

Integrins within the Tumor Microenvironment: Biological Functions and Advances in Therapeutic Targeting

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Abstract: Many cellular functions important for tumor initiation and progression are mediated by members of the integrin family, a diverse family of cell adhesion receptors. With recent studies emphasising on the role of the tumor microenvironment (TME) in tumor initiation and progression, it is not surprising that a lot of attention is being given to integrins. Several integrins are under trial with many demonstrating appealing activity in patients with different cancers. A deeper knowledge of the functions of integrins within the tumor microenvironment is still required, and might lead to better inhibitors being discovered. Integrin expression is commonly dysregulated in many tumors with integrins playing key roles in signaling as well as promotion of tumor cell invasion and migration. This review report new data on the differential expression of integrins within solid tumors using two publicly available resources: The Cancer Genomic Atlas (TCGA) and Gene Expression Profiling Interactive Analysis (GEPIA). In this analysis, I investigated the expression of integrin alpha 2 (*ITGa2*), *ITGa3*, *ITGβ4* and *ITGβ6* in tumor tissues versus adjacent normal tissues. This analysis showed that integrins were differentially expressed in cervical squamous cell carcinoma (CESC), head and neck squamous cell carcinoma (HNSC), esophageal carcinoma (ESCA) and lung adenocarcinoma (LUAD). This analysis showed that *ITGa2* and *ITGβ6* expression are upregulated in CESC and ESCA, *ITGa3* is upregulated in HNSC and ESCA whilst *ITGβ4* is highly expressed in CESC, HNSC, ESCA and LUAD tumor tissues compared to adjacent normal tissues. Integrins also play a major role in adhesion of circulating tumor cells to new sites and the resulting formation of secondary tumors. Furthermore, integrins have demonstrated the ability to promoting stem cell-like properties in tumor cells as well as drug resistance. Anti-integrin therapies rely heavily on the doses or concentrations used as these determine whether the drugs act as antagonists or as integrin agonists. This review offers the latest synthesis in terms of current knowledge of integrins functions within the tumor microenvironment and potential targets for different cancers.

Keywords: Integrins, Tumor Microenvironment, Drug Resistance, Migration, Metastasis, Solid Tumors, The Cancer Genome Atlas, Gene Expression, Computational Biology, Therapeutic Targeting

1.0 Introduction

Tumorigenesis involves the transformation of normal cells into cancer cells via mechanisms that include activation of many signaling cascades. Several studies have shown that integrins are directly involved in tumor initiation and progression via influencing cancer cell proliferation, migration, invasion and survival as well as partaking in cellular signaling [1, 2]. Most studies on integrins have focussed on their role in cellular migration and invasive behaviour. This is mostly due to integrins binding to extracellular matrix (ECM) proteins and aiding in creating traction needed by cells for migration and invasion. In addition, several tumor microenvironment (TME) components including biological molecules such as growth factors and proteases owe their localisation to certain regions to integrins [3, 4]. Thus, integrins can influence cellular proliferation and signaling through 'capturing' growth factors and proteases in certain regions of the TME [5, 6]. In cancer, integrins play a significant role in controlling cellular growth through binding to ECM proteins such as collagens and fibronectin and relay extracellular signals into the cell to affect gene expression [7-9]. It is important to point out that integrins relay both pro- and anti-tumorigenic signals, with the balance determining tumor growth and inhibition. Advances in TME biology have revealed that integrins, bound to ECM proteins or not, influence tumor growth via influence on cancer cell stemness as well as chemoresistance [10, 11]. Understanding the behavior of integrins in normal tissues and cancer has huge implications for their therapeutic targeting.

Beside integrins found on cancer cells, integrins are also present on cells associated with tumors and play a great role in influencing stromal cell-tumour cell interactions [12-14]. These stromal cells range from cancer associated-fibroblasts (CAFs), -macrophages (CAMs), -endothelial cells (CANs) as well as pericytes [15-18]. Most of these stromal cells are directly linked to processes occurring during tumor development and metastasis such as inflammation, angiogenesis and desmoplasia [19-21]. Integrins traverse the lipid bilayer and are the link between the extracellular space and the cytoplasm [22, 23]. Integrins relay extracellular cues through receptors for growth factors and cytokines and thus promote cellular signaling. Being present in both cancer cells and stromal cells, integrins influence tumor development as well as metastasis. New findings show that specific integrins are required by certain growth factors and oncogenes during tumor initiation and growth [5, 6]. This makes it critical to delineate the crosstalk between integrins and growth factors and oncogenes during drug development. To date, several studies both pre-clinical and clinical trials have been done using integrin inhibitors and these have demonstrated

various levels of efficacy at blocking tumor progression [24, 25]. In addition, integrin inhibitors have shown little or no known side effects in some cancer patients [26-28]. The success demonstrated with integrin inhibitors must be augmented by further research into the role of integrins in different cancers as well as in tumor development and growth.

2.0 Literature Search Methodology

A search for literature material was done on PubMed and MEDLINE databases until August 2020 for published articles with the following keywords: integrins, tumor microenvironment, gene expression, solid tumors, signaling, growth factors, angiogenesis and metastasis. Language of communication was set to English and full articles were included (Figure 1). A total of 1106 articles were used and with the aid of the criteria as shown in Figure 1, a final total of 190 articles were obtained. The methodology enabled the synthesis of the review on integrins as key players in cellular processes and signaling and their possible therapeutic targeting using different therapies. Several well written articles by a lot of authors were not cited due to limitations on length and I humbly apologize for those not cited.

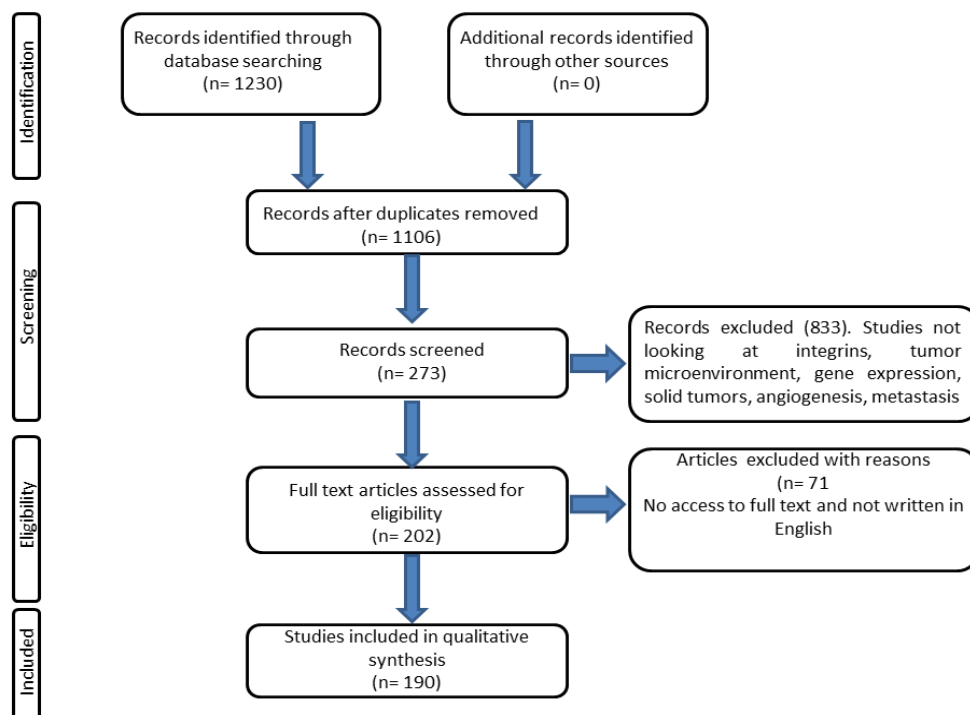


Figure 1. Selection of studies included in the qualitative synthesis of the review manuscript.

3.0 Integrin Biological Properties

Integrins are receptors that traverse the lipid bilayer of the cell membranes and their main function is to relay extracellular cues to cells by binding to the ECM and other immunoglobulin molecules (Figure 2) [23, 29-31]. A minimum of 24 different heterodimer combinations from 18 α -subunits and 8 β -subunits are formed. Each combination of α and β subunits specifically bind to certain ECM proteins and immunoglobulin molecules [23, 31]. The formation of the integrins dimers occur in the endoplasmic reticulum with post-translational changes occurring in the Golgi apparatus before the inactive integrins are transferred to the cell surface [32]. Different cells express different integrins and this greatly influence adhesion to different surfaces as well as ability to migrate [20, 23]. The recognition and binding of integrins to their respective ligands may be influenced by the specific sequence on the ligand. For example, integrins α_v and $\alpha_5\beta_1$ recognize and bind to ligands with the RGD sequence [33]. Furthermore, integrin $\alpha_4\beta_1$ recognizes and binds to the REDV and EILDV adhesive sequences on several ECM proteins [34, 35]. Adhesion to the ECM results in integrins forming focal adhesions which are clusters of integrins and signaling molecules and proteins [36, 37]. Studies done in two-dimensional (2-D) and 3-D report different compositions of focal adhesions for the same cells [38, 39]. Integrins are able to cluster and therefore activate kinases within focal adhesions such as focal adhesion kinases and Src family kinases [40-42]. In addition, integrins are able to couple the cytoskeleton and the ECM through recruiting several proteins such as α -actinin and tensin [43, 44]. Together with parvin and PINCH, integrins are able to form large platforms that interact with actin and several signaling cascades [45, 46]. A family of transmembrane proteins known as tetraspanins cross the cell membrane four times has been shown to form complexes through interaction with several proteins including integrins [47, 48]. Integrins and several of these proteins involved in focal adhesions and other complexes are under investigation as possible target for therapies in many diseases. In addition, oncogene or growth factor-induced signaling may influence integrin binding affinity, contributing to disease states and progression [49, 50].

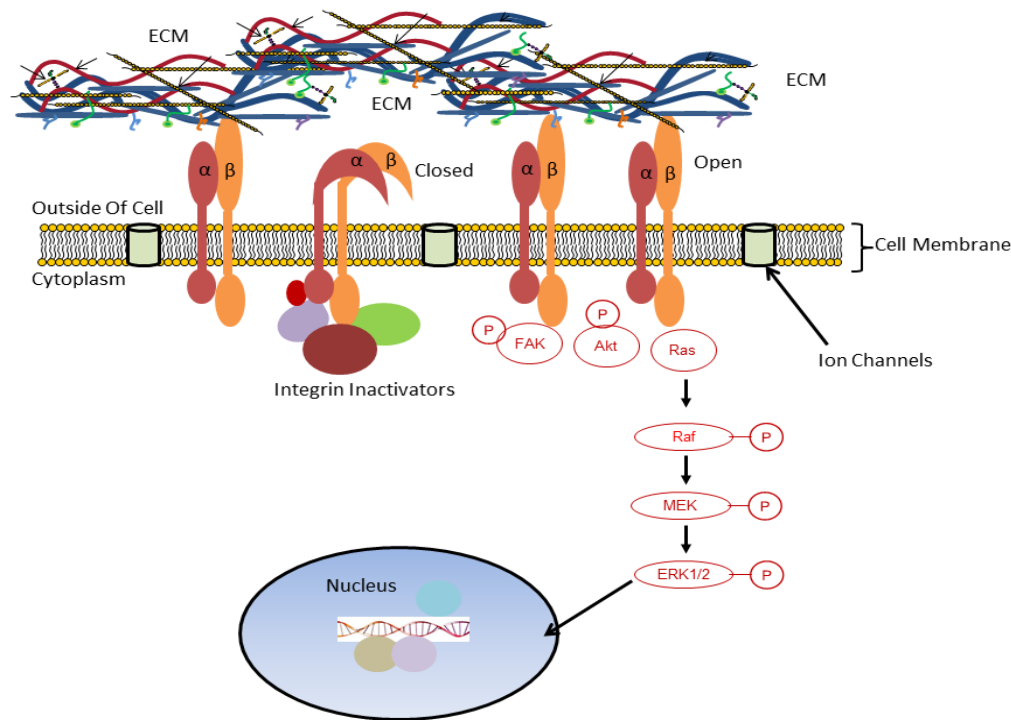


Figure 2. Integrins can have open and closed configurations that influence adhesions to the ECM. The classic outside-in integrin signaling involves integrins binding to the ECM and activation of several intracellular signaling cascades including the Ras-MEK-ERK signaling. The translocation of phosphorylated ERK1/2 molecules to the nucleus results in expression of genes involved in cellular proliferation, migration and survival. Figure was adapted from Dzobo and colleagues [3, 51]

4.0 Integrin Contribution to Tumorigenesis

Several pieces of evidence have shown that integrins contribute toward cancer growth and progression (Figure 3). With many cancers starting in epithelial cells, integrins expressed by these cells play key roles during cancer growth and progression. Integrins increase cellular signaling via interactions with FAK, PI3K-Akt and the MEK-ERK pathways [3, 4]. In addition, stromal cells including cancer-associated fibroblasts synthesize increased amounts of ECM proteins and these display enhanced interaction with integrins. Several reports show that integrins are also involved in metastasis and the priming and colonization of new sites for secondary tumors to form. Furthermore, cancer therapy has been shown to induce integrins expression leading to drug resistance.

