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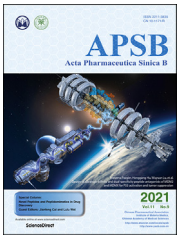

REVIEW

Integrins as attractive targets for cancer therapeutics

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Abstract Integrins are transmembrane receptors that have been implicated in the biology of various human physiological and pathological processes. These molecules facilitate cell–extracellular matrix and cell–cell interactions, and they have been implicated in fibrosis, inflammation, thrombosis, and tumor metastasis. The role of integrins in tumor progression makes them promising targets for cancer treatment, and certain integrin antagonists, such as antibodies and synthetic peptides, have been effectively utilized in the clinic for cancer therapy. Here, we discuss the evidence and knowledge on the contribution of integrins to cancer biology. Furthermore, we summarize the clinical attempts targeting this family in anti-cancer therapy development.

Abbreviations: ADAMs, adisintegrin and metalloproteases; AJ, adherens junctions; CAFs, cancer-associated fibroblasts; CAR, chimeric antigen receptor; CSC, cancer stem cell; CRC, colorectal cancer; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; ERK, extracellular regulated kinase; FAK, focal adhesion kinase; FDA, U.S. Food and Drug Administration; HIF-1α, hypoxia-inducible factor-1α; HUVECs, human umbilical vein endothelial cells; ICAMs, intercellular adhesion molecules; IGFR, insulin-like growth factor receptor; IMD, integrin-mediated death; JNK, c-Jun N-terminal kinase 16; mAb, monoclonal antibodies; MAPK, mitogen-activated protein kinase; MMP2, matrix metalloprotease 2; NF-κB, nuclear factor-κB; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol 3-kinase; RGD, Arg-Gly-Asp; RTKs, receptor tyrosine kinases; SAPKs, stress-activated MAP kinases; sdCAR-T, switchable dual-receptor CAR-engineered T; SDF-1, stromal cell-derived factor-1; SH2, Src homology 2; siRNA, small interference RNA; STAT3, signal transducer and activator of transcription 3; TCGA, The Cancer Genome Atlas; TICs, tumor initiating cells; TNF, tumor necrosis factor; uPA, urokinase-type plasminogen activator; VCAMs, vascular cell adhesion molecules; VEGFR, vascular endothelial growth factor receptor.

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1. Introduction

Integrins are a family of ubiquitous cell membrane adhesion receptors that make up the extracellular matrix (ECM). These include 24 heterodimers that span the plasma membrane and are consist of 18 α and 8 β integrin subunits[1]. The two main functions of integrins include: (1) mechanical attachment to the ECM; and (2) activation of signal transduction pathways that control various cellular functions that are essential to solid tumor initiation, progression, and metastasis[2].

Integrins play a crucial role in several physiological processes by maintaining cell viability *via* its attachment to the ECM. Moreover, these can directly control the migration and invasion of cancer cells by binding to ECM components and establishing traction for cellular motility and invasion[3]. ECM remodeling is also regulated by integrins that control ECM protease localization and activity. Furthermore, integrins also influence the proliferation, survival, and metastasis of cancer cells[4,5]. Integrins have the ability to detect a wide range of extracellular ligands, such as transmembrane receptors on the surface of other cells and ECM proteins involved in cell−cell junctions; integrins bind to different receptors, including adisintegrin and metalloproteases (ADAMs) or molecules expressed by endothelial cells and leukocytes, such as intercellular adhesion molecules (ICAMs) and vascular cell adhesion molecules (VCAMs)[6]. Moreover, various extracellular ligands are involved in cell−ECM interactions, including collagen, laminin, and fibronectin. However, integrins can also recognize various other physiological ligands and act as receptors for viruses, snake venoms, and other pathogens[7,8]. However, some integrins can only bind to particular ECM ligands (*e.g.*, $\alpha 5\beta 1$ integrin binds to fibronectin), whereas others show a wider ligand-binding repertoire (*e.g.*, $\alpha v\beta 3$ integrin binds to vitronectin, fibronectin, thrombospondin, and fibrinogen). Almost all integrins can bind to the ECM using the RGD (Arg-Gly-Asp) peptide motifs. The EILDV and REDV sequences have also been shown to mediate integrin−ECM adhesion[9].

This review presents the crucial and often contradictory function of integrins in controlling tumor cell survival, other than their ligation-dependent effects, as well as recent developments in integrin treatment schemes, particularly in cancer.

2. Integrins in cancer

Integrins occurring on cancer cells and other cell types in the tumor microenvironment have essential roles in controlling intracellular activity as well as intercellular communication. These have a paradoxical role in cancer, ligated integrins can enhance cell survival and promote cell proliferation; in contrast, whereas unligated integrins present in the surroundings of tumor cells can initiate apoptotic cascade. However, cancer cell−ECM interactions are essential to maintaining homeostasis between the two states, including "inside-out" and "outside-in" signaling, which are almost altered during cancer progression[10].

Integrins are proteins that span the plasma membrane and are capable of bidirectional signaling (Fig. 1). Various cytoplasmic interactions control integrin activation, altering its affinity to extracellular ligands that transmit "inside-out" signals[11−13]. Here, the recruitment of the adaptor protein talin to the tail region of the integrin protein induces a conformational change in the extracellular domain of the integrin, resulting in its activation and increase in affinity for ECM ligands. Integrins are capable of regulating intracellular pathways in response to the ECM or other extracellular matrix that binds to "outside-in" signals[14]. Integrin−ECM interactions, in turn, result in the recruitment of adaptors and signaling proteins to the cytoplasmic domain of integrins, and promote macromolecular complex assembly, which is also known as focal adhesion[15].

