

## Roles of integrin in tumor development and the target inhibitors

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**[ABSTRACT]** Integrin is a large family of cell adhesion molecules (CAMs) which involves in the interaction of cells/cells and cells/extracellular matrix (ECM) to mediate cell proliferation, differentiation, adhesion, migration, etc. In recent years, aberrant expression of integrin has been clearly found in many tumor studies, indicating that integrin is closely related to tumor formation and development. Meanwhile, it has effects on tumor cell differentiation, cell migration, proliferation and tumor neovascularization. The study of drugs targeting integrins is of great significance for the clinical treatment of tumors. Because of its important role in tumorigenesis and development, integrin has become a promising target for the treatment of cancer. This review summarizes the role of integrin in tumor development and the current state of integrin inhibitors to provide a valuable reference for subsequent research.

**[KEY WORDS]** Integrin; Tumor development; Target therapy; Natural medicines

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### Introduction

Integrin is a class of cell adhesion molecules receptor that is widely present on the cell surface. Transmembrane heterodimers are formed by two subunits,  $\alpha$  and  $\beta$ . Up to now, about 18  $\alpha$  subunits and 8  $\beta$  subunits have been found. The combination constitutes 24 kinds of integrins<sup>[1]</sup> (Fig. 1). Integrin recognizes and combines with extracellular matrix components, soluble ligands such as fibrinogen, and integrin-binding sites on cell surface such as arginine-glycine-aspartic acid (RGD) sequence and other non-RGD sequences<sup>[2]</sup> (Table 1). Each integrin receptor specifically binds to one or more ligands. Their specific ligand binding ability allows cells to connect to ECM for cell movement and invasion. Integrin has physical connections to the interior and exterior of the cell, which allows for bidirectional sensing of the signal. Through this mechanism, integrin ultimately controls cytoskeletal organi-

zation, which directly affects basic cellular functions such as cell adhesion, migration, proliferation, survival and differentiation<sup>[3]</sup>. The local expression pattern of integrins and their ligands controls the response of cells to their microenvironment, as each individual integrin heterodimer is capable of binding multiple ligands and the ligand can bind multiple integrins polymer. In addition to controlling a range of physiological functions, integrins can also detect ECM-induced extracellular changes in pathological events such as fibrosis, cancer and wound healing, leading to cellular responses that affect ECM remodeling. In addition to binding to ECM components, integrins are also involved in cell-cell adhesion because they bind to counter-receptors on adjacent cells; and immunoglobulin-type receptors expressed on leukocytes and endothelial cells, such as intracellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM)<sup>[4]</sup>. Integrin conducts bidirectional signal transduction between cells and cells, cells and extracellular matrix, mainly through focal adhesion kinase (FAK), integrin-linked protein kinase and phosphatidylinositol 3-phosphokinase (PI3K) signal transduction pathway to regulate the biological behavior of the cells<sup>[5]</sup>. With the increasingly clear structure and mechanism of action of integrin, targeting integrin has become a new direction for tumor therapy<sup>[6]</sup>.