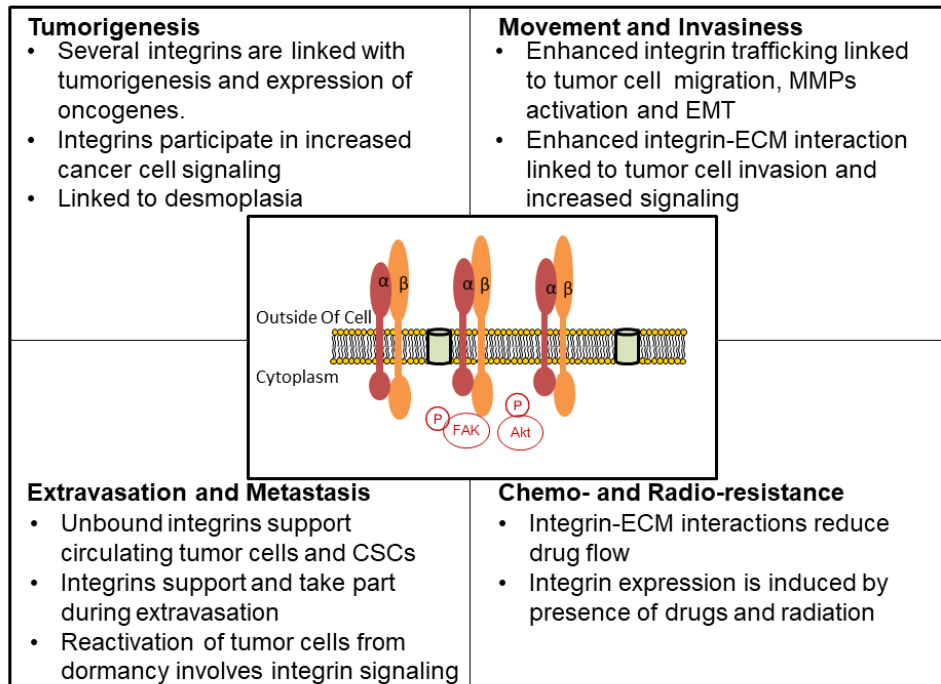


Figure 3. The effect of integrins on different stages of tumor progression. Integrins are involved at every stage of tumor progression starting with tumor initiation to tumor cell migration and invasion, extravasation and metastasis and finally the development of therapy resistance.

5.0 The Significance of Integrins in Tumorigenesis

Examples of integrins expressed by epithelial cells include $\alpha 2\beta 1$, $\alpha 6\beta 4$ and $\alpha 3\beta 1$ and may display dysregulated expression in tumors. Whilst data strongly show these integrins role in cellular attachment to the ECM and the basement membrane, recent data also showed their participation in cellular proliferation, migration and metastatic behaviours [52-54]. Integrins expression has also been shown to change when epithelial cells transform to cancer cells. For example, $\alpha v\beta 6$ and $\alpha v\beta 3$ integrins are known to be highly upregulated in tumors such as ovarian and colon compared to normal cells [55-58]. In addition, these integrins are also associated with increased metastasis and tumor cell proliferation in ovarian cancer [59, 60]. Several reports also show that some integrins decrease in expression in some tumors. For example, $\alpha 2\beta 1$ integrin expression is decreased in breast tumors [61-63]. Decreased integrin expression in cancer cells has been linked with invasion and metastatic behavior [64-66]. Several studies have linked integrin expression in tumors to patient survival and disease progression, with integrins $\alpha v\beta 3$, $\alpha 6\beta 4$ and $\alpha v\beta 6$ among the most studied. As new data is generated, the picture become clear on which integrins are important in different tumors. McCabe and colleagues demonstrated that $\alpha v\beta 3$ integrin is

associated with metastatic behaviour of prostate cancer cells to the bone matrix [67]. In addition, the expression of $\alpha v\beta 3$ and $\alpha v\beta 6$ is linked to decreased cervical cancer patients survival [68, 69]. Integrin $\alpha 5\beta 1$ expression is associated with metastasis and decreased cancer patient survival in melanoma and lung carcinoma [70-72]. The expression of $\alpha v\beta 3$ is linked to pancreatic cancer cells metastasizing to the lymph node [73].

5.1 Bioinformatic Analysis of Integrins' RNA-seq Data

Increasing data indicate that integrins represent an important component of the tumor microenvironment and thus contribute to several malignant phenotypes. Utilizing the publicly available The Cancer Genomic Atlas (<http://cancergenome.nih.gov>), the Gene Expression Profiling Interactive Analysis (<http://gepia.cancer-pku.cn>) datasets and The Human Protein Atlas (www.proteinatlas.org), below this study evaluated the significance of integrins in solid cancer malignance. Integrin differential expression was evaluated in tumor tissues versus the adjacent normal tissues as well as in relation to patients' overall survival. Messenger RNA expression levels of *ITGa2*, *ITGa3*, *ITGb4* and *ITGb6* were evaluated in tumor tissues compared to adjacent normal tissues. Expression data was downloaded in October 2020 via the TCGA portal using available web-based tools allowing deep analysis of the integrins expression. Web-based tools available on the GEPIA website were used for analysis of integrins expression within TCGA and GEPIA databases.

5.2 Statistical Analysis

GraphPad Prism software (version 6, San Diego, USA) was used for the analysis with both Student's t-test and one way analysis of variance test used to analyse significance of differences. Statistical significance was set at $p < 0.05$.

5.3 Differential Expression of Integrins in Tumors

Several pieces of evidence points to integrins contributing to tumor initiation and development of malignant phenotypes, therefore it is important to investigate the significance of integrins in several solid tumors using The Cancer Genomic Atlas dataset. In this analysis, four cancers were used as examples to investigate the relationship between integrin expression and cancer malignance phenotype. The cancers analysed are cervical squamous cell carcinoma (CESC), head

and neck squamous cell carcinoma (HNSC), esophageal carcinoma (ESCA) and lung adenocarcinoma (LUAD). Expression of integrins in tumor tissues was compared to that in adjacent normal tissues (as a box plot) based on TCGA/GEPIA database.

Bioinformatic analysis showed that *ITGa2* expression was significantly upregulated in CESC and ESCA tumor tissues compared to adjacent normal tissues (Figure 4A). The increased *ITGa2* expression observed in ESCA was observed in our previous report [20]. Consistent with the above results, 10 out of 11 cervical cancer specimens showed medium to high *ITGa2* protein expression based on immunohistochemistry data available at The Human Protein Atlas database. There were no significant differences in *ITGa2* expression in HNSC and LUAD tumor tissues compared to adjacent normal tissues (Figure 4A). *ITGa3* expression was upregulated in HNSC and ESCA tumor tissues versus adjacent normal tissues whilst there were not significant differences in *ITGa3* expression in CESC and LUAD tumor tissues versus normal tissues (Figure 4B). Consistent with the data for HNSC, 3 out of 4 HNSC cancer specimens showed medium to high *ITGa3* protein expression based on data available on The Human Protein Atlas database. *ITGb4* expression was upregulated in CESC, HNSC, ESCA and LUAD tumor tissues compared to adjacent normal tissues (Figure 5A). *ITGb6* expression was upregulated in CESC and ESCA tumor tissues versus adjacent normal tissues whilst *ITGb6* expression showed no significant differences in HNSC and LUAD tumor tissues versus adjacent normal tissues (Figure 5B). Consistent with the above, 9 out of 12 CESC cancer specimens showed medium to high *ITGb6* protein expression based on data available on The Human Protein Atlas database. Together, the above data indicate that integrins are an important part of the tumor microenvironment and contribute to cancer malignant phenotype and the process of tumor development.

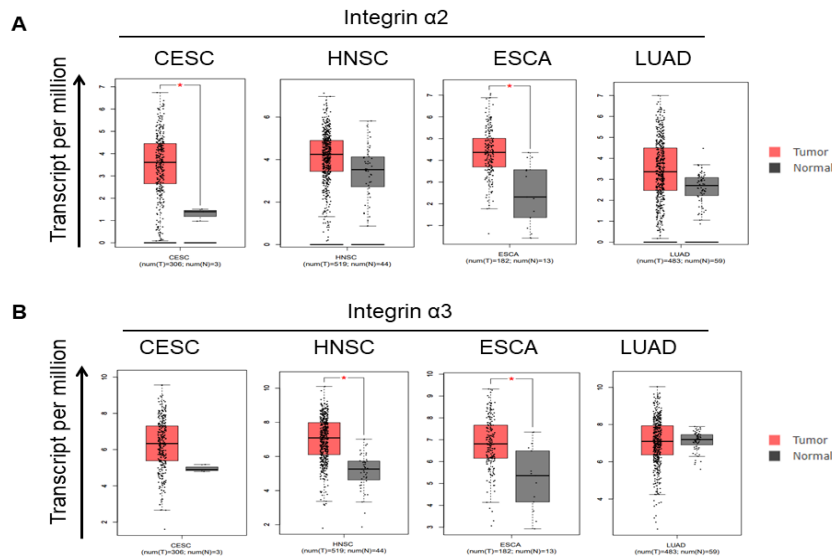


Figure 4. The differential expression of *ITGa2* (A) and *ITGa3* (B) in cervical squamous cell carcinoma (CESC), Head and Neck squamous cell carcinoma (HNSC), Esophageal carcinoma (ESCA) and Lung adenocarcinoma (LUAD) tumor tissues and adjacent normal tissues (box plot) based on TCGA/GEPIA database. Integrin expression showing significant differences between tumor and normal tissues are shown with * indicated for $p < 0.05$. GEPIA- gene expression profiling interactive analysis; TCGA- The Cancer Genome Atlas.

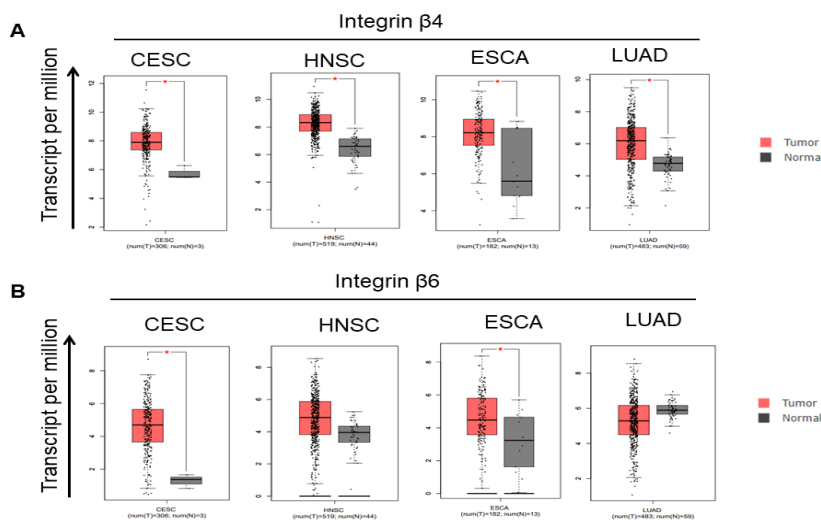


Figure 5. The differential expression of *ITG $\beta 4$* (A) and *ITG $\beta 6$* (B) in cervical squamous cell carcinoma (CESC), Head and Neck squamous cell carcinoma (HNSC), Esophageal carcinoma (ESCA) and Lung adenocarcinoma (LUAD) tumor tissues and adjacent normal tissues (box plot) based on TCGA/GEPIA database. Integrin expression showing significant differences between tumor and normal tissues are shown with * indicated for $p < 0.05$. GEPIA- gene expression profiling interactive analysis; TCGA- The Cancer Genome Atlas.

6.0 Integrin Promotion of Tumor Cell Survival

Integrins have been shown to act in both a pro- and anti-tumorigenic manner, depending on signals within the tumor microenvironment. Tumor cell-expressed integrins promote cell survival via involvement in proliferation, invasion and metastasis among several processes. In the case of invasion, integrins binding to different ECM proteins generates the needed traction for movement and invasive behavior. Formation of focal adhesions and the involvement of MMPs at the leading edge allow cells to invade new territories and tissues [74]. Several reports however point to the involvement of some integrins in preventing tumor cell migration. For example Kren and colleagues demonstrated that the absence of integrin B1 increased cancer cell metastatic behaviour [75]. Integrins can promote tumor cell survival through participation in several signaling mechanisms whilst integrins have also been shown to play a role in the process of apoptosis. How integrins behave depends on whether they are free or bound to their ligands. A critical balance is maintained through integrins interacting with ligands and this helps to maintain cell and organs integrity. For example, the binding of integrins to ligands can activate survival pathways such as MEK-ERK, nuclear factor- κ B (NF- κ B) and PI3-K-Akt pathways [3, 4, 76-78]. Interaction of integrins and the ECM upregulates BCL-2 expression in cancer cells [79, 80]. The interaction between integrins and growth factor receptors also play a role in preventing apoptosis in cells [81, 82]. Deletion of integrins genes or inhibition of integrin-mediated signaling has been shown to activate a compensatory upregulation of vascular endothelial growth factor receptor-2 expression, complicating the targeting of integrins in pathological conditions such as cancer [83-85]. Several data show that integrin function in tumors may be context dependent, with data showing that integrins such as α v β 3 is pro-tumorigenic but can inhibit tumor growth in cancers such as melanoma and glioblastoma [52, 86-88].

A subpopulation of cells known as cancer stem cells (CSCs) that is thought to give rise to all tumor cells present in tumors [89-92]. Several pieces of evidence point to integrins playing a part in tumorigenesis and as markers of CSCs [11, 93]. For example, Asselin-Labat and colleagues demonstrated that stem cell-like cells within the mammary ductal epithelium express α v β 3 integrin and it can be used a marker of these cells [94]. Vaillant and colleagues revealed that β 3 integrin as well as WNT1 were both markers of mammary CSCs [95]. Luo and colleagues demonstrated that removal of integrin-associated focal adhesion kinase signaling reduced the number of CSCs in mammary tumors in mice [96]. Samanna and colleagues showed that α v β 3 expression was linked to tumorigenicity and MMP-2 activity in melanoma cells [97]. Specifically,

the authors showed that integrins influence the expression of CSCs markers such as CD44 [97].

7.0 Integrins Contribution towards Tumor-Host cell interactions

Integrins are also involved in the response of normal cells to the presence of tumor cells. Reports indicate that most cells including fibroblasts, mesenchymal stem cells, pericytes, immune cells and endothelial cells utilise integrins in cellular processes such as migration, angiogenesis and desmoplasia. The targeting of integrins on stromal cells may aid in limiting the 'support' given to tumor cells by normal cells.

