiero F, Murgia C, Wary KK, Curatola AM, Pepe A, Blumenberhg M, Westwick JK, Der CJ, Giancotti FG (1997) The coupling of $\alpha 6\beta 4$ integrin to the Ras-MAP kinase pathways mediated by Shc controls keratinocyte proliferation. EMBO J 16:2365–2375

Malliri A, van der Kammen RA, Clark K, van der Valk M, Michiels F, Collard JG (2002) Mice deficient in the Rac activator Tiam1 are resistant to Ras-induced skin tumours. Nature 417:867–871

Manohar A, Shome SG, Lamar J, Stirling L, Iyer V, Pumiglia K, DiPersio CM (2004) Alpha 3 beta 1 integrin promotes keratinocyte cell survival through activation of a MEK/ERK signaling pathway. J Cell Sci 117:4043–4054

Maragou P, Bazopoulou-Kyrkanidou E, Panotopoulou E, Kakarantza-Angelopoulou E, Sklavounou-Andrikopoulou A, Kotaridis S (1999) Alteration of integrin expression in oral squamous cell carcinomas. Oral Dis 5:20–26

Margadant C, Raymond K, Kreft M, Sachs N, Janssen H, Sonnenberg A (2009) Integrin $\alpha 3\beta 1$ inhibits directional migration and wound re-epithelialization in the skin. J Cell Sci 122:278–288

Marinkovich MP (2007) Tumour microenvironment: Laminin 332 in squamous-cell carcinoma. Nat Rev Cancer 7:370–380

Mariotti A, Kedeshian PA, Dans M, Curatola AM, Gagnoux-Palacios L, Giancotti FG (2001) EGF-R signaling through Fyn kinase disrupts the function of integrin alpha6beta4 at hemidesmosomes: role in epithelial cell migration and carcinoma invasion. J Cell Biol 155:447–458

McCarty JH, Barry M, Crowley D, Bronson RT, Lacy-Hulbert A, Hynes RO (2008) Genetic ablation of alphav integrins in epithelial cells of the eyelid skin and conjunctiva leads to squamous cell carcinoma. Am J Pathol 172:1740–1747

McCawley LJ, Matrisian LM (2001) Matrix metalloproteinases: they're not just for matrix anymore! Curr Opin Cell Biol 13:534–540

McLean GW, Carragher NO, Avizienyte E, Evans J, Brunton VG, Frame MC (2005) The role of focal-adhesion kinase in cancer – a new therapeutic opportunity. Nat Rev Cancer 5:505–515

McLean GW, Komiyama NH, Serrels B, Asano H, Reynolds L, Conti F, Hodivala-Dilke K, Metzger D, Chambon P, Grant SG, Frame MC (2004) Specific deletion of focal adhesion kinase suppresses tumor formation and blocks malignant progression. Genes Dev 18:2998–3003

Menendez JA, Vellon L, Mehmi I, Teng PK, Griggs DW, Lupu R (2005) A novel CYR61-triggered 'CYR61-alphavbeta3 integrin loop' regulates breast cancer cell survival and chemosensitivity through activation of ERK1/ERK2 MAPK signaling pathway. Oncogene 24:761–779

Mercurio AM, Rabinovitz I (2001) Towards a mechanistic understanding of tumor invasion–lessons from the alpha6beta 4 integrin. Semin Cancer Biol 11:129–141

Mercurio AM, Rabinovitz I, Shaw LM (2001) The alpha 6 beta 4 integrin and epithelial cell migration. Curr Opin Cell Biol 13:541–545

Mitchell K, Szekeres C, Milano V, Svenson KB, Nilsen-Hamilton M, Kreidberg JA, DiPersio CM (2009) $\alpha 3\beta 1$ integrin in epidermis promotes wound angiogenesis and keratinocyte-to- endothelial-cell crosstalk through the induction of MRP3. J Cell Sci 122:1778–1787

Mitra SK, Schlaepfer DD (2006) Integrin-regulated FAK-Src signaling in normal and cancer cells. Curr Opin Cell Biol 18:516–523

Miyazaki K, Kikkawa Y, Nakamura A, Yasumitsu H, Umeda M (1993) A large cell-adhesive scatter factor secreted by human gastric carcinoma cells. Proc Natl Acad Sci USA 90:11767–11771

Mogi S, Dang D, Van Waes C, Ellis D, Atakilit A, Ramos DM (2005) The expression of integrin alpha(v)beta6 promotes the epithelial cell morphology and suppresses invasive behavior in transformed oral keratinocytes. Anticancer Res 25:751–75