The major function of integrins expressed on the cell surface is to adhere to the ECM, ligation provides traction that is essential tumor cell survival and invasion. Cell migration and invasion are also controlled by integrins by influencing the activity and localization of matrix-degrading proteases, such as urokinase-type plasminogen activator (uPA) and matrix metalloprotease 2 (MMP2)[16,17]. In addition, deregulation in integrin recycling by the crab GTPases or mediated by integrins themselves also results in enhanced growth factor signaling and cell migration[18]. Integrin-controlled cell migration is largely mediated by signaling pathways involving members of the focal adhesion kinase (FAK)-SRC family kinase. However, it is highly dependent on an integrin-specific mechanism[19]. Integrin−ligand adhesion triggers an increase in FAK tyrosine (Tyr) 397 phosphorylation, which creates a binding site for the SRC kinas domains SRC homology 2 (SH2) and SH3[20]. Then, SRC phosphorylates other tyrosines that contribute to the full activation of FAK. This activated FAK/SRC complex facilitates various key signaling cascades that regulate cell motility[21,22]. The other well-established role of integrins involves cancer cell proliferation and survival. Integrin adhesion activates the cyclin-dependent kinase inhibitor family pathway and cyclin D1[23], thereby regulating the entry of cells into the S phase of the cell cycle[24] while deregulating cell proliferation and anchorage-independent growth. In addition, integrins contribute to cell survival through several complex- and context-dependent pathways. In addition to P53 activation, integrin ligation also triggers the upregulation of BCL-2 and FLIP pro-survival molecules[25,26], the activation of mitogen-activated protein kinase (MAPK)/extracellular regulated kinase (ERK) pathway, phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway, c-Jun N-terminal kinase (JNK)16, and stress-activated MAP kinases (SAPKs) or nuclear factor-κB (NF-κB) signaling[27−29].

However, integrins in the unligated form could in contrast negatively influence tumor survival. Integrins in adherent cells are predominantly unligated and result in the cleavage of caspase 8 that in turn triggers tumor cell apoptosis *via* a mechanism known as integrin-mediated death (IMD)[30,31]. In contrast to IMD, which is induced by cell adhesion, anoikis-induced apoptosis is induced by the complete detachment of the cell from the ECM[32,33]. Recent studies have revealed that tumor cells are resistant to IMD, which is attributable to the complete loss of caspase 8. In this situation, integrins promote cell survival and metastasis[34]. In summary, more studies are required to better understand the effects of

ligated and unligated integrins, which is a determining factor in the clinical evaluation of integrin antagonists.

2.1. *The composition and function of integrin family in cancer*

Numerous integrins have been investigated for their presence and contribution to tumor progression. Some integrins detected in tumors are retained from the normal epithelial cells before tumorigenesis, *i.e.*, $\alpha 2\beta 1$, $\alpha 3\beta 1$, $\alpha v\beta 5$, $\alpha 6\beta 1$, and $\alpha 6\beta 4$, mainly mediate cell adhesion as well as cell migration, proliferation and survival. More interestingly, some integrins have been proven to be upregulated in tumor cells while expressed at low or undetectable levels in normal tissues, notably, integrins $\alpha v\beta 3$, $\alpha 5\beta 1$ and $\alpha v\beta 6$ and with less frequency $\alpha v\beta 5$, $\alpha 6\beta 4$, and $\alpha 4\beta 1$ (Table 1). The expression of these integrins has been correlated with pathological outcomes including disease stage, tumor metastasis, treatment resistance, and patient survival.

2.1.1. $\alpha v\beta 6$

The integrin subunit $\beta 6$ is selectively expressed during wound healing and embryonic development and is associated with tissue remodeling. In cancer, $\alpha v\beta 6$ integrin is upregulated in various carcinomas and strongly correlated to cell migration, invasion, and survival, in particular in breast cancer, and $\alpha v\beta 6$ acts *via* the activation of TGF-β, which is a key initiator of matrix remodeling and fibrosis. Then, subsequent studies have found that colorectal cancer (CRC) cells expressing integrin $\alpha v\beta 6$ secrete inactive TGF-β, which is then activated by integrin $\alpha v\beta 6$ that subsequently activates fibroblasts that promote CRC cell invasion[35]. Furthermore, it has been shown that $\alpha v\beta 6$ expression is correlated to poor prognosis in individuals with triple-negative breast cancer. The crosstalk between $\alpha v\beta 6$ integrin and epidermal growth factor receptor (EGFR) controls bidirectional force transmission and regulates breast cancer invasion; it influences matrix stiffness, transcriptional reprogramming, force transmission to the nucleus, as well as microenvironment rigidity. $\alpha v\beta 6$ interactions trigger EGFR and MAPK signaling, whereas $\alpha v\beta 6$−EGFR crosstalk controls mutual receptor trafficking mechanisms. Blocking $\alpha v\beta 6$ alone or together with trastuzumab administration has been reported for the treatment of high-risk and trastuzumab-resistant breast cancer patients[36].

2.1.2. $\alpha 5\beta 1$

Integrin $\alpha 5\beta 1$ has been described as the central regulator of angiogenesis. High $\alpha 5\beta 1$ integrin expression levels have been observed in endothelial cells, and they are correlated with reduced cellular survival. In addition, vascular remodeling defects were observed in mice with $\alpha 5\beta 1$ integrin abnormalities, leading to adhesion and migration alterations. It has been proven that $\alpha 5\beta 1$ integrin supports survival of cells with fibronectin attachment *via* upregulation of BCL-2 expression, whereas $\alpha v\beta 1$ integrin (binds the fibronectin onto the same RGD such as $\alpha 5\beta 1$) does not suppress cell apoptosis[37].

In colon cancer, HT29 cells expressing $\alpha 5\beta 1$ have been shown to be resistant to serum starvation-induced apoptosis, and a correlation between acquisition of $\alpha 5\beta 1$ integrin and ADAM-15 downregulation and poor prognosis has been reported[38]. In line with this, a previous study described that hypoxia upregulates the $\alpha 5\beta 1$ integrin subunit, which in turn promotes colon cancer progression[39]. In addition, fibronectin generated by peritoneal tissues activates $\alpha 5\beta 1$ integrin on ovarian cancer cells, stimulating their invasiveness by increasing MMP-9 activity[40]. Several human ovarian cancer cell lines express $\alpha 5\beta 1$ integrin, and its binding is disrupted specifically by anti-$\alpha 5\beta 1$ integrin antibodies or a ligand of $\alpha 5\beta 1$ integrin, namely, endostatin[41,42].