Integrins are involved in every stage of tumorigenesis from initiation to metastasis [98]. Several pieces of evidence points to 'leaky' blood vessels in tumors which causes impaired blood flow and drug delivery [99]. In addition, leaky blood vessels are also known to promote fibrosis in tumors [100]. Brooks and colleagues showed that integrin $\alpha v \beta 3$ was upregulated in chick chorioallantoic membrane and associated to angiogenesis [101]. It has been speculated that integrins may enable the interaction between ECM proteins and angiogenic-associated cells such as endothelial cells within the TME [102, 103]. Remodelling of the ECM has also been linked to increased integrin binding to degraded ECM proteins such as collagen [104]. Several reports have demonstrated that integrins are important for cellular processes such as migration and angiogenesis [98]. Various compounds or small molecules in addition to genetic manipulation have confirmed the involvement of integrins including $\alpha 2 \beta 1$, $\alpha 6 \beta 1$ and $\alpha 6 \beta 4$ [3, 4, 98]. Together with growth factor receptors, integrins can relay signals from growth factors to influence angiogenesis in tumors [101, 105, 106]. In elaborate experiments, Friedlander demonstrated that protein factors, basic fibroblast growth factor and tumor necrosis factor- α require the integrin $\alpha v \beta 3$ to induce angiogenesis in corneal [105]. In addition, the same authors also showed that vascular endothelial growth factor and transforming growth factor- α induced angiogenesis through interaction with integrin $\alpha v \beta 5$ [105]. Most importantly, integrins can bring together signals from both the ECM and several growth factors in order to influence cellular processes.

Several cells have been shown to play a role in angiogenesis and these include vascular smooth muscle cells and pericytes. Blood vessel maturation for example requires pericytes and smooth muscle cells [107-110]. Most blood vessels found within the TME are abnormal and leaky, leading to less oxygen reaching all cells. Interaction between pericytes and endothelial cells is via

integrin $\alpha 4\beta 1$ and vascular cell adhesion molecule 1 (VCAM1) for example [111]. This may lead to blood vessel formation and stability [111]. The branching of blood vessels within tumors also require pericytes involvement through integrin binding [112]. Thus a combination of therapeutic targeting tumor cells as well as therapeutics targeting angiogenesis and its associated cells to bring about blood vessel normalization may provide a synergistic and durable effect in cancer treatment [113-115]. Indeed, it has been suggested that treatment with anti-angiogenic therapeutics first before cytotoxic drugs may be better at treating cancer [115]. Thus today, vascular normalization is part of cancer therapies in many settings and clinics.

One of the observed hallmarks of desmoplasia in tumors is the synthesis and deposition of large amount of ECM proteins such as collagens. Increased collagen within the TME means increased integrin signaling allowing promotion of cancer cell survival and resistance to therapy [116]. Integrins on both cancer cells and stromal cells contribute towards cancer cell growth via activation of signaling that promote cancer cell growth. For example, Zhu and colleagues demonstrated that in non-small cell lung carcinoma several integrins including $\alpha 11$ is necessary for cancer cell growth [117]. Integrin $\alpha 11$ was instrumental in inducing insulin-like growth factor 2 release in human non-small-cell lung cancer cells [117]. Integrins inhibitors must therefore target both cancer cells and stromal cells for effective and durable cancer treatment.

Several pieces of evidence have shown that bone marrow-derived cells from the bone marrow are found within solid tumors [21, 118, 119]. Once in the TME, these bone marrow-derived cells can exhibit contrasting effects on cancer cells with some cells having anti-tumorigenic effects whilst others have tumor promoting effects. For example, infiltrating macrophages expressing integrin $\alpha v\beta 3$ are able to have anti-tumorigenic effects [120]. In addition, bone marrow derived cells with no functional integrin $\beta 3$ are not found within tumor sites and cannot therefore promote angiogenesis [121]. Jin and colleagues demonstrated that cells attracted to tumors including endothelial cells require integrin $\alpha 4\beta 1$ [122]. Integrin $\alpha 4\beta 1$ is needed for the binding of bone marrow derived cells to the endothelium within TME [123]. In terms of targeting integrins needed for the homing of bone marrow-derived cells to tumors, a balance must be maintained between anti-tumorigenic and pro-tumorigenic effects.

Tumor metastasis has been associated with the interaction between cancer cells and platelets. For example, Mammadova-Bach and colleagues demonstrated that integrin $\alpha 6\beta 1$ on platelets promotes metastasis via binding to lung cancer cell-derived ADAM9 [124]. In addition, Gay and colleagues showed that platelets can alter tumor cell characteristics and promote metastasis [125]. Furthermore, fibrinogen can behave as act as a connection between platelets and cancer cells via attaching to integrins on both cells and this allows cancer cells to be associated with blood vessels [126, 127]. Metastasis to the bone marrow and the lungs is also made possible via interaction between cancer cells and platelets [127, 128]. Trikha and colleagues demonstrated that the combined inhibition of integrins on both cancer cells and platelets enhances the anti-tumorigenic of the inhibitors compared to inhibition of integrins on tumor cells [129].

8.0 Integrin Crosstalk with Other Receptors

Cooperation between integrins and oncogenes in promoting tumor growth has been noted. Guo and colleagues demonstrated that integrin $\alpha 6\beta 4$ cooperates with ERBB2 and enhances tumor initiation and invasion in breast cancer [130]. There is also an association between integrin $\beta 1$ and polyoma middle T oncoproteins in driving breast cancer [131]. Some lung tumors require the involvement of integrin $\alpha 1$ for the initiation and growth of the tumors [132]. The Src oncogene activity has been shown to be enhanced via its interaction with integrin $\alpha 4\beta 3$ [133]. These several pieces of evidence demonstrate that integrin signaling is involved in enhancing the pro-tumorigenic effect of many oncogenes.

Tumor development and growth studies have shown that integrins play crucial roles through interactions with growth factors as well as cytokines. The involvement of integrins in adhesion, migration and invasion of tumor cells is well documented, however integrins have been shown to play more roles including enhancing angiogenesis and signaling. Interaction between integrins and growth factors and cytokines is not always pro-tumorigenic, with several pieces of data showing that integrins interactions can be anti-tumorigenic [134]. The interaction of integrins and growth factors is likely to influence signaling pathways involving kinases to enhance tumor cell survival and invasiveness [135, 136]. Growth factors can also influence integrin internalisation and activity and vice-versa [137-142].

The cooperation between integrins and growth factors and their receptors has been noted for its role in tumor development, growth and eventual metastasis in several cancers. Involvement of growth factors including the epidermal growth factor receptor family can be through increased expression or activation leading to oncogenic signaling in tumor cells. For example, enhanced expression of ERBB2, also known as v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2, and its receptors is observed in several cancers including breast and nasopharyngeal carcinoma [143-146]. Cooperation between integrins and the EGF receptor family has been reported in breast cancer. Guo and co-workers demonstrated that integrin $\alpha 6 \beta 4$ cooperates with ErbB2 signaling in breast cancer to promote tumor development and growth [130]. This cooperation also promoted invasion of tumor cells [130]. Furthermore, the authors showed that this cooperation causes the activation of the signal transducer and activator of transcription (STAT3) signaling, a signaling pathway known to cause increased cellular proliferation [130]. The targeting of both $\alpha 6 \beta 4$ integrin and the ERBB2 may produce a synergistic therapeutic effect [130]. The interaction between integrins, growth factors and ECM proteins such as collagen and glycoproteins such as vitronectin can promote cancer cell migration and metastasis [147-149]. Integrin $\alpha v \beta 5$ for example interacts with EGF and vitronectin to promote tumor cell migration [147-149]. Pouliot and colleagues demonstrated that EGF cooperates with $\alpha 3 \beta 1$ and the ECM protein laminin for example to promote migration of human colon carcinoma cells [150]. Another important study demonstrated that integrins $\alpha 1 \beta 1$ and $\alpha 2 \beta 1$ interact with EGF to promote the invasive behavior of hepatocarcinoma cells in a fibrotic microenvironment [151].

The cooperation between integrins and the hepatocyte growth factor (HGF) receptor, MET, has been implicated in tumor initiation and invasion. Bertotti and colleagues demonstrated that Integrin $\beta 4$ cooperates with HGF receptor, MET, to promote fibroblasts transformation and the eventual involvement of such transformed fibroblasts in tumorigenesis [152]. In another study, the same authors also showed that through induction of integrin $\beta 4$ phosphorylation, MET signaling upregulates anchorage-independent growth [153]. Reports show that integrin $\alpha v \beta 5$ can regulate the expression of genes induced by HGF and involved in cell invasion [154]. Overall, HGF-MET signaling cascade involvement in tumorigenesis is dependent on cooperation with integrins. Another growth factor shown to be involved in promoting tumorigenesis is transforming growth factor (TGF- β). For example, TGF- β has been shown to play a key role in epithelial-mesenchymal transition (EMT) leading to increased tumor cell movement and invasiveness [155-157]. Integrins such as $\alpha v \beta 6$ and $\alpha v \beta 8$ play a key role in the activation of TGF- β signaling through binding to the RGD sequence of the latency-associated peptide of TGF- $\beta 1$

[158-161]. Marsh and colleagues demonstrated that enhanced integrin $\alpha\beta6$ expression together with increased TGF- β activation leads to aggressive disease in basal cell carcinoma [162]. Immunohistochemical studies and transcriptional activation experiments confirmed that $\alpha\beta6$ activates the TGF- β signaling cascade in vivo and EMT leading to tumor growth [163, 164]. TGF- β signaling together with integrin $\alpha\beta3$ activates EMT process in epithelial cells [165, 166]. Our study demonstrated that both tumor cells and stromal cells secrete TGF- β , and it is plausible that the crosstalk between TGF- β and integrins play a key role in tumor growth and progression [21].

Integrins cooperation with growth factor occurs between tumor cells and stromal cells as well. For example, endothelial cell migration and proliferation require integrin and growth factor interactions during angiogenesis. Several reports have linked specific integrins to specific growth factors during angiogenesis [101, 167-169]. Fibroblast growth factor receptor is known to interact with integrin $\alpha\beta3$ leading to the phosphorylation of serine residues in Raf [170, 171]. The resulting complex known as MAP3K5 complex causes inhibition of the apoptotic pathway thus protects endothelial cells from apoptosis [172]. In addition, VEGFR2 has been shown to interact with integrin $\alpha\beta3$ and $\alpha\beta5$ to inhibit apoptosis by regulating the Ras-ERK pathway [170]. VEGFR2 also interacts with integrin αv in endothelial cells to increase angiogenesis [172-174]. Increased tumor cell proliferation is observed when activated $\alpha\beta3$ causes secretion of growth factor VEGF [175]. Nikolopoulos and colleagues demonstrated that integrin $\beta4$ cooperates with fibroblasts growth factor to induce angiogenesis and increased tumor growth [176]. CXCR4 is expressed by both tumor and stromal cells and its increased expression has been associated with increased expression of several integrins [177-179].

9.0 Targeting Integrins in Cancer Therapy

Integrins are appealing therapeutic targets for cancer therapy due to their increased expression in several cancers and cooperation with growth factors during tumor development and metastasis. Furthermore, integrins have been shown to play a key role in the development of drug resistance. Our work and that of others have specifically shown the involvement of integrins and their ligands in cancer cell drug resistance [11, 20, 21, 180, 181]. Several in vitro and animal studies have shown that inhibition of integrin function through the use of antagonists is effective at blocking tumor development and metastasis. Integrin function blockage can affect

both tumor cells and stromal cells [98, 182-184]. For example, cilengitide is currently under Phase 3 clinical trial for the treatment of glioblastoma. Cilengitide is also under study for its effectiveness against lung, glioblastoma and prostate cancer [185-188]. A monoclonal antibody, LM609 or its humanized version Etaracizumab, demonstrated anti-angiogenic activity in many studies including breast cancer studies [189]. Mulgrew and colleagues demonstrated that blocking $\alpha v \beta 3$ with the monoclonal antibody Abegrin can result in inhibition of tumor growth [190]. Integrin $\alpha v \beta 3$ is one of the major integrins expressed by osteoclasts and its inhibition through the use of monoclonal antibody Vitaxin®, blocks bone metastasis [191]. Vitaxin also demonstrated efficacy in patients with renal cancer and other solid tumors [192, 193]. Trikha and colleagues and Chen and co-workers demonstrated that the monoclonal antibody CNTO95 have anti-angiogenic effects and can block cell signaling and invasion in breast cancer cells, respectively [194, 195]. The amount of integrin antagonists used in studies is very important as some studies demonstrated that certain concentrations of doses of antagonists can act as integrin agonist fashion [196-198]. Most anti-angiogenic drugs increase tumor perfusion which is linked to better drug delivery in tumors [199, 200]. Thus, several studies have demonstrated that anti-angiogenic therapy targeting integrins works well when combined with chemotherapy. In addition, integrin targeting affects not only tumor cells but several stromal cells within the TME. Integrin $\beta 1$ via interaction with several signaling cascades including the Akt and the FAK pathways has been shown to play key roles in development of lung cancer and head and neck drug resistance [201, 202]. Hirata and colleagues demonstrated that enhanced integrin $\beta 1$ signaling via interaction with FAK was associated with resistance to the highly selective inhibitor of B-Raf, PLX4720 [203].

Vascularized tumors including glioblastomas demonstrate increased expression of integrins such as integrin $\alpha v \beta 3$ and $\beta 8$ [204-206]. In most cases, these tumors are aggressive and exhibit low patient survival making the development of integrin antagonists necessary to increase patient survival [207-209]. It has been shown that tumor microenvironment is a crucial determinant of therapy effectiveness, thus targeting angiogenesis and stromal integrins is a viable option [15, 16, 20, 21, 89, 206, 207]. For example, esophageal carcinoma abundantly express ECM proteins some of which are ligands for several integrins and thus can influence cancer cell survival and migration [20]. Thus, it is possible to target integrins such as $\alpha 2 \beta 1$ as the ECM ligands including fibronectin and collagen are abundantly expressed in esophageal cancer [3, 4, 20, 21]. Several clinical trials have been performed or under way to determine the effectiveness of integrin targeting in different cancers [186-188].