### Biological Roles of Integrin In Tumor Development

#### *Facilitation of integrins on proliferation*

Integrin plays an important role in regulating the prolif-

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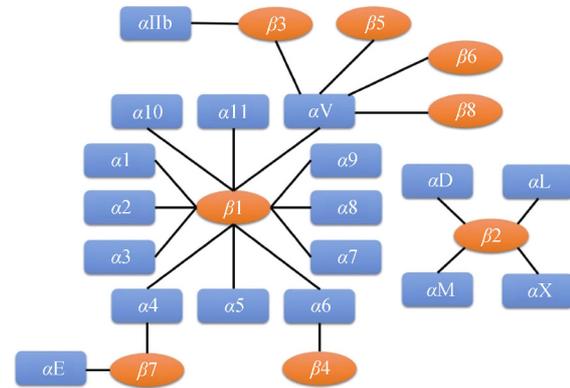
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eration of tumor cells. Studies have shown that the expression of integrin  $\beta 1$  could promote tumor growth<sup>[4]</sup>. Integrin  $\beta 1$  on the cell surface promotes cancer cell survival by activating different cellular signaling proteins such as phosphoinositide 3-kinase (PI3K)/RAC- $\alpha$  serine/threonine protein kinase (AKT). Integrin  $\beta 1$  can also promote cell proliferation by phosphorylating FAK and regulate cell proliferation<sup>[7]</sup>. The Aurora B and Survivin genes are important factors in the integrin signaling pathway. It has been found that the effective binding of integrin  $\beta 1$  to fibronectin (FN) stimulates the transcription of Aurora B and Survivin genes, further translating effector proteins and promoting cell proliferation and division<sup>[3,5]</sup>. Integrin  $\alpha v\beta 6$  is a special integrin subtype that is expressed only in embryogenesis, tissue repair and epithelial malignancy, and is not expressed in normal epithelial or benign tumors<sup>[8]</sup>. Studies have shown that integrin  $\alpha v\beta 6$  is closely related to the malignant biological behavior of tumors and participates in the regulation of many links. It is found that the induction of integrin  $\alpha v\beta 6$  expression in colon cancer cells can promote the secretion of MMP-9 by tumor cells and degrade the extracellular matrix, thus creating a favorable external environment for the proliferation of tumor cells.

The secretion of MMP-9 was positively correlated with the expression of integrin  $\beta 6$ . On the basis of this, integrin  $\alpha v\beta 6$  can promote the metastasis and colonization of colon cancer cells to the liver. In addition, in the colon cancer HT-29 cell line, aberrant expression of integrin  $\alpha v\beta 6$  leads to inhibition of the mitochondrial apoptotic pathway and promotes malignant proliferation of colon cancer cells<sup>[8-9]</sup>.



**Fig. 1** Combinations of 24 different receptors of integrin subunits

**Table 1** List of ligands and recognition sequences of integrin receptors

Integrin ligands	Integrin types	Recognition sequences
Vitronectin, Fibronectin, Osteopontin, Fibrinogen	$\alpha v\beta 1, \alpha v\beta 3, \alpha v\beta 5, \alpha v\beta 6$ $\alpha v\beta 8, \alpha 5\beta 1, \alpha 8\beta 1, \alpha 11b\beta 3$	RGD
Fibronectin, Vascular cell adhesion molecule1, Mucosal adhesion cell adhesion molecule1, Intercellular cell adhesion molecule1	$\alpha 4\beta 1, \alpha 4\beta 7, \alpha 9\beta 1, \alpha E\beta 7$ $\alpha 1\beta 2, \alpha M\beta 2, \alpha X\beta 2, \alpha D\beta 2$	LDV
Collagen, Laminin	$\alpha 1\beta 1, \alpha 2\beta 1, \alpha 10\beta 1, \alpha 11\beta 1$	GFOGER
Laminin	$\alpha 3\beta 1, \alpha 6\beta 1, \alpha 7\beta 1, \alpha 6\beta 4$	other

*Activation of invasion and migration in tumor*

The classic process of tumor invasion and metastasis is that the tumor cells break through the ECM barrier and detach from the primary lesion into the blood vessels or lymphatic vessels. It runs to a distant place to bind to the basement membrane of the endothelial cells, and the extravasation of the vessel invades the surrounding tissues to form a foci. From this point of view, the adhesion relationship between tumor cells and ECM is the key link. In the early stage of tumorigenesis, decreased expression of integrin can weaken the adhesion of tumor cells and ECM barrier. The process is conducive to the local growth and spread of tumor. Then, tumor cells enter the blood circulation. After that, the increased expression of integrin is beneficial to the adhesion of tumor cells to the vascular endothelium, localization and proliferation<sup>[3]</sup>. There are two major types of matrix degrading enzymes involved in tumor invasion and metastasis: proteases and glycosidases<sup>[10]</sup>. The former mainly reduces protein components in ECM, such as matrix metalloproteinase (MMP) and urokinase plasminogen activator (uPA). The latter mainly degrades the glycoprotein and the polysaccharide chain in the proteoglycan<sup>[11]</sup>. In some neurological tumors, integrin  $\alpha v\beta 3$  is a component of the MMP-activated complex. Without in-