Morini M, Mottolese M, Ferrari N, Ghiorzo F, Buglioni S, Mortarini R, Noonan DM, Natali PG, Albini A (2000) The alpha 3 beta 1 integrin is associated with mammary carcinoma cell metastasis, invasion, and gelatinase B (MMP-9) activity. Int J Cancer 87:336–342

Mulgrew K, Kinneer K, Yao XT, Ward BK, Damschroder MM, Walsh B, Mao SY, Gao C, Kiener PA, Coats S, Kinch MS, Tice DA (2006) Direct targeting of alphavbeta3 integrin on tumor cells with a monoclonal antibody, Abegrin. Mol Cancer Ther 5:3122–3129

Munger JS, Huang X, Kawakatsu H et al (1999) The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell 96:319–328

Nguyen BP, Ryan MC, Gil SG, Carter WG (2000) Deposition of laminin 5 in epidermal wounds regulates integrin signaling and adhesion. Curr Opin Cell Biol 12:554–562

Nystrom L, McCulloch D, Weinreb PH, Violette SM, Speight PM, Marshall JF, Hart IR, Thomas GJ (2006) Cyclooxygenase-2 inhibition suppresses alphavbeta6 integrin-dependent oral squamous carcinoma invasion. Cancer Res 66:10833–10842

Oba M, Fukushima S, Kanayama N, Aoyagi K, Nishiyama N, Koyama H, Kataoka K (2007) Cyclic RGD peptide-conjugated polyplex micelles as a targetable gene delivery system directed to cells possessing alphavbeta3 and alphavbeta5 integrins. Bioconjug Chem 18:1415–1423

O'Connor KL, Nguyen BK, Mercurio AM (2000) RhoA function in lamellae formation and migration is regulated by the alpha6beta4 integrin and cAMP metabolism. J Cell Biol 148:253–238

Okamoto O, Bachy S, Odenthal U, Bernaud J, Rigal D, Lortat-Jacob H, Smyth N, Rousselle P (2003) Normal human keratinocytes bind to the alpha3LG4/5 domain of unprocessed laminin-5 through the receptor syndecan-1. J Biol Chem 278:44168–44177

Ono Y, Nakanishi Y, Ino Y, Niki T, Yamada T, Yoshimura K, Saikawa M, Nakajima T, Hirohashi S (1999) Clinocopathologic significance of laminin-5 gamma2 chain expression in squamous cell carcinoma of the tongue: immunohistochemical analysis of 67 lesions. Cancer 85:2315–2321

Owens DM, Broad S, Yan X, Benitah SA, Watt FM (2005) Suprabasal alpha5 beta1 integrin expression stimulates formation of epidermal squamous cell carcinomas without disrupting TGFbeta signaling or inducing spindle cell tumors. Mol Carcinog 44:60–66

Owens DM, Romero MR, Gardner C, Watt FM (2003) Suprabasal alpha6beta4 integrin expression in epidermis results in enhanced tumourigenesis and disruption of TGFbeta signalling. J Cell Sci 116:3783–3791

Owens DM, Watt FM (2001) Influence of beta1 integrins on epidermal squamous cell carcinoma formation in a transgenic mouse model: alpha3beta1, but not alpha2beta1, suppresses malignant conversion. Cancer Res 61:5248–5254

Owens DM, Watt FM (2003) Contribution of stem cells and differentiated cells to epidermal tumours. Nat Rev Cancer 3:444–451

Park CC, Zhang H, Pallavicini M, Gray JW, Baehner F, Park CJ, Bissell MJ (2006) Beta1 integrin inhibitory antibody induces apoptosis of breast cancer cells, inhibits growth, and distinguishes malignant from normal phenotype in three dimensional cultures and in vivo. Cancer Res 66:1526–1535

Pilcher BK, Dumin JA, Sudbeck BD, Krane SM, Welgus HG, Parks WC (1997) The activity of collagenase-1 is required for keratinocyte migration on a type I collagen matrix. J Cell Biol 137:1445–1457

Porter JC, Hogg N (1998) Integrins take partners: cross-talk between integrins and other membrane receptors. Trends Cell Biol 8:390–396