Park and colleagues demonstrated that an integrin $\beta 1$ inhibitory, AIIB2, was able to reduce breast cancer survival through activation of apoptosis [210]. In yet another study, Bhaskar and colleagues showed that chimeric integrin $\alpha 5\beta 1$ antibody, Volociximab, displayed anti-angiogenic activity and inhibited tumor growth [211]. Khalili and colleagues also showed that peptide inhibitor of integrin $\alpha 5\beta 1$, ATN-161, was able to inhibit cancer growth as well as metastasis [212]. The same peptide inhibitor, ATN-161, together with commonly used drug fluorouracil were able to inhibit colon metastasis to the liver [213]. A small molecule integrin $\alpha v\beta 3$ inhibitor S247 was able to breast cancer cell metastasis to the bone [214]. The same effect was demonstrated by another integrin $\alpha v\beta 3$ inhibitor PSK1404 [215]. S137 and S247 are RGD peptide mimetics and have been shown to inhibit metastasis [216]. 6.3G9 is an integrin $\alpha v\beta 6$ antibody that has been shown to have anti-cancer activity in pharyngeal carcinoma cells [163].

One major challenge associated with targeting integrins and its associated cellular processes such as angiogenesis is the lack of validated biomarkers. Several markers such as serum levels of fibroblast growth factor and vascular endothelial growth factor have been suggested to indicate the efficacy of anti-integrin therapy. However, few or no reports have shown the efficacy of such biomarkers in the clinical setting. Current investigations involving coupling integrin antagonists and radionuclides aim to identify newly formed blood vessels in tumors [217]. In addition, newly formed vessels can also be identified via the use of ultrasound with microbubbles as shown for αv -integrins by Leong-Poi and colleagues [218]. Angiogenesis in tumors can also be detected via the use of ^{18}F -labeled PEGylated RGD peptide [219]. The above noted examples and others demonstrate the potential use of labelled integrins antagonists as both treatment options and as diagnostic tools in cancer therapy. Furthermore, therapeutics targeting integrins can also be used to deliver drugs and proapoptotic peptides to tumor cells. For example, Hood and co-workers targeted integrin $\alpha v\beta 3$ with a nanoparticle whilst delivering mutant RAF1 gene to blood vessels within the tumor, leading to tumor shrinkage [81]. Nanoparticles can also be coupled to drugs such as doxorubicin and be able to target integrins and tumor vasculature [220].

10.0 Conclusion

Whilst most cells within the human body express integrins, those expressed by tumor cells and stromal cells within the TME are involved in several processes along the tumorigenic path.

Importantly, integrins have been shown to partake in promoting tumor cell proliferation, survival, migration as well as metastasis. Recent studies have demonstrated the role played by both bound and unbound integrins with both integrins playing a role in promoting tumor cell survival and metastasis. These newly discovered properties of integrins are important in drug discovery and integrin targeting. Integrins also cooperates with growth factors in promoting tumorigenesis and formation of secondary tumors. Furthermore, integrin investigations must be coupled to ECM studies as both play a role in tumor cell response to therapy and development of therapy resistance.

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Definitions

Endothelial to mesenchymal transition – Transformation of endothelial cells into mesenchymal cells.

Epithelial to mesenchymal transition – Transformation of epithelial cells into mesenchymal cells.

Extracellular Matrix – Extracellular fibrous proteins synthesized by both tumor and stromal cells such as macrophages, fibroblasts, mesenchymal stem cells and pericytes. The ECM's main functions are to provide structural support and biochemical cues to surrounding cells. Within the ECM are biomolecules such as growth factors, cytokines and chemokines and these in turn influence tumor and stromal cell behaviour.

Desmoplasia – Tissue response to injury or insult causing synthesis of huge amounts of ECM resulting in fibrosis.

Matrix Metalloproteases – Zinc-containing protease enzymes that degrade ECM proteins.

Tumor microenvironment – Cellular and non-cellular components of the environment surrounding cancer cells. Cells would normally include both resident and infiltrating stromal cells such as cancer-associated fibroblasts, pericytes and immune cells

Stromal cells- Cells within the TME that actively support tumor growth.

References

1. Mitra, S. K.; Schlaepfer, D. D., Integrin-regulated FAK–Src signaling in normal and cancer cells. *Current opinion in cell biology* **2006**, *18*, (5), 516-523.
2. Guo, W.; Giancotti, F. G., Integrin signalling during tumour progression. *Nature reviews Molecular cell biology* **2004**, *5*, (10), 816-826.
3. Dzobo, K.; Leaner, V. D.; Parker, M. I., Feedback regulation of the alpha2(1) collagen gene via the Mek-Erk signaling pathway. *IUBMB Life* **2012**, *64*, (1), 87-98.
4. Dzobo, K.; Leaner, V. D.; Parker, M. I., Absence of feedback regulation in the synthesis of COL1A1. *Life sciences* **2014**, *103*, (1), 25-33.
5. Assoian, R. K.; Klein, E. A., Growth control by intracellular tension and extracellular stiffness. *Trends in cell biology* **2008**, *18*, (7), 347-352.
6. Vellon, L.; Menendez, J. A.; Lupu, R., α V β 3 integrin regulates heregulin (HRG)-induced cell proliferation and survival in breast cancer. *Oncogene* **2005**, *24*, (23), 3759-3773.
7. Han, S.; Khuri, F. R.; Roman, J., Fibronectin stimulates non–small cell lung carcinoma cell growth through activation of Akt/mammalian target of rapamycin/S6 kinase and inactivation of LKB1/AMP-activated protein kinase signal pathways. *Cancer research* **2006**, *66*, (1), 315-323.
8. Gopal, S.; Veracini, L.; Grall, D.; Butori, C.; Schaub, S.; Audebert, S.; Camoin, L.; Baudalet, E.; Radwanska, A.; Beghelli-de la Forest Divonne, S., Fibronectin-guided migration of carcinoma collectives. *Nature communications* **2017**, *8*, (1), 1-15.
9. Erdogan, B.; Ao, M.; White, L. M.; Means, A. L.; Brewer, B. M.; Yang, L.; Washington, M. K.; Shi, C.; Franco, O. E.; Weaver, A. M., Cancer-associated fibroblasts promote directional cancer cell migration by aligning fibronectin. *Journal of Cell Biology* **2017**, *216*, (11), 3799-3816.
10. Seguin, L.; Desgrosellier, J. S.; Weis, S. M.; Cheresch, D. A., Integrins and cancer: regulators of cancer stemness, metastasis, and drug resistance. *Trends in cell biology* **2015**, *25*, (4), 234-240.
11. Hamidi, H.; Pietilä, M.; Ivaska, J., The complexity of integrins in cancer and new scopes for therapeutic targeting. *British journal of cancer* **2016**, *115*, (9), 1017-1023.
12. Attieh, Y.; Clark, A. G.; Grass, C.; Richon, S.; Pocard, M.; Mariani, P.; Elkhatib, N.; Betz, T.; Gurchenkov, B.; Vignjevic, D. M., Cancer-associated fibroblasts lead tumor invasion through integrin- β 3–dependent fibronectin assembly. *Journal of Cell Biology* **2017**, *216*, (11), 3509-3520.
13. Izumi, D.; Ishimoto, T.; Miyake, K.; Sugihara, H.; Eto, K.; Sawayama, H.; Yasuda, T.; Kiyozumi, Y.; Kaida, T.; Kurashige, J., CXCL12/CXCR4 activation by cancer-associated fibroblasts promotes integrin β 1 clustering and invasiveness in gastric cancer. *International journal of cancer* **2016**, *138*, (5), 1207-1219.
14. Zeltz, C.; Primac, I.; Erusappan, P.; Alam, J.; Noel, A.; Gullberg, D. In *Cancer-associated fibroblasts in desmoplastic tumors: emerging role of integrins*, Seminars in cancer biology, 2020; Elsevier: 2020; pp 166-181.

15. Dzobo, K.; Dandara, C., Broadening Drug Design and Targets to Tumor Microenvironment? Cancer-Associated Fibroblast Marker Expression in Cancers and Relevance for Survival Outcomes. *Omics : a journal of integrative biology* **2020**, *24*, (6), 340-351.
16. Dzobo, K.; Dandara, C., Architecture of Cancer-Associated Fibroblasts in Tumor Microenvironment: Mapping Their Origins, Heterogeneity, and Role in Cancer Therapy Resistance. *Omics : a journal of integrative biology* **2020**, *24*, (6), 314-339.
17. Franco, O. E.; Shaw, A. K.; Strand, D. W.; Hayward, S. W. In *Cancer associated fibroblasts in cancer pathogenesis*, Seminars in cell & developmental biology, 2010; Elsevier: 2010; pp 33-39.
18. Bussard, K. M.; Mutkus, L.; Stumpf, K.; Gomez-Manzano, C.; Marini, F. C., Tumor-associated stromal cells as key contributors to the tumor microenvironment. *Breast Cancer Research* **2016**, *18*, (1), 1-11.
19. Castells, M.; Thibault, B.; Delord, J. P.; Couderc, B., Implication of tumor microenvironment in chemoresistance: tumor-associated stromal cells protect tumor cells from cell death. *International journal of molecular sciences* **2012**, *13*, (8), 9545-71.
20. Senthebane, D.; Jonker, T.; Rowe, A.; Thomford, N.; Munro, D.; Dandara, C.; Wonkam, A.; Govender, D.; Calder, B.; Soares, N., The role of tumor microenvironment in chemoresistance: 3D extracellular matrices as accomplices. *International journal of molecular sciences* **2018**, *19*, (10), 2861.
21. Senthebane, D. A.; Rowe, A.; Thomford, N. E.; Shipanga, H.; Munro, D.; Al Mazeedi, M. A.; Almazyadi, H. A.; Kallmeyer, K.; Dandara, C.; Pepper, M. S., The role of tumor microenvironment in chemoresistance: to survive, keep your enemies closer. *International journal of molecular sciences* **2017**, *18*, (7), 1586.
22. Bianconi, D.; Unseld, M.; Prager, G. W., Integrins in the Spotlight of Cancer. *International journal of molecular sciences* **2016**, *17*, (12).
23. Hynes, R. O., Integrins: bidirectional, allosteric signaling machines. *Cell* **2002**, *110*, (6), 673-87.
24. Altei, W. F.; Pachane, B. C.; Dos Santos, P. K.; Ribeiro, L. N. M.; Sung, B. H.; Weaver, A. M.; Selistre-de-Araújo, H. S., Inhibition of $\alpha\beta 3$ integrin impairs adhesion and uptake of tumor-derived small extracellular vesicles. *Cell communication and signaling : CCS* **2020**, *18*, (1), 158.
25. Zhang, Y.; Xu, B.; Shi, J.; Li, J.; Lu, X.; Xu, L.; Yang, H.; Hamad, N.; Wang, C.; Napier, D.; He, S.; Liu, C.; Liu, Z.; Qian, H.; Chen, L.; Wei, X.; Zheng, X.; Huang, J. A.; Thibault, O.; Craven, R.; Wei, D.; Pan, Y.; Zhou, B. P.; Wu, Y.; Yang, X. H., BRD4 modulates vulnerability of triple-negative breast cancer to targeting of integrin-dependent signaling pathways. *Cellular oncology (Dordrecht)* **2020**.
26. He, F.; Wang, Y.; Cai, W.; Li, M.; Dong, L., Reversal of EGFR inhibitors' resistance by co-delivering EGFR and integrin $\alpha\beta 3$ inhibitors with nanoparticles in non-small cell lung cancer. *Bioscience reports* **2019**, *39*, (8).
27. Zhang, L.; Gülses, A.; Purcz, N.; Weimer, J.; Wiltfang, J.; Açil, Y., A comparative assessment of the effects of integrin inhibitor cilengitide on primary culture of head and neck squamous cell carcinoma (HNSCC) and HNSCC cell lines. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico* **2019**, *21*, (8), 1052-1060.
28. Zhu, X.; Tao, X.; Lu, W.; Ding, Y.; Tang, Y., Blockade of integrin $\beta 3$ signals to reverse the stem-like phenotype and drug resistance in melanoma. *Cancer chemotherapy and pharmacology* **2019**, *83*, (4), 615-624.
29. Hynes, R. O., The emergence of integrins: a personal and historical perspective. *Matrix Biol* **2004**, *23*, (6), 333-40.