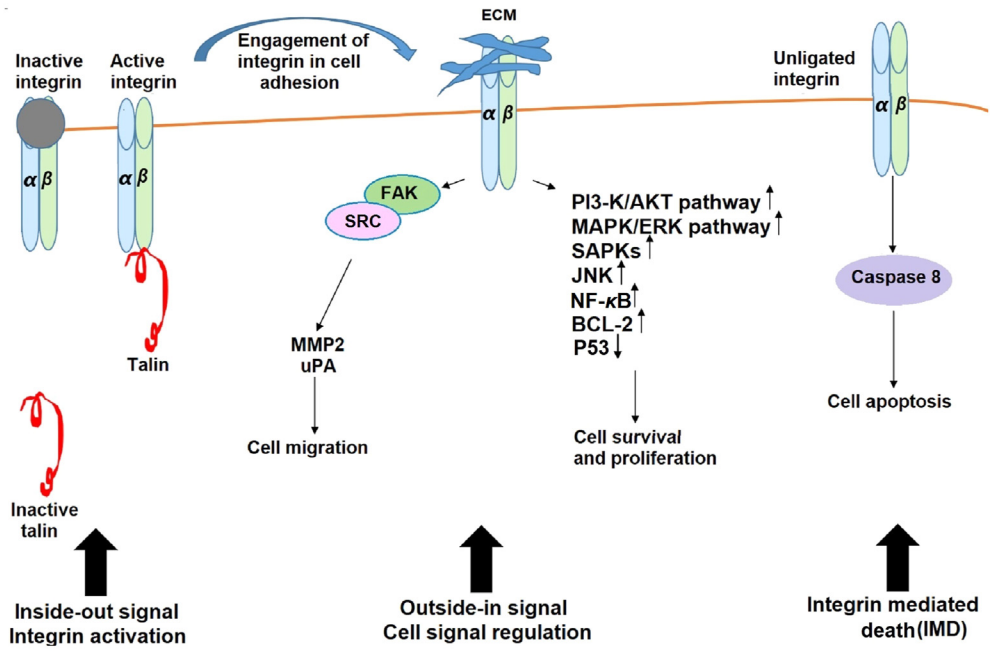

Figure 1 Composition and signal transduction of the integrin family in cancer progression. Depending on the ligation status of integrins expressed by the cancer cells or cells present in TME, they can trigger pro-survival or paradoxically a pro-apoptotic signal. In the most commune situations, integrins are ligated and initiate the pro-survival signal by overexpression of the pro-survival molecules BCL-2 and FLIP factor-κB, activation of NF-κB or PI3K-AKT, and downregulation of P53. In an unligated status, the integrins initiate a process known as integrin-mediated death (IMD) *via* the cleavage of caspase 8.

Table 1 Applications of preclinical and clinical integrin antagonists in different cancers.

Drug	Target	Cancer type	Effect	Clinical trial phase
Etaracizumab (Abegrin)	$\alpha v\beta 3$	Colorectal/melanoma/prostate/ thyroid cancer	Cell survival and metastasis	Phase II
Intetumumab (CNTO 95)	$\alpha v\beta 1$, $\alpha v\beta 3$, $\alpha v\beta 5$, $\alpha v\beta 6$	Prostate cancer/melanoma	Cell survival and metastasis, tumor angiogenesis	Phase II
Abciximab (c7E3)	$\alpha IIb\beta 3$, $\alpha v\beta 3$	Melanoma/breast cancer	Cell migration, invasion, and apoptosis	Pre-clinical
Vitaxin (MEDI-532)	$\alpha v\beta 3$	Melanoma/prostate cancer	Cell survival and angiogenesis	Phase II
Volociximab (M200)	$\alpha 5\beta 1$	NSCLC/metastatic melanoma	Apoptosis reduction, therapeutic resistance	Phase II
Cilengitide	$\alpha v\beta 3$, $\alpha v\beta 5$	Glioblastoma/lung cancer/melanoma	Cancer metastatic, vascularization and poor prognosis	Phase II
ATN-161	$\alpha 5\beta 1$	Glioblastoma	Tumor angiogenesis and metastasis	Phase II
HM-3	$\alpha v\beta 3$	Lung/liver/stomach cancer	Tumor angiogenesis and cell survival	Phase I
AP25	$\alpha v\beta 3$, $\alpha 5\beta 1$	Melanoma/gastric/hepatic/breast carcinoma	Cell survival and angiogenesis	Pre-clinical

ERBB2, an oncogene strongly associated with metastasis and poor prognosis in breast cancer, triggers the upregulation of $\alpha 5\beta 1$ integrin in mammary adenocarcinomas, thereby promoting tumor cell survival[43,44]. A recent study has indicated that hypoxia selectively enhances the expression of integrin $\alpha 5\beta 1$ receptor in breast cancer to promote metastasis as well[45]. The expression of $\alpha 5\beta 1$ integrin has also been reported in lung cancer[46], melanoma[47] and glioma[48,49] and it has respectively been associated with the activation of the PI3K/AKT pathway, Rho-GTPases, and the IL6-STAT3 pathway.