Pyke C, Salo S, Ralfkiaer E, Romer J, Dano K, Tryggvason K (1995) Laminin-5 is a marker of invading cancer cells in some human carcinomas and is coexpressed with the receptor for urokinase plasminogen activator in budding cancer cells in colon adenocarcinomas. Cancer Res 55:4132–4139

Rabinovitz I, Mercurio AM (1996) The integrin alpha 6 beta 4 and the biology of carcinoma. Biochem Cell Biol 74:811–821

Rabinovitz I, Toker A, Mercurio AM (1999) Protein kinase C-dependent mobilization of the alpha6beta4 integrin from hemidesmosomes and its association with actin-rich cell protrusions drive the chemotactic migration of carcinoma cells. J Cell Biol 146:1147–1160

Raghavan S, Bauer C, Mundschau G, Li Q, Fuchs E (2000) Conditional ablation of beta1 integrin in skin. Severe defects in epidermal proliferation, basement membrane formation, and hair follicle invagination. J Cell Biol 150:1149–1160

Ramos DM, But M, Regezi J, Schmidt BL, Atakilit A, Dang D, Ellis D, Jordan R, Li X (2002) Expression of integrin beta 6 enhances invasive behavior in oral squamous cell carcinoma. Matrix Biol 21:297–307

Raymond K, Kreft M, Song JY, Janssen H, Sonnenberg A (2007) Dual Role of α6β4 Integrin in Epidermal Tumor Growth: Tumor-suppressive Versus Tumor-promoting Function. Mol Biol Cell 18:4210–4221

Reardon DA, Nabors LB, Stupp R, Mikkelsen T (2008) Cilengitide: an integrin-targeting arginine-glycine-aspartic acid peptide with promising activity for glioblastoma multiforme. Expert Opin Investig Drugs 17:1225–1235

Reynolds LE, Conti FJ, Silva R, Robinson SD, Iyer V, Rudling R, Cross B, Nye E, Hart IR, Dipersio CM, Hodivala-Dilke KM (2008) alpha3beta1 integrin-controlled Smad7 regulates reepithelialization during wound healing in mice. J Clin Invest 118:965–974

Reynolds AR, Hart IR, Watson AR et al (2009) Stimulation of tumor growth and angiogenesis by low concentrations of RGD-mimetic integrin inhibitors. Nat Med 15:392–400

Ridley AJ, Schwartz MA, Burridge K, Firtel RA, Ginsberg MH, Borisy G, Parsons JT, Horwitz AR (2003) Cell migration: integrating signals from front to back. Science 302:1704–1709

Russell AJ, Fincher EF, Millman L, Smith R, Vela V, Waterman EA, Dey CN, Guide S, Weaver VM, Marinkovich MP (2003) Alpha 6 beta 4 integrin regulates keratinocyte chemotaxis through differential GTPase activation and antagonism of alpha 3 beta 1 integrin. J Cell Sci 116:3543–3556

Rust WL, Carper SW, Plopper GE (2002) The promise of integrins as effective targets for anticancer agents. J Biomed Biotechnol 2:124–130

Sadej R, Romanska H, Baldwin G et al (2009) CD151 regulates tumorigenesis by modulating the communication between tumor cells and endothelium. Mol Cancer Res 7:787–798

Safina A, Vandette E, Bakin AV (2007) ALK5 promotes tumor angiogenesis by upregulating matrix metalloproteinase-9 in tumor cells. Oncogene 26:2407–2422

Salanueva IJ, Cerezo A, Guadamillas MC, del Pozo MA (2007) Integrin regulation of caveolin function. J Cell Mol Med 11:969–980

Santoro MM, Gaudino G, Marchisio PC (2003) The MSP receptor regulates alpha6beta4 and alpha3beta1 integrins via 14-3-3 proteins in keratinocyte migration. Dev Cell 5:257–271

Sato Y, Tsuboi R, Lyons R, Moses H, Rifkin DB (1990) Characterization of the activation of latent TGF-beta by co-cultures of endothelial cells and pericytes or smooth muscle cells: a self-regulating system. J Cell Biol 111:757–763

Schaller MD, Hildebrand JD, Parsons JT (1999) Complex formation with focal adhesion kinase: A mechanism to regulate activity and subcellular localization of Src kinases. Mol Biol Cell 10:3489–3505

Schenk S, Hintermann E, Bilban M, Koshikawa N, Hojilla C, Khokha R, Quaranta V (2003) Binding to EGF receptor of a laminin-5 EGF-like fragment liberated during MMP-dependent mammary gland involution. J Cell Biol 161:197–209