30. Hynes, R. O.; Lively, J. C.; McCarty, J. H.; Taverna, D.; Francis, S. E.; Hodivala-Dilke, K.; Xiao, Q., The diverse roles of integrins and their ligands in angiogenesis. *Cold Spring Harb Symp Quant Biol* **2002**, 67, 143-53.
31. Juliano, R. L.; Varner, J. A., Adhesion molecules in cancer: the role of integrins. *Curr Opin Cell Biol* **1993**, 5, (5), 812-8.
32. De Franceschi, N.; Hamidi, H.; Alanko, J.; Sahgal, P.; Ivaska, J., Integrin traffic—the update. *Journal of cell science* **2015**, 128, (5), 839-852.
33. Pytela, R.; Pierschbacher, M. D.; Ruoslahti, E., Identification and isolation of a 140 kd cell surface glycoprotein with properties expected of a fibronectin receptor. *Cell* **1985**, 40, (1), 191-198.
34. Aota, S. I.; Yamada, K. M., Fibronectin and cell adhesion: specificity of integrin-ligand interaction. *Advances in enzymology and related areas of molecular biology* **1995**, 70, 1-22.
35. Desgrosellier, J. S.; Cheresch, D. A., Integrins in cancer: biological implications and therapeutic opportunities. *Nature Reviews Cancer* **2010**, 10, (1), 9-22.
36. Critchley, D. R., Focal adhesions—the cytoskeletal connection. *Current opinion in cell biology* **2000**, 12, (1), 133-139.
37. Burridge, K.; Chrzanowska-Wodnicka, M., Focal adhesions, contractility, and signaling. *Annual review of cell and developmental biology* **1996**, 12, (1), 463-519.
38. Berrier, A. L.; Yamada, K. M., Cell–matrix adhesion. *Journal of cellular physiology* **2007**, 213, (3), 565-573.
39. Lock, J. G.; Wehrle-Haller, B.; Strömblad, S. In *Cell–matrix adhesion complexes: master control machinery of cell migration*, Seminars in cancer biology, 2008; Elsevier: 2008; pp 65-76.
40. Arias-Salgado, E. G.; Lizano, S.; Sarkar, S.; Brugge, J. S.; Ginsberg, M. H.; Shattil, S. J., Src kinase activation by direct interaction with the integrin β cytoplasmic domain. *Proceedings of the National Academy of Sciences* **2003**, 100, (23), 13298-13302.
41. Miyamoto, S.; Teramoto, H.; Gutkind, J. S.; Yamada, K. M., Integrins can collaborate with growth factors for phosphorylation of receptor tyrosine kinases and MAP kinase activation: roles of integrin aggregation and occupancy of receptors. *Journal of Cell Biology* **1996**, 135, (6), 1633-1642.
42. Xue, Z.-H.; Zhao, C.-Q.; Chua, G.-L.; Tan, S.-W.; Tang, X.-Y.; Wong, S.-C.; Tan, S.-M., Integrin α M β 2 clustering triggers phosphorylation and activation of protein kinase C δ that regulates transcription factor Foxp1 expression in monocytes. *The Journal of Immunology* **2010**, 184, (7), 3697-3709.
43. Calderwood, D. A.; Shattil, S. J.; Ginsberg, M. H., Integrins and actin filaments: reciprocal regulation of cell adhesion and signaling. *Journal of Biological Chemistry* **2000**, 275, (30), 22607-22610.
44. Schwartz, M. A., Integrins and extracellular matrix in mechanotransduction. *Cold Spring Harbor perspectives in biology* **2010**, 2, (12), a005066.
45. Legate, K. R.; Montañez, E.; Kudlacek, O.; Füssler, R., ILK, PINCH and parvin: the tIPP of integrin signalling. *Nature reviews Molecular cell biology* **2006**, 7, (1), 20-31.
46. Sakai, T.; Li, S.; Docheva, D.; Grashoff, C.; Sakai, K.; Kostka, G.; Braun, A.; Pfeifer, A.; Yurchenco, P. D.; Fässler, R., Integrin-linked kinase (ILK) is required for polarizing the epiblast, cell adhesion, and controlling actin accumulation. *Genes & development* **2003**, 17, (7), 926-940.
47. Zöller, M., Tetraspanins: push and pull in suppressing and promoting metastasis. *Nature Reviews Cancer* **2009**, 9, (1), 40-55.
48. Hemler, M. E., Tetraspanin functions and associated microdomains. *Nature reviews Molecular cell biology* **2005**, 6, (10), 801-811.
49. Han, J.; Lim, C. J.; Watanabe, N.; Soriani, A.; Ratnikov, B.; Calderwood, D. A.; Puzon-McLaughlin, W.; Lafuente, E. M.; Boussiotis, V. A.; Shattil, S. J., Reconstructing and

- deconstructing agonist-induced activation of integrin α IIb β 3. *Current Biology* **2006**, 16, (18), 1796-1806.
50. Lee, H.-S.; Lim, C. J.; Puzon-McLaughlin, W.; Shattil, S. J.; Ginsberg, M. H., RIAM activates integrins by linking talin to ras GTPase membrane-targeting sequences. *Journal of Biological Chemistry* **2009**, 284, (8), 5119-5127.
 51. Dzobo, K.; Motaung, K.; Adesida, A., Recent Trends in Decellularized Extracellular Matrix Bioinks for 3D Printing: An Updated Review. *International journal of molecular sciences* **2019**, 20, (18).
 52. Petitclerc, E.; Strömlad, S.; von Schalscha, T. L.; Mitjans, F.; Piulats, J.; Montgomery, A. M.; Cheresch, D. A.; Brooks, P. C., Integrin α v β 3 promotes M21 melanoma growth in human skin by regulating tumor cell survival. *Cancer research* **1999**, 59, (11), 2724-2730.
 53. Lamb, L. E.; Zarif, J. C.; Miranti, C. K., The androgen receptor induces integrin α 6 β 1 to promote prostate tumor cell survival via NF- κ B and Bcl-xL Independently of PI3K signaling. *Cancer research* **2011**, 71, (7), 2739-2749.
 54. Aoudjit, F.; Vuori, K., Integrin signaling in cancer cell survival and chemoresistance. *Chemotherapy research and practice* **2012**, 2012.
 55. Ahmed, N.; Riley, C.; Rice, G. E.; Quinn, M. A.; Baker, M. S., α v β 6 integrin-A marker for the malignant potential of epithelial ovarian cancer. *Journal of Histochemistry & Cytochemistry* **2002**, 50, (10), 1371-1379.
 56. Ahmed, N.; Pansino, F.; Clyde, R.; Murthi, P.; Quinn, M.; Rice, G.; Agrez, M.; Mok, S.; Baker, M., Overexpression of α v β 6 integrin in serous epithelial ovarian cancer regulates extracellular matrix degradation via the plasminogen activation cascade. *Carcinogenesis* **2002**, 23, (2), 237-244.
 57. Agrez, M.; Gu, X.; Turton, J.; Meldrum, C.; Niu, J.; Antalis, T.; Howard, E. W., The α v β 6 integrin induces gelatinase B secretion in colon cancer cells. *International journal of cancer* **1999**, 81, (1), 90-97.
 58. Thomas, G. J.; Lewis, M. P.; Whawell, S. A.; Russell, A.; Sheppard, D.; Hart, I. R.; Speight, P. M.; Marshall, J. F., Expression of the α v β 6 integrin promotes migration and invasion in squamous carcinoma cells. *Journal of Investigative Dermatology* **2001**, 117, (1), 67-73.
 59. Slack-Davis, J. K.; Atkins, K. A.; Harrer, C.; Hershey, E. D.; Conaway, M., Vascular cell adhesion molecule-1 is a regulator of ovarian cancer peritoneal metastasis. *Cancer research* **2009**, 69, (4), 1469-1476.
 60. Landen, C. N.; Kim, T.-J.; Lin, Y. G.; Merritt, W. M.; Kamat, A. A.; Han, L. Y.; Spannuth, W. A.; Nick, A. M.; Jennings, N. B.; Kinch, M. S., Tumor-selective response to antibody-mediated targeting of α v β 3 integrin in ovarian cancer. *Neoplasia (New York, NY)* **2008**, 10, (11), 1259.
 61. Zutter, M. M.; Santoro, S. A.; Staatz, W. D.; Tsung, Y. L., Re-expression of the alpha 2 beta 1 integrin abrogates the malignant phenotype of breast carcinoma cells. *Proceedings of the National Academy of Sciences* **1995**, 92, (16), 7411-7415.
 62. Zutter, M. M.; Krigman, H. R.; Santoro, S., Altered integrin expression in adenocarcinoma of the breast. Analysis by in situ hybridization. *The American journal of pathology* **1993**, 142, (5), 1439.
 63. Zutter, M. M.; Mazoujian, G.; Santoro, S., Decreased expression of integrin adhesive protein receptors in adenocarcinoma of the breast. *The American journal of pathology* **1990**, 137, (4), 863.
 64. Kaur, S.; Kenny, H. A.; Jagadeeswaran, S.; Zillhardt, M. R.; Montag, A. G.; Kistner, E.; Yamada, S. D.; Mitra, A. K.; Lengyel, E., β 3-integrin expression on tumor cells inhibits tumor progression, reduces metastasis, and is associated with a favorable prognosis in patients with ovarian cancer. *The American journal of pathology* **2009**, 175, (5), 2184-2196.
 65. Thomas, G.; Jones, J.; Speight, P., Integrins and oral cancer. *Oral oncology* **1997**, 33, (6), 381-388.

66. Meyer, A.; van Golen, C. M.; Kim, B.; van Golen, K. L.; Feldman, E. L., Integrin expression regulates neuroblastoma attachment and migration. *Neoplasia* **2004**, 6, (4), 332-342.
67. McCabe, N. P.; De, S.; Vasanji, A.; Brainard, J.; Byzova, T. V., Prostate cancer specific integrin $\alpha v \beta 3$ modulates bone metastatic growth and tissue remodeling. *Oncogene* **2007**, 26, (42), 6238-6243.
68. Gruber, G.; Hess, J.; Stiefel, C.; Aebersold, D.; Zimmer, Y.; Greiner, R.; Studer, U.; Altermatt, H.; Hlushchuk, R.; Djonov, V., Correlation between the tumoral expression of $\beta 3$ -integrin and outcome in cervical cancer patients who had undergone radiotherapy. *British journal of cancer* **2005**, 92, (1), 41-46.
69. Hazelbag, S.; Kenter, G. G.; Gorter, A.; Dreef, E. J.; Koopman, L. A.; Violette, S. M.; Weinreb, P. H.; Fleuren, G. J., Overexpression of the $\alpha v \beta 6$ integrin in cervical squamous cell carcinoma is a prognostic factor for decreased survival. *The Journal of Pathology: A Journal of the Pathological Society of Great Britain and Ireland* **2007**, 212, (3), 316-324.
70. Hieken, T. J.; Ronan, S. G.; Farolan, M.; Shilkaitis, A. L.; Das Gupta, T. K., Molecular prognostic markers in intermediate-thickness cutaneous malignant melanoma. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **1999**, 85, (2), 375-382.
71. Nip, J.; Shibata, H.; Loskutoff, D. J.; Cheresch, D. A.; Brodt, P., Human melanoma cells derived from lymphatic metastases use integrin alpha v beta 3 to adhere to lymph node vitronectin. *The Journal of clinical investigation* **1992**, 90, (4), 1406-1413.
72. Adachi, M.; Taki, T.; Higashiyama, M.; Kohno, N.; Inufusa, H.; Miyake, M., Significance of integrin $\alpha 5$ gene expression as a prognostic factor in node-negative non-small cell lung cancer. *Clinical cancer research* **2000**, 6, (1), 96-101.
73. Hosotani, R.; Kawaguchi, M.; Masui, T.; Koshihara, T.; Ida, J.; Fujimoto, K.; Wada, M.; Doi, R.; Imamura, M., Expression of integrin $\alpha v \beta 3$ in pancreatic carcinoma: relation to MMP-2 activation and lymph node metastasis. *Pancreas* **2002**, 25, (2), e30-e35.
74. Das, A.; Monteiro, M.; Barai, A.; Kumar, S.; Sen, S., MMP proteolytic activity regulates cancer invasiveness by modulating integrins. *Scientific reports* **2017**, 7, (1), 14219.
75. Kren, A.; Baeriswyl, V.; Lehembre, F.; Wunderlin, C.; Strittmatter, K.; Antoniades, H.; Fässler, R.; Cavallaro, U.; Christofori, G., Increased tumor cell dissemination and cellular senescence in the absence of $\beta 1$ -integrin function. *The EMBO Journal* **2007**, 26, (12), 2832-2842.
76. Aoudjit, F.; Vuori, K., Integrin signaling inhibits paclitaxel-induced apoptosis in breast cancer cells. *Oncogene* **2001**, 20, (36), 4995-5004.
77. Scatena, M.; Almeida, M.; Chaisson, M. L.; Fausto, N.; Nicosia, R. F.; Giachelli, C. M., NF- κB mediates $\alpha v \beta 3$ integrin-induced endothelial cell survival. *The Journal of cell biology* **1998**, 141, (4), 1083-1093.
78. Courter, D. L.; Lomas, L.; Scatena, M.; Giachelli, C. M., Src kinase activity is required for integrin $\alpha v \beta 3$ -mediated activation of nuclear factor- κB . *Journal of Biological Chemistry* **2005**, 280, (13), 12145-12151.
79. Matter, M. L.; Ruoslahti, E., A Signaling Pathway from the $\alpha 5 \beta 1$ and $\alpha v \beta 3$ Integrins That Elevates bcl-2 Transcription. *Journal of Biological Chemistry* **2001**, 276, (30), 27757-27763.
80. Uhm, J. H.; Dooley, N. P.; Kyritsis, A. P.; Rao, J. S.; Gladson, C. L., Vitronectin, a glioma-derived extracellular matrix protein, protects tumor cells from apoptotic death. *Clinical Cancer Research* **1999**, 5, (6), 1587-1594.
81. Hood, J. D.; Frausto, R.; Kioussis, W. B.; Schwartz, M. A.; Cheresch, D. A., Differential αv integrin-mediated Ras-ERK signaling during two pathways of angiogenesis. *The Journal of cell biology* **2003**, 162, (5), 933-943.
82. Alavi, A.; Hood, J. D.; Frausto, R.; Stupack, D. G.; Cheresch, D. A., Role of Raf in vascular protection from distinct apoptotic stimuli. *Science* **2003**, 301, (5629), 94-96.
83. Reynolds, L. E.; Wyder, L.; Lively, J. C.; Taverna, D.; Robinson, S. D.; Huang, X.; Sheppard, D.; Hynes, R. O.; Hodivala-Dilke, K. M., Enhanced pathological angiogenesis in mice lacking $\beta 3$ integrin or $\beta 3$ and $\beta 5$ integrins. *Nature medicine* **2002**, 8, (1), 27-34.