2.1.3. $\alpha v\beta 3$

Beside its role in various physiologic processes such as wound healing and angiogenesis, $\alpha v\beta 3$ integrin is highly involved in tumor pathogenesis. It has been associated with the growth, survival, invasion, and metastasis of various cancer cells[50]. It has also been correlated with tumor progression and lower patient survival rates in breast cancer, melanoma, and colon carcinoma, in addition to increasing migration and invasion of tumor cells[51,52]. Integrin $\alpha v\beta 3$ binds to a spectrum of ECM molecules using the RGD triple-peptide motif[53], which includes von Willebrand factor, fibronectin, fibrinogen, proteolyzed forms of collagen and laminin, and vitronectin, whereas other integrins, including $\alpha 5\beta 1$, can only selectively bind to fibronectin[54,55]. In prostate cancer, the upregulation of $\alpha v\beta 3$ has been associated with resistance to radiotherapy *via* the regulation of survivin expression levels[56]. The application of $\alpha v\beta 3$ integrin antagonist or survivin inhibition with siRNA enhances IR-induced inhibition of anchorage-independent cell-growth.

2.1.4. $\beta 1/\beta 3$ balance

A strong correlation has been reported between $\beta 1$ and $\beta 3$ integrin expression in cancer cells[57,58]. The association between the two integrins remains complicated and paradoxical, but it has been utilized as an indicator of cancer prognosis and in clinical treatment. The downregulation of $\beta 1$ integrin has been shown to be compensated by an upregulation of $\beta 3$ integrin to maintain the metastasis of breast cancer cells, and tumor proliferation was only affected when $\beta 1$ and $\beta 3$ integrins were simultaneously downregulated. This effect has not been observed in normal cells. Furthermore, the roles of $\beta 1$ integrin include promoting proliferation and inhibiting metastasis, and $\beta 1$ integrin inhibition affects TGF-β function that in turn attenuates the expression of E-cadherin, decreasing the activity of cell−cell junctions while enhancing motility and migration[59]. In contrast, $\beta 3$ integrin induces epithelial−mesenchymal transition (EMT) and activates a non-canonical FAKs-independent signaling pathway that in turn prevents cancer cells from undergoing IMD and promoting cancer cell metastasis[60].

2.2. *Integrins and angiogenesis*

Angiogenesis plays a central role in wound healing and embryonic development, various diseases, such as cancer, psoriasis, rheumatoid arthritis, and diabetic retinopathy, are orchestrated, in part, by a pathological angiogenic response[61−64]. Angiogenesis also plays a major role in tumorigenesis, and the formation of new blood vessels is important to provide tumor cells with oxygen and nutrients for the maintenance of growth of solid tumors. In addition, neovascularized tumor cells could be shed into the circulation, leading to cancer metastases[65]. Harold Dvorak has stated “tumors make bad blood vessels” and tumor-associated blood vessels are structurally and biologically different from quiescent vessels in that their tortuous and leaky characteristics influence blood flow, disrupt drug delivery, promote fibrosis, and allow tumor cell intravasation[64]. Angiogenesis is dependent on endothelial cell adhesion to ECM proteins, such as vitronectin, through integrins, particularly, integrin $\beta 1$, $\beta 3$, and $\alpha v\beta 3$. Lugano et al.[66] demonstrated that $\beta 1$ integrin activation is critical for the organization of fibronectin fibrillogenesis during tumor vascularization. They claimed that CD93 controls $\beta 1$ integrin signaling, phosphorylation of focal adhesion kinase (FAK), as well as fibronectin fibrillogenesis in endothelial cells. In turn, tumor vessels in gliomas orthotopically implanted in CD93-deficient mice exhibited diminished activation of $\beta 1$ integrin, with fibronectin showing disorganized fibrillar structures[67]. In addition, studies have revealed $\beta 3$ upregulation on newly developed blood vessels in tumors, whereas it is not generally observed on blood vessels of normal tissues, and it acts through the ligation onto proteolyzed collagen at its RGD site to induce tumor neovascularization. In fact, various animal models lacking $\beta 3$ integrin expression or directly blocking $\beta 3$ integrin have been shown to have decreased angiogenesis and induction of tumor regression[68,69]. Moreover, $\alpha v\beta 3$ integrin has been investigated for its indirect effect *via* VEGFR2 promoting a VEGF-induced angiogenesis. In endothelial cells, an interaction between VEGFR2 and integrin $\alpha v\beta 3$ is an essential process during vascularization, and studies have shown that the disruption of the $\alpha v\beta 3$/VEGFR2 crosstalk and its downstream pathways slows down tumor angiogenesis[70,71].

2.3. Integrins and cancer stem cells

Cancer stem cell (CSC)-tumor initiating cells (TICs) are the most aggressive and dangerous cells in tumors as these have the capacity to self-renew and differentiate[72,73]. Accumulated evidence suggests that CSCs are drivers of tumor progression, disease relapse, and drug resistance. Integrins have been proved to have a pivotal part in both during cancer initiation and progression, as well as cell differentiation, which may serve as evidence for their contribution to CSC biology. However, several of these integrins that are enriched in normal adult stem cells and progenitor cells are also indicators of CSCs, including $\beta1$, $\alpha6$, $\beta3$, and $\beta4$ integrin subunits[74,75]. Interestingly, a complete inhibition of tumorigenesis was detected in mice lacking $\beta1$-integrin function[76], and the mammary gland-specific loss of function of $\beta1$ integrin can essentially block the generation or the amplification of $CD24^{high}CD29^{low}CD61^{high}$ cancer cells, thereby resulting tumorigenesis[77]. Barnawi et al.[78] analyzed the expression profiles of 530 patients from the TCGA (The Cancer Genome Atlas) database and reported a statistically significant correlation between $\beta1$ integrin and fascin expression; fascin-mediated regulation of $\beta1$ integrin plays a critical role for various breast cancer cell functions, such as adhesion to different ECMs, self-renewability, and chemoresistance. Furthermore, a significant relationship among coexpression of fascin and $\beta1$ integrin, short disease-free intervals, and overall survival was reported in chemo-treated breast cancer[79].