Schultz-Cherry S, Chen H, Mosher DF, Misenheimer TM, Krutzsch HC, Roberts DD, Murphy-Ullrich JE (1995) Regulation of transforming growth factor-beta activation by discrete sequences of thrombospondin 1. J Biol Chem 270:7304–7310

Schwartz MA, Ginsberg MH (2002) Networks and crosstalk: integrin signalling spreads. Nat Cell Biol 4:E65–E68

Scott KA, Arnott CH, Robinson SC, Moore RJ, Thompson RG, Marshall JF, Balkwill FR (2004) TNF-alpha regulates epithelial expression of MMP-9 and integrin alphavbeta6 during tumour promotion. A role for TNF-alpha in keratinocyte migration? Oncogene 23:6954–6966

Sehgal BU, DeBiase PJ, Matzno S, Chew TL, Claiborne JN, Hopkinson SB, Russell A, Marinkovich MP, Jones JC (2006) Integrin beta4 regulates migratory behavior of keratinocytes by determining laminin-332 organization. J Biol Chem 281:35487–35498

Sheppard D (2005) Integrin-mediated activation of latent transforming growth factor beta. Cancer Metastasis Rev 24:395–402

Shinohara M, Nakamura S, Sasaki M, Kurahara S, Ikebe T, Harada T, Shirasuna K (1999) Expression of integrins in squamous cell carcinoma of the oral cavity. Correlations with tumor invasion and metastasis. Am J Clin Pathol 111:75–88

Sieg DJ, Hauck CR, Ilic D, Klingbeil CK, Schaefer E, Damsky CH, Schlaepfer DD (2000) FAK integrates growth-factor and integrin signals to promote cell migration. Nat Cell Biol 2:249–256

Singh P, Chen C, Pal-Ghosh S, Stepp MA, Sheppard D, Van De Water L (2009) Loss of integrin alpha9beta1 results in defects in proliferation, causing poor re-epithelialization during cutaneous wound healing. J Invest Dermatol 129:217–228

Stoeltzing O, Liu W, Reinmuth N et al (2003) Inhibition of integrin alpha5beta1 function with a small peptide (ATN-161) plus continuous 5-FU infusion reduces colorectal liver metastases and improves survival in mice. Int J Cancer 104:496–503

Stupp R, Ruegg C (2007) Integrin inhibitors reaching the clinic. J Clin Oncol 25:1637–1638

Sugiura T, Berditchevski F (1999) Function of $\alpha 3\beta 1$-tetraspan protein complexes in tumor cell invasion. Evidence for the role of the complexes in production of matrix metalloproteinase 2 (MMP-2). J Cell Biol 146:1375–1389

Symowicz J, Adley BP, Gleason KJ, Johnson JJ, Ghosh S, Fishman DA, Hudson LG, Stack MS (2007) Engagement of collagen-binding integrins promotes matrix metalloproteinase-9-dependent E-cadherin ectodomain shedding in ovarian carcinoma cells. Cancer Res 67:2030–2039

Taipale J, Miyazono K, Heldin CH, Keski-Oja J (1994) Latent transforming growth factor-beta 1 associates to fibroblast extracellular matrix via latent TGF-beta binding protein. J Cell Biol 124:171–181

Tawil NJ, Gowri V, Djoneidi M, Nip J, Carbonetto S, Brodt P (1996) Integrin alpha3beta1 can promote adhesion and spreading of metastatic breast carcinoma cells on the lymph node stroma. Int J Cancer 66:703–710

Tennenbaum T, Weiner AK, Belanger AJ, Glick AB, Hennings H, Yuspa SH (1993) The suprabasal expression of alpha 6 beta 4 integrin is associated with a high risk for malignant progression in mouse skin carcinogenesis. Cancer Res 53:4803–4810

Tentori L, Dorio AS, Muzi A, Lacal PM, Ruffini F, Navarra P, Graziani G (2008) The integrin antagonist cilengitide increases the antitumor activity of temozolomide against malignant melanoma. Oncol Rep 19:1039–1043

Terunuma A, Kapoor V, Yee C, Telford WG, Udey MC, Vogel JC (2007) Stem cell activity of human side population and alpha6 integrin-bright keratinocytes defined by a quantitative in vivo assay. Stem Cells 25:664–669

Thomas GJ, Lewis MP, Hart IR, Marshall JF, Speight PM (2001a) AlphaVbeta6 integrin promotes invasion of squamous carcinoma cells through up-regulation of matrix metalloproteinase-9. Int J Cancer 92:641–650