84. Reynolds, A. R.; Reynolds, L. E.; Nagel, T. E.; Lively, J. C.; Robinson, S. D.; Hicklin, D. J.; Bodary, S. C.; Hodivala-Dilke, K. M., Elevated Flk1 (vascular endothelial growth factor receptor 2) signaling mediates enhanced angiogenesis in β 3-integrin-deficient mice. *Cancer Research* **2004**, 64, (23), 8643-8650.
85. Weis, S. M.; Lindquist, J. N.; Barnes, L. A.; Lutu-Fuga, K. M.; Cui, J.; Wood, M. R.; Cheresch, D. A., Cooperation between VEGF and β 3 integrin during cardiac vascular development. *Blood* **2007**, 109, (5), 1962-1970.
86. Varner, J. A.; Emerson, D. A.; Juliano, R. L., Integrin alpha 5 beta 1 expression negatively regulates cell growth: reversal by attachment to fibronectin. *Molecular biology of the cell* **1995**, 6, (6), 725-740.
87. Kanamori, M.; Berg, S. R. V.; Bergers, G.; Berger, M. S.; Pieper, R. O., Integrin β 3 overexpression suppresses tumor growth in a human model of gliomagenesis: implications for the role of β 3 overexpression in glioblastoma multiforme. *Cancer research* **2004**, 64, (8), 2751-2758.
88. Danen, E. H.; van Kraats, A. A.; Cornelissen, I. M.; Ruiter, D. J.; van Muijen, G. N., Integrin β 3 cDNA transfection into a highly metastatic α β 3-negative human melanoma cell line inhibits invasion and experimental metastasis. *Biochemical and biophysical research communications* **1996**, 226, (1), 75-81.
89. Dzobo, K., Taking a Full Snapshot of Cancer Biology: Deciphering the Tumor Microenvironment for Effective Cancer Therapy in the Oncology Clinic. *Omics : a journal of integrative biology* **2020**.
90. Dzobo, K.; Senthebane, D.; Ganz, C.; Thomford, N., The Significance of Cancer Stem Cell Markers' Gene Expression and Relevance for Survival Outcomes. In Preprints.org: 2020.
91. Dzobo, K.; Senthebane, D. A.; Ganz, C.; Thomford, N. E.; Wonkam, A.; Dandara, C., Advances in Therapeutic Targeting of Cancer Stem Cells within the Tumor Microenvironment: An Updated Review. *Cells* **2020**, 9, (8).
92. Dzobo, K.; Senthebane, D. A.; Rowe, A.; Thomford, N. E.; Mwapagha, L. M.; Al-Awwad, N.; Dandara, C.; Parker, M. I., Cancer Stem Cell Hypothesis for Therapeutic Innovation in Clinical Oncology? Taking the Root Out, Not Chopping the Leaf. *Omics : a journal of integrative biology* **2016**, 20, (12), 681-691.
93. Nieberler, M.; Reuning, U.; Reichart, F.; Notni, J.; Wester, H.-J.; Schwaiger, M.; Weinmüller, M.; Räder, A.; Steiger, K.; Kessler, H., Exploring the role of RGD-recognizing integrins in cancer. *Cancers* **2017**, 9, (9), 116.
94. Asselin-Labat, M.-L.; Sutherland, K. D.; Barker, H.; Thomas, R.; Shackleton, M.; Forrest, N. C.; Hartley, L.; Robb, L.; Grosveld, F. G.; van der Wees, J., Gata-3 is an essential regulator of mammary-gland morphogenesis and luminal-cell differentiation. *Nature cell biology* **2007**, 9, (2), 201-209.
95. Vaillant, F.; Asselin-Labat, M.-L.; Shackleton, M.; Forrest, N. C.; Lindeman, G. J.; Visvader, J. E., The mammary progenitor marker CD61/ β 3 integrin identifies cancer stem cells in mouse models of mammary tumorigenesis. *Cancer research* **2008**, 68, (19), 7711-7717.
96. Luo, M.; Fan, H.; Nagy, T.; Wei, H.; Wang, C.; Liu, S.; Wicha, M. S.; Guan, J.-L., Mammary epithelial-specific ablation of the focal adhesion kinase suppresses mammary tumorigenesis by affecting mammary cancer stem/progenitor cells. *Cancer research* **2009**, 69, (2), 466-474.
97. Samanna, V.; Wei, H.; Ego-Osuala, D.; Chellaiah, M. A., Alpha-V-dependent outside-in signaling is required for the regulation of CD44 surface expression, MMP-2 secretion, and cell migration by osteopontin in human melanoma cells. *Experimental Cell Research* **2006**, 312, (12), 2214-2230.
98. Avraamides, C. J.; Garmy-Susini, B.; Varner, J. A., Integrins in angiogenesis and lymphangiogenesis. *Nature Reviews Cancer* **2008**, 8, (8), 604-617.
99. McDonald, D. M.; Baluk, P., Significance of blood vessel leakiness in cancer. In AACR: 2002.

100. Brown, L. F.; Dvorak, A. M.; Dvorak, H. F., Leaky vessels, fibrin deposition, and fibrosis: a sequence of events common to solid tumors and to many other types of disease. *Am Rev Respir Dis* **1989**, 140, (4), 1104-1107.
101. Brooks, P. C.; Clark, R. A.; Chersesh, D. A., Requirement of vascular integrin $\alpha v \beta 3$ for angiogenesis. *Science* **1994**, 264, (5158), 569-571.
102. Stupack, D. G.; Chersesh, D. A., ECM remodeling regulates angiogenesis: endothelial integrins look for new ligands. *Science's STKE* **2002**, 2002, (119), pe7-pe7.
103. Eliceiri, B. P.; Chersesh, D. A., The role of αv integrins during angiogenesis: insights into potential mechanisms of action and clinical development. *The Journal of clinical investigation* **1999**, 103, (9), 1227-1230.
104. Davis, G. E., Affinity of integrins for damaged extracellular matrix: $\alpha v \beta 3$ binds to denatured collagen type I through RGD sites. *Biochemical and biophysical research communications* **1992**, 182, (3), 1025-1031.
105. Friedlander, M.; Brooks, P. C.; Shaffer, R. W.; Kincaid, C. M.; Varner, J. A.; Chersesh, D. A., Definition of two angiogenic pathways by distinct αv integrins. *Science* **1995**, 270, (5241), 1500-1502.
106. Brooks, P. C.; Montgomery, A. M.; Rosenfeld, M.; Reisfeld, R. A.; Hu, T.; Klier, G.; Chersesh, D. A., Integrin $\alpha v \beta 3$ antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. *Cell* **1994**, 79, (7), 1157-1164.
107. Goede, V.; Schmidt, T.; Kimmina, S.; Kozian, D.; Augustin, H. G., Analysis of blood vessel maturation processes during cyclic ovarian angiogenesis. *Laboratory investigation* **1998**, 78, (11), 1385-1394.
108. Raza, A.; Franklin, M. J.; Dudek, A. Z., Pericytes and vessel maturation during tumor angiogenesis and metastasis. *American journal of hematology* **2010**, 85, (8), 593-598.
109. Korff, T.; Kimmina, S.; MARTINY-BARON, G.; Augustin, H. G., Blood vessel maturation in a 3-dimensional spheroidal coculture model: direct contact with smooth muscle cells regulates endothelial cell quiescence and abrogates VEGF responsiveness. *The FASEB journal* **2001**, 15, (2), 447-457.
110. Klein, D.; Weißhardt, P.; Kleff, V.; Jastrow, H.; Jakob, H. G.; Ergün, S., Vascular wall-resident CD44+ multipotent stem cells give rise to pericytes and smooth muscle cells and contribute to new vessel maturation. *PloS one* **2011**, 6, (5), e20540.
111. Garmy-Susini, B.; Jin, H.; Zhu, Y.; Sung, R.-J.; Hwang, R.; Varner, J., Integrin $\alpha 4 \beta 1$ -VCAM-1-mediated adhesion between endothelial and mural cells is required for blood vessel maturation. *The Journal of clinical investigation* **2005**, 115, (6), 1542-1551.
112. Fukumura, D.; Jain, R. K., Tumor microvasculature and microenvironment: Targets for anti-angiogenesis and normalization. *Microvascular Research* **2007**, 74, (2), 72-84.
113. Fukumura, D.; Jain, R. K., Tumor microenvironment abnormalities: causes, consequences, and strategies to normalize. *Journal of cellular biochemistry* **2007**, 101, (4), 937-949.
114. Jain, R. K.; Tong, R. T.; Munn, L. L., Effect of vascular normalization by antiangiogenic therapy on interstitial hypertension, peritumor edema, and lymphatic metastasis: insights from a mathematical model. *Cancer research* **2007**, 67, (6), 2729-2735.
115. Tong, R. T.; Boucher, Y.; Kozin, S. V.; Winkler, F.; Hicklin, D. J.; Jain, R. K., Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. *Cancer research* **2004**, 64, (11), 3731-3736.
116. Conti, J. A.; Kendall, T. J.; Bateman, A.; Armstrong, T. A.; Papa-Adams, A.; Xu, Q.; Packham, G.; Primrose, J. N.; Benyon, R. C.; Iredale, J. P., The desmoplastic reaction surrounding hepatic colorectal adenocarcinoma metastases aids tumor growth and survival via αv integrin ligation. *Clinical Cancer Research* **2008**, 14, (20), 6405-6413.
117. Zhu, C.-Q.; Popova, S. N.; Brown, E. R.; Barysyt-Lovejoy, D.; Navab, R.; Shih, W.; Li, M.; Lu, M.; Jurisica, I.; Penn, L. Z., Integrin $\alpha 11$ regulates IGF2 expression in fibroblasts to enhance

- tumorigenicity of human non-small-cell lung cancer cells. *Proceedings of the National Academy of Sciences* **2007**, 104, (28), 11754-11759.
118. Ghossein, R. A.; Bhattacharya, S.; Rosai, J., Molecular detection of micrometastases and circulating tumor cells in solid tumors. *Clinical Cancer Research* **1999**, 5, (8), 1950-1960.
119. Adams, D. L.; Martin, S. S.; Alpaugh, R. K.; Charpentier, M.; Tsai, S.; Bergan, R. C.; Ogden, I. M.; Catalona, W.; Chumsri, S.; Tang, C.-M., Circulating giant macrophages as a potential biomarker of solid tumors. *Proceedings of the National Academy of Sciences* **2014**, 111, (9), 3514-3519.
120. Taverna, D.; Moher, H.; Crowley, D.; Borsig, L.; Varki, A.; Hynes, R. O., Increased primary tumor growth in mice null for $\beta 3$ -or $\beta 3/\beta 5$ -integrins or selectins. *Proceedings of the National Academy of Sciences* **2004**, 101, (3), 763-768.
121. Feng, W.; McCabe, N. P.; Mahabeleshwar, G. H.; Somanath, P. R.; Phillips, D. R.; Byzova, T. V., The angiogenic response is dictated by $\beta 3$ integrin on bone marrow-derived cells. *The Journal of cell biology* **2008**, 183, (6), 1145-1157.
122. Jin, H.; Aiyer, A.; Su, J.; Borgstrom, P.; Stupack, D.; Friedlander, M.; Varner, J., A homing mechanism for bone marrow-derived progenitor cell recruitment to the neovasculature. *The Journal of clinical investigation* **2006**, 116, (3), 652-662.
123. Jin, H.; Su, J.; Garmy-Susini, B.; Kleeman, J.; Varner, J., Integrin $\alpha 4\beta 1$ promotes monocyte trafficking and angiogenesis in tumors. *Cancer research* **2006**, 66, (4), 2146-2152.
124. Mammadova-Bach, E.; Zigrino, P.; Brucker, C.; Bourdon, C.; Freund, M.; De Arcangelis, A.; Abrams, S. I.; Orend, G.; Gachet, C.; Mangin, P. H., Platelet integrin $\alpha 6\beta 1$ controls lung metastasis through direct binding to cancer cell-derived ADAM9. *JCI insight* **2016**, 1, (14).
125. Gay, L. J.; Felding-Habermann, B., Platelets alter tumor cell attributes to propel metastasis: programming in transit. *Cancer cell* **2011**, 20, (5), 553-554.
126. Bakewell, S. J.; Nestor, P.; Prasad, S.; Tomasson, M. H.; Dowland, N.; Mehrotra, M.; Scarborough, R.; Kanter, J.; Abe, K.; Phillips, D., Platelet and osteoclast $\beta 3$ integrins are critical for bone metastasis. *Proceedings of the National Academy of Sciences* **2003**, 100, (24), 14205-14210.
127. Felding-Habermann, B.; Habermann, R.; Saldívar, E.; Ruggeri, Z. M., Role of 3 integrins in melanoma cell adhesion to activated platelets under flow. *Journal of Biological Chemistry* **1996**, 271, (10), 5892-5900.
128. Jain, S.; Zuka, M.; Liu, J.; Russell, S.; Dent, J.; Guerrero, J. A.; Forsyth, J.; Maruszak, B.; Gartner, T. K.; Felding-Habermann, B., Platelet glycoprotein Iba supports experimental lung metastasis. *Proceedings of the National Academy of Sciences* **2007**, 104, (21), 9024-9028.
129. Trikha, M.; Zhou, Z.; Timar, J.; Raso, E.; Kennel, M.; Emmell, E.; Nakada, M. T., Multiple roles for platelet GPIIb/IIIa and $\alpha v\beta 3$ integrins in tumor growth, angiogenesis, and metastasis. *Cancer research* **2002**, 62, (10), 2824-2833.
130. Guo, W.; Pylayeva, Y.; Pepe, A.; Yoshioka, T.; Muller, W. J.; Inghirami, G.; Giancotti, F. G., $\beta 4$ integrin amplifies ErbB2 signaling to promote mammary tumorigenesis. *Cell* **2006**, 126, (3), 489-502.
131. White, D. E.; Kurpios, N. A.; Zuo, D.; Hassell, J. A.; Blaess, S.; Mueller, U.; Muller, W. J., Targeted disruption of $\beta 1$ -integrin in a transgenic mouse model of human breast cancer reveals an essential role in mammary tumor induction. *Cancer cell* **2004**, 6, (2), 159-170.
132. Macias-Perez, I.; Borza, C.; Chen, X.; Yan, X.; Ibanez, R.; Mernaugh, G.; Matrisian, L. M.; Zent, R.; Pozzi, A., Loss of integrin $\alpha 1\beta 1$ ameliorates Kras-induced lung cancer. *Cancer research* **2008**, 68, (15), 6127-6135.
133. Huvneers, S.; van den Bout, I.; Sonneveld, P.; Sancho, A.; Sonnenberg, A.; Danen, E. H., Integrin $\alpha v\beta 3$ controls activity and oncogenic potential of primed c-Src. *Cancer research* **2007**, 67, (6), 2693-2700.