The expression of a dominant-negative $\beta4$ integrin mutant has been shown to delay the progression and to inhibit metastasis in a breast-cancer mouse model that was induced by an activated version of human oncogene *ERBB2*[80,81]. The proposed mechanism was that $\beta4$ integrin directly interacts with the ERBB2 receptor, and activates the JUN and STAT3 pathways, which have been associated with tumor proliferation, survival, and resistance to immunotherapy[82]. Other signaling pathways have also shown that $\beta4$ integrin is essential to cell survival and resistance to apoptosis. The P63 pathway, which is normally and particularly expressed in basal cells (either normal or cancerous mammary basal epithelial cells or stem cells) can activate $\beta4$-integrin expression that mediates resistance to anoikis (an apoptotic mechanism that is caused by loss of cell anchorage) *via* a STAT3-dependent mechanism[83]. The second pathway is through NF-κB signaling mechanism that promotes $\beta4$-integrin-mediated resistance to apoptosis. Hoogland et al.[84] assessed the immunohistochemical expression of stem cell markers in 481 patients with prostate cancer, and $\alpha6$ expression was observed in 28.4% of these patients and was described as a predictive biochemical marker for local recurrence of prostate cancer and disease-specific death. Furthermore, integrin expression was correlated to high aggressiveness of squamous cell carcinomas, and serial limit dilution transplantation assays revealed that $\alpha_6^{hi}\beta_1^{hi}$ populations can initiate secondary tumors, but $\alpha_6^{lo}\beta_1^{lo}$ populations cannot, regardless of whether the cells were $CD34^{lo}$ or $CD34^{hi}$[85].

Taken together, these findings strongly argue that targeting integrins may potentially be utilized as a relevant strategy for cancer treatment to restrict cancer-stem cell survival and aggressiveness.

2.4. Integrins and cancer-associated fibroblasts (CAFs)

CAFs are the predominant stromal cell type in the tumor microenvironment that can contribute to cancer progression through interactions with tumor cells[86]. Numerous experimental studies support that integrins play bidirectional regulatory roles between cancer cells and CAFs. CAFs that express IL-32 contain an RGD cell attachment sequence that binds to integrin $\beta3$-positive cancer cells to promote breast cancer cell invasion and metastasis[87]. CAF-derived extracellular vesicles that express annexin A6 plays a pivotal role in gastric cancer drug resistance *via* activation of $\beta1$ integrin-FAK-YAP signaling[88]. CRC cells express integrin $\alpha v\beta6$-activated CAFs through TGF-β, which subsequently secrete stromal cell-derived factor-1 (SDF-1) and promote CRC cell metastasis[89]. These research studies reveal that integrins act as receptors that regulate the interactions between CAFs and cancer cells in tumor progression and drug resistance.

2.5. Integrins and cancer immunity

Myeloid cells and lymphocytes rely on cell adhesion receptors (including integrins) for trafficking inflamed tissues and tumors, which are involved in both innate immune and adaptive immune responses. Previous studies have revealed that integrin $\alpha4\beta1$ regulates myeloid cell trafficking into tumors during tumor progression[90]. Integrin $\alpha M\beta2$ inhibits immune suppression by restraining immunosuppressive macrophage polarization[91]. Moreover, the relative expression level and activation state of integrin $\alpha e\beta7$ and $\alpha L\beta2$ on T cells mediates movement within the tumor microenvironment through direct interactions with ligands on tumor cells, stromal cells, and other immune cells[92]. Integrin $\beta3$ signaling regulates the balance between protumor and antitumor immune cells *via* STAT6/STAT1 signaling[93], which partly explains the varied clinical results of integrin antagonists. Thus, integrins may serve as critical components of the tumor immune microenvironment and can be an effective immunotherapeutic target.

3. Crosstalk between integrins and other signaling pathways in cancer

Integrins signaling in cancer involves not only activation of certain pathways downstream of specific receptors, but also crosstalk with growth factors, growth factor receptors, cytokines, oncogenes, and enzymes. Integrins can associate with numerous receptor tyrosine kinases (RTKs) and trigger their cross-phosphorylation, such as EGFR, vascular endothelial growth factor receptor (VEGFR), insulin-like growth factor receptor (IGFR), platelet-derived growth factor receptor (PDGFR), and c-Met[94,95]. This cooperative signaling differentially activates RAF, which in turn enhances cell survival. Signaling *via* integrin $\alpha v\beta3$ and the fibroblast growth factor receptor induces the phosphorylation of RAF Ser338 and Ser339, thereby protecting cells from the intrinsic apoptosis pathway. The ligation of integrin $\alpha v\beta5$ and VEGFR2 phosphorylates RAF Tyr340 and Tyr341, preventing apoptosis through the extrinsic pathway. The engagement of integrin $\alpha5\beta1$ with fibronectin controls the activity of RhoA by inducing Src-mediated P190 RhoGAP tyrosine phosphorylation[94].

In addition to the crosstalk, integrin-mediated adhesion to ECM can also enhance growth factor signaling on its receptor, and in some cases, interactions with ECM may aid in the effective presentation of growth factors to their receptors[95].

Integrins crosstalk with EGF and/or its receptor EGFR has been extensively investigated. It has been revealed that cooperation between integrins and members of the EGFR family (EGFR and ERBB2) may affect tumor initiation, proliferation, migration,

and invasion. Examples include $\alpha6\beta4$, $\alpha v\beta6$, and $\alpha v\beta5$ integrins. $\alpha6\beta4$-ERBB2 induces the activation of signal transducer and activator of transcription 3 (STAT3) and Jun, resulting in the loss of cell polarity and hyperproliferation, respectively[96]. A previous study has also revealed the consequence of $\alpha v\beta6$−EGFR crosstalk in the bidirectional transmission of mechanical signals between the nucleus and ECM. The crosstalk between $\alpha v\beta6$ integrin and EGFR involves a complex regulatory mechanism that impacts matrix stiffness and force transmission to the nucleus. The adhesion of $\alpha v\beta6$ to ECM induces EGFR and MAPK signaling, and $\alpha v\beta6$−EGFR crosstalk controls mutual receptor trafficking mechanisms that in turn regulate tumor cell invasion[97]. Furthermore, the activation of $\alpha v\beta5$ integrin in breast cancer is EGF-dependent and occurs *via* SRC phosphorylation of the p130CAs substrate domain, followed by the activation of the GTPase RAP1A, which is a known mediator of integrin activation[98]. Similar as that in breast cancer, it has been published that integrin ligation itself regulates EGF signaling, inducing an EGF-independent EGFR phosphorylation and crucially influencing tumor cell susceptibility to treatment, resulting in increased MAPK activation, tumor cell proliferation, survival, and resistance for anticancer therapy[99−101].