Thomas GJ, Lewis MP, Whawell SA, Russell A, Sheppard D, Hart IR, Speight PM, Marshall JF (2001b) Expression of the alphavbeta6 integrin promotes migration and invasion in squamous carcinoma cells. J Invest Dermatol 117:67–73

Thomas GJ, Nystrom ML, Marshall JF (2006) Alphavbeta6 integrin in wound healing and cancer of the oral cavity. J Oral Pathol Med 35:1–10

Townsend PA, Villanova I, Uhlmann E, Peyman A, Knolle J, Baron R, Teti A, Horton MA (2000) An antisense oligonucleotide targeting the alphaV integrin gene inhibits adhesion and induces apoptosis in breast cancer cells. Eur J Cancer 36:397–409

Trusolino L, Bertotti A, Comoglio PM (2001) A signaling adapter function for alpha6beta4 integrin in the control of HGF-dependent invasive growth. Cell 107:643–654

Tscharntke M, Pofahl R, Chrostek-Grashoff A et al (2007) Impaired epidermal wound healing in vivo upon inhibition or deletion of Rac1. J Cell Sci 120:1480–1490

Tsuji T, Kawada Y, Kai-Murozono M, Komatsu S, Han SA, Takeuchi K, Mizushima H, Miyazaki K, Irimura T (2002) Regulation of melanoma cell migration and invasion by laminin-5 and alpha3beta1 integrin (VLA-3). Clin Exp Metastasis 19:127–134

Tucker GC (2006) Integrins: molecular targets in cancer therapy. Curr Oncol Rep 8:96–103

van der Neut R, Krimpenfort P, Calafat J, Niessen CM, Sonnenberg A (1996) Epithelial detachment due to absence of hemidesmosomes in integrin β4 null mice. Nat Genet 13:366–369

Van Waes C, Enamorado-Ayala I, Hecht D, Sulica L, Chen Z, Batt DG, Mousa S (2000) Effects of the novel alphav integrin antagonist SM256 and cis-platinum on growth of murine squamous cell carcinoma PAM LY8. Int J Oncol 16:1189–1195

Van Waes C, Kozarsky KF, Warren AB, Kidd L, Paugh D, Liebert M, Carey TE (1991) The A9 antigen associated with aggressive human squamous carcinoma is structurally and functionally similar to the newly defined integrin alpha 6 beta 4. Cancer Res 51:2395–2402

Van Waes C, Surh DM, Chen Z, Kirby M, Rhim JS, Brager R, Sessions RB, Poore J, Wolf GT, Carey TE (1995) Increase in suprabasilar integrin adhesion molecule expression in human epidermal neoplasms accompanies increased proliferation occurring with immortalization and tumor progression. Cancer Res 55:5434–5444

Wakefield LM, Roberts AB (2002) TGF-beta signaling: positive and negative effects on tumorigenesis. Curr Opin Genet Dev 12:22–29

Wang XJ (2001) Role of TGFbeta signaling in skin carcinogenesis. Microsc Res Tech 52:420–429

Wang H, Fu W, Im JH, Zhou Z, Santoro SA, Iyer V, DiPersio CM, Yu QC, Quaranta V, Al-Mehdi A, Muschel RJ (2004) Tumor cell α3β1 integrin and vascular laminin-5 mediate pulmonary arrest and metastasis. J Cell Biol 164:935–941

Watt FM (2002) Role of integrins in regulating epidermal adhesion, growth and differentiation. EMBO J 21:3919–26

Wei Y, Eble JA, Wang Z, Kreidberg JA, Chapman HA (2001) Urokinase receptors promote beta1 integrin function through interactions with integrin alpha3beta1. Mol Biol Cell 12:2975–2986

Weller M, Reardon D, Nabors B, Stupp R (2009) Will integrin inhibitors have proangiogenic effects in the clinic? Nat Med 15:726

White DE, Kurpios NA, Zuo D, Hassell JA, Blaess S, Mueller U, Muller WJ (2004) Targeted disruption of beta1-integrin in a transgenic mouse model of human breast cancer reveals an essential role in mammary tumor induction. Cancer Cell 6:159–170

Winterwood NE, Varzavand A, Meland MN, Ashman LK, Stipp CS (2006) A critical role for tetraspanin CD151 in alpha3beta1 and alpha6beta4 integrin-dependent tumor cell functions on laminin-5. Mol Biol Cell 17:2707–2721