134. Shimizu, H.; Seiki, T.; Asada, M.; Yoshimatsu, K.; Koyama, N., $\alpha 6 \beta 1$ integrin induces proteasome-mediated cleavage of erbB2 in breast cancer cells. *Oncogene* **2003**, *22*, (6), 831-839.
135. Assoian, R. K.; Schwartz, M. A., Coordinate signaling by integrins and receptor tyrosine kinases in the regulation of G1 phase cell-cycle progression. *Current opinion in genetics & development* **2001**, *11*, (1), 48-53.
136. Tai, Y.-T.; Podar, K.; Catley, L.; Tseng, Y.-H.; Akiyama, M.; Shringarpure, R.; Burger, R.; Hideshima, T.; Chauhan, D.; Mitsiades, N., Insulin-like growth factor-1 induces adhesion and migration in human multiple myeloma cells via activation of $\beta 1$ -integrin and phosphatidylinositol 3'-kinase/AKT signaling. *Cancer research* **2003**, *63*, (18), 5850-5858.
137. Ning, Y.; Buranda, T.; Hudson, L. G., Activated epidermal growth factor receptor induces integrin $\alpha 2$ internalization via caveolae/raft-dependent endocytic pathway. *Journal of Biological Chemistry* **2007**, *282*, (9), 6380-6387.
138. Ning, Y.; Zeineldin, R.; Liu, Y.; Rosenberg, M.; Stack, M. S.; Hudson, L. G., Down-regulation of integrin $\alpha 2$ surface expression by mutant epidermal growth factor receptor (EGFRvIII) induces aberrant cell spreading and focal adhesion formation. *Cancer research* **2005**, *65*, (20), 9280-9286.
139. Ignatz, R. A.; Massagué, J., Cell adhesion protein receptors as targets for transforming growth factor- β action. *Cell* **1987**, *51*, (2), 189-197.
140. Wang, D.; Sun, L.; Zborowska, E.; Willson, J. K.; Gong, J.; Verraraghavan, J.; Brattain, M. G., Control of type II transforming growth factor- β receptor expression by integrin ligation. *Journal of Biological Chemistry* **1999**, *274*, (18), 12840-12847.
141. De, S.; Razorenova, O.; McCabe, N. P.; O'Toole, T.; Qin, J.; Byzova, T. V., VEGF-integrin interplay controls tumor growth and vascularization. *Proceedings of the National Academy of Sciences* **2005**, *102*, (21), 7589-7594.
142. Wang, S. E.; Xiang, B.; Zent, R.; Quaranta, V.; Pozzi, A.; Arteaga, C. L., Transforming growth factor β induces clustering of HER2 and integrins by activating Src-focal adhesion kinase and receptor association to the cytoskeleton. *Cancer research* **2009**, *69*, (2), 475-482.
143. Joensuu, H.; Isola, J.; Lundin, M.; Salminen, T.; Holli, K.; Kataja, V.; Pylkkänen, L.; Turpeenniemi-Hujanen, T.; von Smitten, K.; Lundin, J., Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. *Clinical cancer research* **2003**, *9*, (3), 923-930.
144. Tsutsui, S.; Ohno, S.; Murakami, S.; Hachitanda, Y.; Oda, S., Prognostic value of c-erbB2 expression in breast cancer. *Journal of surgical oncology* **2002**, *79*, (4), 216-223.
145. Shen, Z. Y.; Zhang, Z. Z.; Liu, H.; Zhao, E. H.; Cao, H., miR-375 inhibits the proliferation of gastric cancer cells by repressing ERBB2 expression. *Experimental and therapeutic medicine* **2014**, *7*, (6), 1757-1761.
146. Roychowdhury, D. F.; Tseng Jr, A.; Fu, K. K.; Weinberg, V.; Weidner, N., New prognostic factors in nasopharyngeal carcinoma: Tumor angiogenesis and C-erbB2 expression. *Cancer: Interdisciplinary International Journal of the American Cancer Society* **1996**, *77*, (8), 1419-1426.
147. Brooks, P. C.; Klemke, R. L.; Schon, S.; Lewis, J. M.; Schwartz, M. A.; Cheresch, D. A., Insulin-like growth factor receptor cooperates with integrin alpha v beta 5 to promote tumor cell dissemination in vivo. *The Journal of clinical investigation* **1997**, *99*, (6), 1390-1398.
148. Klemke, R. L.; Yebra, M.; Bayna, E. M.; Cheresch, D. A., Receptor tyrosine kinase signaling required for integrin alpha v beta 5-directed cell motility but not adhesion on vitronectin. *The Journal of Cell Biology* **1994**, *127*, (3), 859-866.
149. Ricono, J. M.; Huang, M.; Barnes, L. A.; Lau, S. K.; Weis, S. M.; Schlaepfer, D. D.; Hanks, S. K.; Cheresch, D. A., Specific cross-talk between epidermal growth factor receptor and integrin

- $\alpha\beta 5$ promotes carcinoma cell invasion and metastasis. *Cancer research* **2009**, 69, (4), 1383-1391.
150. Pouliot, N.; Nice, E. C.; Burgess, A. W., Laminin-10 mediates basal and EGF-stimulated motility of human colon carcinoma cells via $\alpha 3\beta 1$ and $\alpha 6\beta 4$ integrins. *Experimental cell research* **2001**, 266, (1), 1-10.
151. Yang, C.; Zeisberg, M.; Lively, J. C.; Nyberg, P.; Afdhal, N.; Kalluri, R., Integrin $\alpha 1\beta 1$ and $\alpha 2\beta 1$ are the key regulators of hepatocarcinoma cell invasion across the fibrotic matrix microenvironment. *Cancer research* **2003**, 63, (23), 8312-8317.
152. Bertotti, A.; Comoglio, P. M.; Trusolino, L., $\beta 4$ integrin is a transforming molecule that unleashes Met tyrosine kinase tumorigenesis. *Cancer research* **2005**, 65, (23), 10674-10679.
153. Bertotti, A.; Comoglio, P. M.; Trusolino, L., $\beta 4$ integrin activates a Shp2–Src signaling pathway that sustains HGF-induced anchorage-independent growth. *The Journal of cell biology* **2006**, 175, (6), 993-1003.
154. Crouch, S.; Spidel, C. S.; Lindsey, J. S., HGF and ligation of $\alpha\beta 5$ integrin induce a novel, cancer cell-specific gene expression required for cell scattering. *Experimental cell research* **2004**, 292, (2), 274-287.
155. Oft, M.; Peli, J.; Rudaz, C.; Schwarz, H.; Beug, H.; Reichmann, E., TGF-beta1 and Ha-Ras collaborate in modulating the phenotypic plasticity and invasiveness of epithelial tumor cells. *Genes & development* **1996**, 10, (19), 2462-2477.
156. Welch, D. R.; Fabra, A.; Nakajima, M., Transforming growth factor beta stimulates mammary adenocarcinoma cell invasion and metastatic potential. *Proceedings of the National Academy of Sciences* **1990**, 87, (19), 7678-7682.
157. Vo, B. T.; Morton Jr, D.; Komaragiri, S.; Millena, A. C.; Leath, C.; Khan, S. A., TGF- β effects on prostate cancer cell migration and invasion are mediated by PGE2 through activation of PI3K/AKT/mTOR pathway. *Endocrinology* **2013**, 154, (5), 1768-1779.
158. Ludbrook, S. B.; Barry, S. T.; Delves, C. J.; Horgan, C. M., The integrin $\alpha\beta 3$ is a receptor for the latency-associated peptides of transforming growth factors beta1 and beta3. *Biochemical Journal* **2003**, 369, (2), 311-318.
159. Lu, M.; Munger, J. S.; Steadele, M.; Busald, C.; Tellier, M.; Schnapp, L. M., Integrin $\alpha 8\beta 1$ mediates adhesion to LAP-TGF $\beta 1$. *Journal of Cell Science* **2002**, 115, (23), 4641-4648.
160. Munger, J. S.; Harpel, J. G.; Giancotti, F. G.; Rifkin, D. B., Interactions between growth factors and integrins: latent forms of transforming growth factor- β are ligands for the integrin $\alpha\beta 1$. *Molecular biology of the cell* **1998**, 9, (9), 2627-2638.
161. Annes, J. P.; Rifkin, D. B.; Munger, J. S., The integrin $\alpha\beta 6$ binds and activates latent TGF $\beta 3$. *FEBS letters* **2002**, 511, (1-3), 65-68.
162. Marsh, D.; Dickinson, S.; Neill, G. W.; Marshall, J. F.; Hart, I. R.; Thomas, G. J., $\alpha\beta 6$ integrin promotes the invasion of morphoeic basal cell carcinoma through stromal modulation. *Cancer research* **2008**, 68, (9), 3295-3303.
163. Van Aarsen, L. A. K.; Leone, D. R.; Ho, S.; Dolinski, B. M.; McCoon, P. E.; LePage, D. J.; Kelly, R.; Heaney, G.; Rayhorn, P.; Reid, C., Antibody-mediated blockade of integrin $\alpha\beta 6$ inhibits tumor progression in vivo by a transforming growth factor- β -regulated mechanism. *Cancer research* **2008**, 68, (2), 561-570.
164. Bates, R. C.; Bellovin, D. I.; Brown, C.; Maynard, E.; Wu, B.; Kawakatsu, H.; Sheppard, D.; Oettgen, P.; Mercurio, A. M., Transcriptional activation of integrin $\beta 6$ during the epithelial-mesenchymal transition defines a novel prognostic indicator of aggressive colon carcinoma. *The Journal of clinical investigation* **2005**, 115, (2), 339-347.
165. Galliher, A. J.; Schiemann, W. P., $\beta 3$ integrin and Src facilitate transforming growth factor- β mediated induction of epithelial-mesenchymal transition in mammary epithelial cells. *Breast cancer research* **2006**, 8, (4), R42.

166. Galliher, A. J.; Schiemann, W. P., Beta3 integrin and Src facilitate transforming growth factor-beta mediated induction of epithelial-mesenchymal transition in mammary epithelial cells. *Breast cancer research : BCR* **2006**, *8*, (4), R42.
167. Brooks, P. C.; Montgomery, A. M.; Rosenfeld, M.; Reisfeld, R. A.; Hu, T.; Klier, G.; Cheresch, D. A., Integrin alpha v beta 3 antagonists promote tumor regression by inducing apoptosis of angiogenic blood vessels. *Cell* **1994**, *79*, (7), 1157-64.
168. Lehmann, M.; Rabenandrasana, C.; Tamura, R.; Lissitzky, J. C.; Quaranta, V.; Pichon, J.; Marvaldi, J., A monoclonal antibody inhibits adhesion to fibronectin and vitronectin of a colon carcinoma cell line and recognizes the integrins alpha v beta 3, alpha v beta 5, and alpha v beta 6. *Cancer Res* **1994**, *54*, (8), 2102-7.
169. Varner, J. A., The role of vascular cell integrins alpha v beta 3 and alpha v beta 5 in angiogenesis. *Exs* **1997**, *79*, 361-90.
170. Hood, J. D.; Frausto, R.; Kiosses, W. B.; Schwartz, M. A.; Cheresch, D. A., Differential alphav integrin-mediated Ras-ERK signaling during two pathways of angiogenesis. *J Cell Biol* **2003**, *162*, (5), 933-43.
171. Bao, W.; Strömblad, S., Integrin alphav-mediated inactivation of p53 controls a MEK1-dependent melanoma cell survival pathway in three-dimensional collagen. *J Cell Biol* **2004**, *167*, (4), 745-56.
172. Mahabeleshwar, G. H.; Feng, W.; Reddy, K.; Plow, E. F.; Byzova, T. V., Mechanisms of integrin-vascular endothelial growth factor receptor cross-activation in angiogenesis. *Circulation research* **2007**, *101*, (6), 570-80.
173. Reynolds, L. E.; Wyder, L.; Lively, J. C.; Taverna, D.; Robinson, S. D.; Huang, X.; Sheppard, D.; Hynes, R. O.; Hodivala-Dilke, K. M., Enhanced pathological angiogenesis in mice lacking beta3 integrin or beta3 and beta5 integrins. *Nat Med* **2002**, *8*, (1), 27-34.
174. Byzova, T. V.; Goldman, C. K.; Pampori, N.; Thomas, K. A.; Bett, A.; Shattil, S. J.; Plow, E. F., A mechanism for modulation of cellular responses to VEGF: activation of the integrins. *Mol Cell* **2000**, *6*, (4), 851-60.
175. De, S.; Razorenova, O.; McCabe, N. P.; O'Toole, T.; Qin, J.; Byzova, T. V., VEGF-integrin interplay controls tumor growth and vascularization. *Proceedings of the National Academy of Sciences of the United States of America* **2005**, *102*, (21), 7589-94.
176. Nikolopoulos, S. N.; Blaikie, P.; Yoshioka, T.; Guo, W.; Giancotti, F. G., Integrin beta4 signaling promotes tumor angiogenesis. *Cancer Cell* **2004**, *6*, (5), 471-83.
177. Cardones, A. R.; Murakami, T.; Hwang, S. T., CXCR4 enhances adhesion of B16 tumor cells to endothelial cells in vitro and in vivo via beta(1) integrin. *Cancer Res* **2003**, *63*, (20), 6751-7.
178. Engl, T.; Relja, B.; Marian, D.; Blumenberg, C.; Müller, I.; Beecken, W. D.; Jones, J.; Ringel, E. M.; Bereiter-Hahn, J.; Jonas, D.; Blaheta, R. A., CXCR4 chemokine receptor mediates prostate tumor cell adhesion through alpha5 and beta3 integrins. *Neoplasia* **2006**, *8*, (4), 290-301.
179. Sun, Y. X.; Fang, M.; Wang, J.; Cooper, C. R.; Pienta, K. J.; Taichman, R. S., Expression and activation of alpha v beta 3 integrins by SDF-1/CXC12 increases the aggressiveness of prostate cancer cells. *The Prostate* **2007**, *67*, (1), 61-73.
180. Seguin, L.; Kato, S.; Franovic, A.; Camargo, M. F.; Lesperance, J.; Elliott, K. C.; Yebra, M.; Mielgo, A.; Lowy, A. M.; Husain, H., An integrin β 3–KRAS–RalB complex drives tumour stemness and resistance to EGFR inhibition. *Nature cell biology* **2014**, *16*, (5), 457-468.
181. Sethi, T.; Rintoul, R. C.; Moore, S. M.; MacKinnon, A. C.; Salter, D.; Choo, C.; Chilvers, E. R.; Dransfield, I.; Donnelly, S. C.; Strieter, R., Extracellular matrix proteins protect small cell lung cancer cells against apoptosis: a mechanism for small cell lung cancer growth and drug resistance in vivo. *Nature medicine* **1999**, *5*, (6), 662-668.
182. Curley, G.; Blum, H.; Humphries, M., Integrin antagonists. *Cellular and Molecular Life Sciences CMLS* **1999**, *56*, (5-6), 427-441.
183. Shimaoka, M.; Springer, T. A., Therapeutic antagonists and conformational regulation of integrin function. *Nature Reviews Drug Discovery* **2003**, *2*, (9), 703-716.