Integrins and VEGF/VEGFR interaction is another example of integrin crosstalk occurring on endothelial cells not tumor cells themselves and promoting tumor angiogenesis. The VEGFR2−integrin $\alpha v\beta5$ pair induces SRC-dependent phosphorylation of RAF (Tyr340 and Tyr341) and resistance to extrinsic vascular endothelial cellular apoptosis that is induced by inflammatory mediators, including tumor necrosis factor (TNF)[102]. Furthermore, VEGF influences integrin $\alpha v\beta3$ signaling by controlling the affinity state or activating integrins[103,104]. $\alpha v\beta3$ integrin activation can in turn enhance tumor cell secretion of VEGF, thereby providing a feedback loop that increases tumor growth. In addition, the recruitment of SRC to VEGFR2 promotes the SRC-dependent tyrosine phosphorylation of the integrin $\alpha v\beta3$ cytoplasmic domain, thereby enhancing angiogenesis[105].

Integrins and MMPs also exhibit strong cross-reactivity. MMP-2 and MMP-9 are major factors influencing cancer cell migration and invasion; these degrade ECM proteins and facilitate tumor invasion. It has been reported that $\alpha v\beta3$ is essential to MMP-2 activation, its blockade inhibits MMP-2 activation by collagen 1, consequently affecting cell migration and invasion[106]. $\alpha v\beta5$ ligation participates in the activation of MMP-9 and an upregulation of VEGF, inducing an increase in cell migration in melanoma[107,108].

E-cadherin is a Ca^{2+}-dependent cell surface glycoprotein that influences cell−cell adhesion. It acts as a single-pass transmembrane protein that controls homophilic cell−cell interactions. During tumorigenesis E-cadherin loses its function and transforms to a more motile and invasive phenotype in coordination with integrin-mediated adhesions to the surrounding ECM. An ultimate crosstalk exists between integrin and E-cadherin in controlling cell motility and invasiveness. Integrin engagement activates several signaling cascades that are controlled by FAK and SRC and Rho GTPases[109]. This signaling network downstream of integrins alters actin dynamics, which regulate adheren junctions (AJ) principally formed by E-cadherin[110]. In addition, activation of these pathways results in changes in the transcriptional and post-transcriptional regulation of AJ components, the regulation of E-cadherin endocytosis, and the enhancement of the cell motility and migration[111].

In addition to the direct phosphorylation of AJ components, AJs may also be regulated by SRC and FAK by altering the expression and stability of E-cadherin protein expression *via* the transcriptional control of the E-cadherin promoter[112,113]. SRC and FAK can also control the endocytosis of E-cadherin and thus its membrane localization and control of the strength of AJs, Canel et al.[114] reported that small interference RNA (siRNA)-mediated depletion of $\beta1$ integrin or FAK inhibits E-cadherin endocytosis and is correlated to strengthening of cell−cell adhesion and decrease in collective invasion.

4. Integrin targeted therapy

The importance of integrins as indicated by earlier studies has prompted the development of integrin−antagonist molecules that disrupt tumor growth of both tumor cells and tumor-associated cells, notably endothelial cells. Current integrin antagonists that are now being investigated in clinical trials include RGD peptide mimetics and monoclonal antibodies (mAb).

4.1. Antibodies

4.1.1. Bevacizumab

Bevacizumab (Avastin, LM609, Genentech) is a mouse anti-human integrin $\alpha v\beta3$ and anti-VEGF mAb[115]. Its anti-angiogenic mechanism is attributed to the inhibition of bFGF and TNF-α induced angiogenesis[116]. Avastin shows good efficacy and tolerance in all of the clinical trials and thus has been approved by the U.S. Food and Drug Administration (FDA) as a first- or second-line treatment for metastatic breast cancer or as part of a combination chemotherapy scheme for metastatic colorectal cancer. Avastin is also used in glioblastoma, metastatic renal carcinoma, and NSCLC[117]. Several humanized versions of Avastin, such as Vitaxin I (MEDI-523)[118] and Abegrin (Vitaxin II, MEDI-522) have been developed, but these failed to show antitumor efficacy in clinical trials. Recently, it has been revealed that Avastin treatment may increase the number of CSCs in breast cancer, suggesting a possible explanation for why this molecule does not lead to longer survival. Conley et al.[119] attributed this effect to enhanced intra-tumoral hypoxia that in turn activates hypoxia-inducible factor-1α (HIF-1α). Furthermore, several reports have shown the critical role of hypoxia and HIF in the proliferation, self-renewal, and maintenance of cancer stem cells.

Becherirat et al.[120] observed a significant increase in proangiogenic factors when therapy was stopped in mice with colorectal cancer. Upon withdrawal of bevacizumab, and after a drug-break period, a notable increase in CSCs was observed, indicating that Avastin treatment needs to be maintained because discontinuous administration triggers tumor regrowth and increases tumor resistance and CSC heterogeneity.

4.1.2. Intetumumab

Intetumumab (CNTO 95, Centocor) is a fully humanized antibody with multiple integrin inhibition property, it recognizes and binds with high affinity multiple αv integrins. In a phase I clinical trial, CNTO 95 has been shown to be safe and well tolerated, and a prolonged response was observed in patients with tumor cells expressing $\alpha v\beta3$ integrin, whereas a partial response was detected in a patient whose tumor expressed $\alpha v\beta1$ integrin. The development of this drug was discontinued during its phase II clinical trial for treatment of melanoma and prostate cancer[121].