Wu H, Beuerlein G, Nie Y, Smith H, Lee BA, Hensler M, Huse WD, Watkins JD (1998) Stepwise in vitro affinity maturation of Vitaxin, an alphav beta3-specific humanized mAb. Proc Natl Acad Sci USA 95:6037–6042

Yang XH, Richardson AL, Torres-Arzayus MI, Zhou P, Sharma C, Kazarov AR, Andzelm MM, Strominger JL, Brown M, Hemler ME (2008) CD151 accelerates breast cancer by regulating alpha 6 integrin function, signaling, and molecular organization. Cancer Res 68:3204–3213

Yap LF, Jenei V, Robinson CM, Moutasim K, Benn TM, Threadgold SP, Lopes V, Wei W, Thomas GJ, Paterson IC (2009) Upregulation of Eps8 in oral squamous cell carcinoma promotes cell migration and invasion through integrin-dependent Rac1 activation. Oncogene 28:2524–2534

Yauch RL, Berditchevsky F, Harler MB, Reichner J, Hemler ME (1998) Highly stoichiometric, stable, and specific association of integrin α3β1 with CD151 provides a major link to phosphatidylinositol 4-kinase, and may regulate cell migration. Mol Biol Cell 9:2751–2765

Yauch RL, Kazarov AR, Desai B, Lee RT, Hemler ME (2000) Direct extracellular contact between integrin α3β1 and TM4SF protein CD151. J Biol Chem 275:9230–9238

Yoon SO, Shin S, Lipscomb EA (2006) A novel mechanism for integrin-mediated ras activation in breast carcinoma cells: the alpha6beta4 integrin regulates ErbB2 translation and transactivates epidermal growth factor receptor/ErbB2 signaling. Cancer Res 66:2732–2739

Yu Q, Stamenkovic I (2000) Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. Genes Dev 14:163–176

Zahir N, Lakins JN, Russell A, Ming W, Chatterjee C, Rozenberg GI, Marinkovich MP, Weaver VM (2003) Autocrine laminin-5 ligates alpha6beta4 integrin and activates RAC and NFkappaB to mediate anchorage-independent survival of mammary tumors. J Cell Biol 163:1397–1407

Zambruno G, Marchisio PC, Marconi A, Vaschieri C, Melchiori A, Giannetti A, De Luca M (1995) Transforming growth factor-beta 1 modulates beta 1 and beta 5 integrin receptors and induces the de novo expression of the alpha v beta 6 heterodimer in normal human keratinocytes: implications for wound healing. J Cell Biol 129:853–865

Zavadil J, Bottinger EP (2005) TGF-beta and epithelial-to-mesenchymal transitions. Oncogene 24:5764–5774

Zavadil J, Bitzer M, Liang D, Yang YC, Massimi A, Kneitz S, Piek E, Bottinger EP (2001) Genetic programs of epithelial cell plasticity directed by transforming growth factor-beta. Proc Natl Acad Sci USA 98:6686–6691

Zhao J, Guan JL (2009) Signal transduction by focal adhesion kinase in cancer. Cancer Metastasis Rev 28:35–49

Zhu AJ, Haase I, Watt FM (1999) Signaling via beta1 integrins and mitogen-activated protein kinase determines human epidermal stem cell fate in vitro. Proc Natl Acad Sci USA 96:6728–6733

Zijlstra A, Lewis J, Degryse B, Stuhlmann H, Quigley JP (2008) The inhibition of tumor cell intravasation and subsequent metastasis via regulation of in vivo tumor cell motility by the tetraspanin CD151. Cancer Cell 13:221–234

Ziober BL, Silverman SS Jr, Kramer RH (2001) Adhesive mechanisms regulating invasion and metastasis in oral cancer. Crit Rev Oral Biol Med 12:499–510

Zweers MC, Davidson JM, Pozzi A, Hallinger R, Janz K, Quondamatteo F, Leutgeb B, Krieg T, Eckes B (2007) Integrin alpha2beta1 is required for regulation of murine wound angiogenesis but is dispensable for reepithelialization. J Invest Dermatol 127:467–478

http://www.springer.com/978-1-4419-7202-6

Signaling Pathways in Squamous Cancer
Glick, A.B.; Waes, C.V. (Eds.)
2011, XX, 462 p., Hardcover
ISBN: 978-1-4419-7202-6