184. Scarborough, R. M.; Naughton, M. A.; Teng, W.; Rose, J.; Phillips, D.; Nannizzi, L.; Arfsten, A.; Campbell, A.; Charo, I., Design of potent and specific integrin antagonists. Peptide antagonists with high specificity for glycoprotein IIb-IIIa. *Journal of Biological Chemistry* **1993**, 268, (2), 1066-1073.
185. Beekman, K. W.; Colevas, A. D.; Cooney, K.; DiPaola, R.; Dunn, R. L.; Gross, M.; Keller, E. T.; Pienta, K. J.; Ryan, C. J.; Smith, D., Phase II evaluations of cilengitide in asymptomatic patients with androgen-independent prostate cancer: scientific rationale and study design. *Clinical genitourinary cancer* **2006**, 4, (4), 299-302.
186. Nabors, L. B.; Mikkelsen, T.; Rosenfeld, S.; Hochberg, F.; Akella, N. S.; Fisher, J. D.; Cloud, G.; Zhang, Y.; Carson, K. A.; Wittemer, S. M., A phase I and correlative biology study of cilengitide in patients with recurrent malignant glioma. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* **2007**, 25, (13).
187. MacDonald, T. J.; Stewart, C. F.; Kocak, M.; Goldman, S.; Ellenbogen, R. G.; Phillips, P.; Lafond, D.; Poussaint, T. Y.; Kieran, M. W.; Boyett, J. M., Phase I clinical trial of cilengitide in children with refractory brain tumors: Pediatric Brain Tumor Consortium Study PBTC-012. *Journal of clinical oncology* **2008**, 26, (6), 919-924.
188. Reardon, D. A.; Fink, K. L.; Mikkelsen, T.; Cloughesy, T. F.; O'Neill, A.; Plotkin, S.; Glantz, M.; Ravin, P.; Raizer, J. J.; Rich, K. M., Randomized phase II study of cilengitide, an integrin-targeting arginine-glycine-aspartic acid peptide, in recurrent glioblastoma multiforme. *Journal of Clinical Oncology* **2008**, 26, (34), 5610-5617.
189. Brooks, P. C.; Strömblad, S.; Klemke, R.; Visscher, D.; Sarkar, F. H.; Cheresch, D. A., Antiintegrin alpha v beta 3 blocks human breast cancer growth and angiogenesis in human skin. *The Journal of clinical investigation* **1995**, 96, (4), 1815-1822.
190. Mulgrew, K.; Kinneer, K.; Yao, X.-T.; Ward, B. K.; Damschroder, M. M.; Walsh, B.; Mao, S.-Y.; Gao, C.; Kiener, P. A.; Coats, S., Direct targeting of $\alpha\beta 3$ integrin on tumor cells with a monoclonal antibody, Abegrin™. *Molecular cancer therapeutics* **2006**, 5, (12), 3122-3129.
191. Gramoun, A.; Shorey, S.; Bashutski, J. D.; Dixon, S. J.; Sims, S. M.; Heersche, J. N.; Manolson, M. F., Effects of Vitaxin®, a novel therapeutic in trial for metastatic bone tumors, on osteoclast functions in vitro. *Journal of Cellular Biochemistry* **2007**, 102, (2), 341-352.
192. Delbaldo, C.; Raymond, E.; Vera, K.; Hammershaimb, L.; Kaucic, K.; Lozahic, S.; Marty, M.; Faivre, S., Phase I and pharmacokinetic study of etaracizumab (Abegrin™), a humanized monoclonal antibody against $\alpha v \beta 3$ integrin receptor, in patients with advanced solid tumors. *Investigational new drugs* **2008**, 26, (1), 35-43.
193. McNeel, D. G.; Eickhoff, J.; Lee, F. T.; King, D. M.; Alberti, D.; Thomas, J. P.; Friedl, A.; Kolesar, J.; Marnocha, R.; Volkman, J., Phase I trial of a monoclonal antibody specific for $\alpha\beta 3$ integrin (MEDI-522) in patients with advanced malignancies, including an assessment of effect on tumor perfusion. *Clinical Cancer Research* **2005**, 11, (21), 7851-7860.
194. Trikha, M.; Zhou, Z.; Nemeth, J. A.; Chen, Q.; Sharp, C.; Emmell, E.; Giles-Komar, J.; Nakada, M. T., CNTO 95, a fully human monoclonal antibody that inhibits αv integrins, has antitumor and antiangiogenic activity in vivo. *International journal of cancer* **2004**, 110, (3), 326-335.
195. Chen, Q.; Manning, C. D.; Millar, H.; McCabe, F. L.; Ferrante, C.; Sharp, C.; Shahied-Arruda, L.; Doshi, P.; Nakada, M. T.; Anderson, G. M., CNTO 95, a fully human anti αv integrin antibody, inhibits cell signaling, migration, invasion, and spontaneous metastasis of human breast cancer cells. *Clinical & experimental metastasis* **2008**, 25, (2), 139-148.
196. Odekon, L.; Frewin, M.; Del Vecchio, P.; Saba, T.; Gudewicz, P., Fibronectin fragments released from phorbol ester-stimulated pulmonary artery endothelial cell monolayers promote neutrophil chemotaxis. *Immunology* **1991**, 74, (1), 114.
197. Legler, D. F.; Wiedle, G.; Ross, F. P.; Imhof, B. A., Superactivation of integrin (α) v (β) 3 by low antagonist concentrations. *Journal of cell science* **2001**, 114, (8), 1545-1553.

198. Aznavoorian, S.; Stracke, M. L.; Krutzsch, H.; Schiffmann, E.; Liotta, L. A., Signal transduction for chemotaxis and haptotaxis by matrix molecules in tumor cells. *The Journal of cell biology* **1990**, 110, (4), 1427-1438.
199. Ebos, J. M.; Lee, C. R.; Cruz-Munoz, W.; Bjarnason, G. A.; Christensen, J. G.; Kerbel, R. S., Accelerated metastasis after short-term treatment with a potent inhibitor of tumor angiogenesis. *Cancer cell* **2009**, 15, (3), 232-239.
200. Pàez-Ribes, M.; Allen, E.; Hudock, J.; Takeda, T.; Okuyama, H.; Viñals, F.; Inoue, M.; Bergers, G.; Hanahan, D.; Casanovas, O., Antiangiogenic therapy elicits malignant progression of tumors to increased local invasion and distant metastasis. *Cancer cell* **2009**, 15, (3), 220-231.
201. Kanda, R.; Kawahara, A.; Watari, K.; Murakami, Y.; Sonoda, K.; Maeda, M.; Fujita, H.; Kage, M.; Uramoto, H.; Costa, C., Erlotinib resistance in lung cancer cells mediated by integrin $\beta 1$ /Src/Akt-driven bypass signaling. *Cancer research* **2013**, 73, (20), 6243-6253.
202. Eke, I.; Zscheppang, K.; Dickreuter, E.; Hickmann, L.; Mazzeo, E.; Unger, K.; Krause, M.; Cordes, N., Simultaneous $\beta 1$ integrin-EGFR targeting and radiosensitization of human head and neck cancer. *JNCI: Journal of the National Cancer Institute* **2015**, 107, (2).
203. Hirata, E.; Girotti, M. R.; Viros, A.; Hooper, S.; Spencer-Dene, B.; Matsuda, M.; Larkin, J.; Marais, R.; Sahai, E., Intravital imaging reveals how BRAF inhibition generates drug-tolerant microenvironments with high integrin $\beta 1$ /FAK signaling. *Cancer cell* **2015**, 27, (4), 574-588.
204. Tchaicha, J. H.; Reyes, S. B.; Shin, J.; Hossain, M. G.; Lang, F. F.; McCarty, J. H., Glioblastoma angiogenesis and tumor cell invasiveness are differentially regulated by $\beta 8$ integrin. *Cancer research* **2011**, 71, (20), 6371-6381.
205. Gladson, C. L., Expression of integrin $\alpha v \beta 3$ in small blood vessels of glioblastoma tumors. *Journal of Neuropathology & Experimental Neurology* **1996**, 55, (11), 1143-1149.
206. Giovanna, M.; Kaye, A. H., Integrins: molecular determinants of glioma invasion. *Journal of clinical neuroscience* **2007**, 14, (11), 1041-1048.
207. Giatromanolaki, A.; Sivridis, E.; Koukourakis, M. I., Tumour angiogenesis: vascular growth and survival. *Apmis* **2004**, 112, (7-8), 431-440.
208. MacDonald, T. J.; Taga, T.; Shimada, H.; Tabrizi, P.; Zlokovic, B. V.; Cheresch, D. A.; Laug, W. E., Preferential susceptibility of brain tumors to the antiangiogenic effects of an $\alpha(v)$ integrin antagonist. *Neurosurgery* **2001**, 48, (1), 151-7.
209. Yamada, S.; Bu, X. Y.; Khankaldyyan, V.; Gonzales-Gomez, I.; McComb, J. G.; Laug, W. E., Effect of the angiogenesis inhibitor Cilengitide (EMD 121974) on glioblastoma growth in nude mice. *Neurosurgery* **2006**, 59, (6), 1304-12; discussion 1312.
210. Park, C. C.; Zhang, H.; Pallavicini, M.; Gray, J. W.; Baehner, F.; Park, C. J.; Bissell, M. J., $\beta 1$ 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 research* **2006**, 66, (3), 1526-1535.
211. Bhaskar, V.; Fox, M.; Breinberg, D.; Wong, M. H.; Wales, P. E.; Rhodes, S.; DuBridge, R. B.; Ramakrishnan, V., Volociximab, a chimeric integrin $\alpha 5 \beta 1$ antibody, inhibits the growth of VX2 tumors in rabbits. *Investigational new drugs* **2008**, 26, (1), 7-12.
212. Khalili, P.; Arakelian, A.; Chen, G.; Plunkett, M. L.; Beck, I.; Parry, G. C.; Doñate, F.; Shaw, D. E.; Mazar, A. P.; Rabbani, S. A., A non-RGD-based integrin binding peptide (ATN-161) blocks breast cancer growth and metastasis in vivo. *Molecular cancer therapeutics* **2006**, 5, (9), 2271-2280.
213. Stoeltzing, O.; Liu, W.; Reinmuth, N.; Fan, F.; Parry, G. C.; Parikh, A. A.; McCarty, M. F.; Bucana, C. D.; Mazar, A. P.; Ellis, L. M., Inhibition of integrin $\alpha 5 \beta 1$ function with a small peptide (ATN-161) plus continuous 5-FU infusion reduces colorectal liver metastases and improves survival in mice. *International journal of cancer* **2003**, 104, (4), 496-503.
214. Harms, J. F.; Welch, D. R.; Samant, R. S.; Shevde, L. A.; Miele, M. E.; Babu, G. R.; Goldberg, S. F.; Gilman, V. R.; Sosnowski, D. M.; Campo, D. A., A small molecule antagonist of the $\alpha v \beta 3$

- integrin suppresses MDA-MB-435 skeletal metastasis. *Clinical & experimental metastasis* **2004**, 21, (2), 119-128.
215. Zhao, Y.; Bachelier, R.; Treilleux, I.; Pujuguet, P.; Peyruchaud, O.; Baron, R.; Clément-Lacroix, P.; Clézardin, P., Tumor $\alpha\beta 3$ integrin is a therapeutic target for breast cancer bone metastases. *Cancer research* **2007**, 67, (12), 5821-5830.
216. Shannon, K. E.; Keene, J. L.; Settle, S. L.; Duffin, T. D.; Nickols, M. A.; Westlin, M.; Schroeter, S.; Ruminski, P. G.; Griggs, D. W., Anti-metastatic properties of RGD-peptidomimetic agents S137 and S247. *Clinical & experimental metastasis* **2004**, 21, (2), 129-138.
217. Cai, W.; Wu, Y.; Chen, K.; Cao, Q.; Tice, D. A.; Chen, X., In vitro and in vivo characterization of ^{64}Cu -labeled AbegrinTM, a humanized monoclonal antibody against integrin $\alpha\beta 3$. *Cancer research* **2006**, 66, (19), 9673-9681.
218. Leong-Poi, H.; Christiansen, J.; Klibanov, A. L.; Kaul, S.; Lindner, J. R., Noninvasive assessment of angiogenesis by ultrasound and microbubbles targeted to αv -integrins. *Circulation* **2003**, 107, (3), 455-460.
219. Chen, X.; Park, R.; Hou, Y.; Khankaldyyan, V.; Gonzales-Gomez, I.; Tohme, M.; Bading, J. R.; Laug, W. E.; Conti, P. S., MicroPET imaging of brain tumor angiogenesis with ^{18}F -labeled PEGylated RGD peptide. *European journal of nuclear medicine and molecular imaging* **2004**, 31, (8), 1081-1089.
220. Murphy, E. A.; Majeti, B. K.; Barnes, L. A.; Makale, M.; Weis, S. M.; Lutu-Fuga, K.; Wrasidlo, W.; Cheresch, D. A., Nanoparticle-mediated drug delivery to tumor vasculature suppresses metastasis. *Proceedings of the National Academy of Sciences* **2008**, 105, (27), 9343-9348.