4.1.3. Abciximab

Abciximab (c7E3) is a Fab fragment of the 7E3 chimeric human-murine monoclonal antibody. It has been developed as a platelet aggregation inhibitor mainly by targeting αIIbβ3 receptors on platelets. However, it can also effectively bind to αvβ3 integrin, and, more importantly, it can redistribute between the two receptors *in vitro*[122]. The FDA has approved c7E3 Fab as adjunct therapy against cardiac ischemic complications in individuals undergoing percutaneous coronary intervention[123]. An *in vitro* angiogenesis assay has shown that c7E3 Fab inhibits the migration of αvβ3-mediated human umbilical vein endothelial cells (HUVECs) and cell adhesion, migration, and invasion in melanoma, in addition to bFGF stimulating the proliferation of HUVECs[124,125]. An animal study has shown that c7E3 Fab partially suppresses human melanoma tumor growth in nude mice and completely interferes with the formation and growth of human melanoma tumor in nude rats[126,127]. Furthermore, it has been reported that abciximab could induce a proapoptotic effect in MCF-7 breast cancer cells through the activities of proline oxidase, ERK1/2, NF-κB, HIF-A1, VEGF, and collagen biosynthesis[128].

4.1.4. LM609-derived antibody

Vitaxin (MEDI-532) is the developmental precursor of Abegrin (Etaracizumab, MEDI-522). These are two humanized versions of the LM609 monoclonal antibody that have been shown to specifically recognize αvβ3 integrin and target angiogenic blood vessels, thereby suppressing tumor growth in various animal models. It has been revealed that Vitaxin has no effect on the rates of wound closure or integrity (indicating a disadvantage to anti-angiogenic therapy) in two different animal species, implying that this molecule is safe[129]. In a pilot trial involving patients with metastatic cancer who failed standard therapy, no significant toxicity and no immune response to Vitaxin were noted. In addition, three patients who received two cycles of therapy had stable disease on Day 85 when taken off study[130].

Phase I clinical trial revealed that Vitaxin treatment provides clinical benefit to patients with tumors without causing significant side effects. The two antibodies are currently being assessed in phase II clinical trials as a therapeutic regimen for melanoma and prostate cancer[131]. Combination therapy with paclitaxel generated better results in reducing tumor weight, and tumors showed lower levels of p-AKT and p-mTOR; however, no change in the microvessel density of resected tumors was observed after therapy. In a recent study by Wallstabe et al.[132], αvβ3-specific chimeric antigen receptor (CAR) T cells comprising a super-humanized hLM609 targeting domain were generated and preclinically tested *in vivo* and *in vitro*. αvβ3-CAR-T cells rapidly and specifically eliminated αvβ3-positive tumor cells *in vitro*. A murine xenograft model of metastatic A-375 melanoma exhibited a strong antitumor effect, which was mediated by hLM609 αvβ3-CAR. Here, a single administration of hLM609 αvβ3-CAR-T cells resulted in the complete elimination of melanoma lesions and in turn, long term tumor-free survival.

4.1.5. Volociximab (M200)

A chimeric monoclonal antibody that particularly targets α5β1 integrin and disrupts its interaction with fibronectin[133] has been assessed both as single therapy and combined with classical drugs including carboplatin and paclitaxel in phase I and II clinical trials to treat specific tumor types, including advanced non-small cell lung cancer (NSCLC) and metastatic melanoma. The preliminary results revealed a 6.3-month increase in median progression-free survival and reduced levels of potential biomarkers of angiogenesis or metastasis after receiving six cycles of treatment. Randomized trials are now required to verify the early results[134].

4.2. Synthetic peptides

Synthetic peptides mimic the organization of the natural ligands of integrins, these are mostly RGD mimetics that effectively bind to integrins and block their effect. There is no currently FDA-approved integrin-blocking peptide for cancer.

4.2.1. Cilengitide

Cilengitide (EMD 12) is a cyclic RGD pentapeptide [Arg-Gly-Asp-D-Phe-(NMeVal)] that acts as a potent αvβ3 and αvβ5 integrin inhibitor of integrin-mediated adhesion and migration[135]. This αv inhibitor apparently acts by inhibiting the FAK/SRC/AKT pathway and triggering apoptosis in endothelial cells. Preclinical studies have revealed positive antiangiogenic effects *in vitro*[136] and antitumor effects *in vivo* against melanoma, and also in head and neck cancer, breast cancer, and brain tumor[137,138]. Cilengitide has been used in trials for the treatment of sarcoma, glioma, lymphoma, leukemia, and lung cancer.

Phase I clinical trials involving patients with recurrent malignant glioma has shown that its well-tolerated doses are 2400 mg/m^2, with stable disease observed in four patients[139]. In phase II clinical trials, cilengitide showed a high efficacy and safety in an individual with glioblastoma. Unfortunately, in a randomized, controlled, multicenter UEORTC phase III clinical trial, treatment with cilengitide did not improve the overall survival of patients with newly diagnosed glioblastoma, which may be due to various reasons such as dose dependency, absence of reliable biomarker for the assessment of tumor activity and/or the selection of cancer type. Future investigations need to take account into the unique pharmacokinetics of the drug[140,141].

4.2.2. ATN-161

ATN-161 is a non-RGD-based pentapeptide (PHSRN) derived from the fibronectin synergy region. This noncompetitive inhibitor of fibronectin binds exclusively to the integrin β subunit[142], and it inhibits the function of several integrins implicated in tumor angiogenesis[143]. *In vivo* experiments revealed that treatment with ATN-161 alone or combined with 5-fluorouracil (5-FU) could significantly reduce tumor cell proliferation and enhance overall survival in mice with metastatic colon cancer[144], and promising effects were detected in breast cancer treatment, in which ATN-161 caused a significant dose-dependent reduction in tumors and blocked the incidence and frequency of metastases[145].

A phase I clinical trial[146] revealed that the drug is safe and potentially active, and it does not induce dose-limiting toxicity, with prolonged stable disease occurring in some of the treated patients.

4.2.3. HM-3 and PEG-HM-3

HM-3 is 18-amino-acids RGD-containing peptide that specifically targets integrin αvβ3[147]. Its long-lasting form PEG-HM-3 was developed to prolong its half-life and change its mode of administration from IV injection to subcutaneous administration[148]. It has been proven that this molecule, not only targets the endothelial cells, but also some integrin-expressing tumor cells[149,150]. Preclinical tests revealed that the drug exhibits a strong anti-angiogenic and antitumor bioactivity, and the PEGylated peptide achieved an impressive tumor inhibitory rate in human NSCLC,

gastric, breast, and colon cancer xenograft models with minimal cytotoxicity[151]. A mechanistic study[152] revealed that PEG-HM-3 targets integrin $\alpha v\beta 3$, thus disrupting the downstream ERK and AKT pathways, resulting in the downregulation of VEGF, AKT1, p-AKT1, MEK1, p-MEK1, ERK1/2, and p-ERK1/2 and the expression of integrins αv and $\beta 3$ decreased after HUVECs were incubated in the presence of mPEG-SC20k-HM-3 for 24 h. Recently, Zhao et al.[153] reported that an enhanced therapeutic effect of HM-3 on lung cancer *in vivo* by administering a combination of *Salmonella* VNP20009 carrying a *SOX2* shRNA construct and targeting cancer stem cells and the *SOX2* gene.

4.2.4. AP25

AP25 is a 25-amino acid RGD-modified polypeptide that targets $\alpha v\beta 3$ and $\alpha 5\beta 1$ integrins that are secreted by endothelial and tumor cells. AP25 has an extraordinary antitumor effect on different types of cancer, including gastric carcinoma[154], melanoma, hepatic carcinoma, and breast cancer[155]. Recently, Li et al.[156] presented a novel strategy involving fusion of the AP25 peptide and GnRH Fc fragment that not only retains the bifunctional biological activity of angiogenesis inhibition as well as GnRH receptor blocking, but it also prolongs its half-life, which provides a reliable approach for future pre-clinical research.

4.3. New emerging integrin-targeted therapy

Whilding et al.[157] developed $\alpha v\beta 3$-specific CAR-T cells and assessed their antitumor function in preclinical models both *in vitro* and *in vivo*. $\alpha v\beta 3$-CAR-T cells rapidly and specifically destroyed $\alpha v\beta 3$-positive tumor cells, secreted IFN-γ and IL-2 ($CD4^+ > CD8^+$), and underwent productive proliferation *in vitro*. In a murine xenograft model for metastatic A-375 melanoma, the molecule triggered complete elimination of melanoma lesions, resulting in long-term tumor-free survival.

Integrins have also been employed to generate specific, controllable, and improved cytotoxicity of CAR-T therapy in a novel approach that was developed by our team with novel switchable dual-receptor CAR-engineered T (sdCAR-T) cells as well as a new switch FITC-HM-3 molecule, as described earlier (above, bifunctional molecule, FHBM). Furthermore, to improve the specificity of CAR-T cells, human mesothelin-expressing sdCAR-T cells against cognate tumor cells and integrin $\alpha v\beta 3$ were also generated. The results of the study revealed that in the presence of FHBM, these designed sdCAR-T cells were highly active, which include activation and proliferation and exhibited specific cytotoxicity following a time- and dose-dependent manner *in vitro*. In nude mice treated with a combination of FHBM, sdCAR-T cells disrupted the growth of MSLN K562 cells and exhibited downregulation of cytokines, including interleukin-2, interleukin-6, interferon γ, and TNF-α relative to conventional CAR-T cells[158]. These findings imply that targeting integrins can effectively control the timing and dose of injected CAR-T cells. Furthermore, sdCAR-T cells exert significant antitumor activity as these releasing lower amounts of cytokines for MSLN- and integrin $\alpha v\beta 3$-expressing cognate tumor cells.

5. Conclusions

In the past few years, pre-clinical assays have revealed that integrin targeted therapy, including mAbs and synthetic molecules, imparts strong antitumor effects. However, clinical assays have failed to translate this effect on tumor progression inhibition. The disappointing results in relation to patient survival time, disease stabilization, and occurrence of metastasis may be due to the complexity of integrin mechanisms, the development of resistance to anoikis, and their ability to compensate each other and induce a poor phenotype. Using a more complex mechanism, a vessel co-option was reported as a pathway that allows tumor cells to receive nutrients from blood *via* pre-existing vasculature without developing new vessels as a resistance response against anti-angiogenic therapy.

In addition, studies have also shown that improper doses of integrin inhibitors may break the balance and produce the opposite effect. For example, Xu et al.[147] found that RGD modified peptide HM-3 has significant anti-tumor activity at the effective dose, while HM-3 promotes tumor growth and metastasis when exceeded the effective dose. Therefore, to improve the efficacy of integrin targeted therapy, the mechanism of integrins should be comprehensively investigated. Furthermore, exploring the appropriate drug dosage is important to rationally design clinical dosing regimens. Recently, the endocytosis of integrins and their transfer through exosomes were described as key factors in integrin-therapy failure by influencing integrin recycling. Integrin inhibition in the tumor microenvironment remains challenging because in complex organisms, factors systemically interfere with each other, making drug development even more difficult.

Together, integrin inhibition may be potentially utilized as a target for drug development when combined with other targeted therapies (tyrosine kinase inhibitors, anti-growth factors antibodies, or CAR-T therapy) for anticancer treatment, but it needs to be extensively assessed in the pre-clinical phase, possibly considering all of the plausible escape mechanisms by which tumor cells can develop.

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Author contributions

Meng Li and Hanmei Xu were responsible for the conception and design of the review. Meng Li, Sarra Setrerrahmane and Mengwei Li analyzed the reports, summarized the results, and wrote the manuscript. Ying Wang and Xuezhen Wu revised the manuscript. All of the authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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