tegrin  $\alpha v\beta 3$ , MMP-2 does not function. Controlling the binding of MMP-2 to integrin  $\alpha v\beta 3$  can sufficiently inhibit the growth of melanoma and glioma and the formation of tumor blood vessels. *In vitro* experiments, it has showed that the expression of integrin  $\alpha v\beta 3$  by transgene induction can increase the secretion of MMP-9 in colon cancer cells<sup>[12]</sup>. In addition, it can accelerate the destruction of extracellular matrix and promote liver metastasis of colon cancer. There may be a physiological direct link between the intracellular domain of the integrin  $\beta 6$  chain and the extracellular signal-regulated protein kinase<sup>[13]</sup>. The enzymes involved in destroying ECM have different degrees of specificity. MMP is the main direct antagonist, which plays a key role in tumor invasion and metastasis by degrading different components in ECM. Integrin can regulate the expression and activity of MMP in tumor cells and thus affect the invasion and metastasis ability of tumors<sup>[10]</sup>.

*Promotional effect of evading apoptosis*

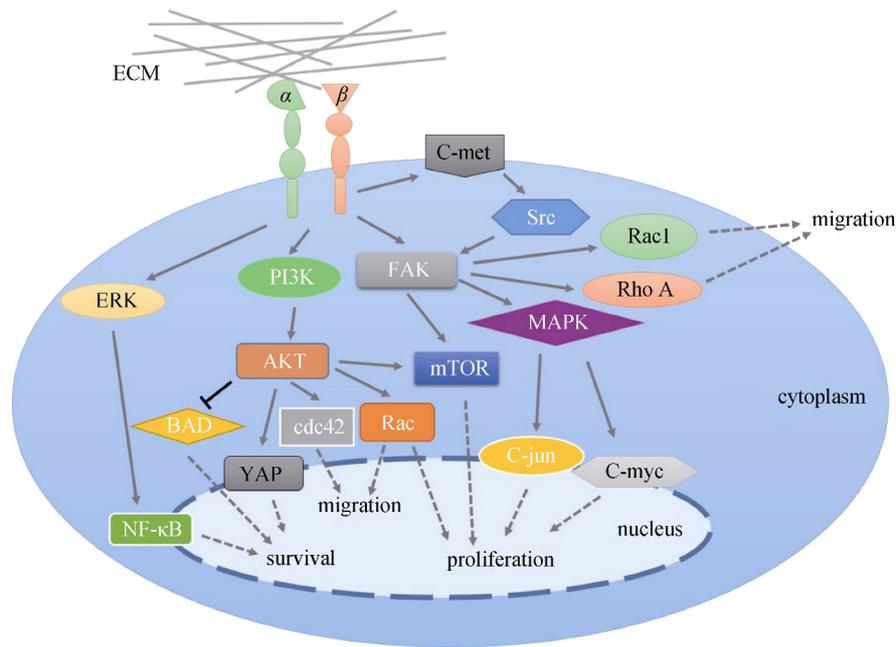
Apoptosis is a very complex process that is regulated and restricted by a variety of factors. The living microenvironment of tumor cells is multifarious which is surrounded by ECM (such as FN). Cells adhere to ECM through adhesion molecules on the surface, and cells with loss of adhesion are

more likely to head for apoptosis. Integrin  $\alpha v\beta 3$  inhibits endothelial cell apoptosis [3]. Studies have shown that integrin  $\alpha v\beta 3$  could inhibit endothelial cell apoptosis by activating FAK-PI3K/Akt-mTOR and ERK signaling pathways. It is reported that the apoptosis of ovarian cancer cells is closely related to integrin  $\alpha v$  and the interaction of integrin  $\alpha v$  with its ligand fibronectin can promote cell survival [14]. When both are blocked, it also blocks the transmission of survival signals from extracellular. This process may inhibit cell proliferation and cause apoptosis by arresting cells in the  $G_1/G_0$  phase. For example, clinically, by blocking the interaction between integrin  $\alpha v$  and its ligand fibronectin, it can promote the apoptosis of ovarian cancer cells, which is expected to improve the therapeutic effect of ovarian cancer and provide a new therapeutic approach for the clinical treatment of ovarian cancer. The signal molecules in the integrin signal transduction pathway are numerous and complex. Studies have shown that integrin binding to ECM leads to the continuous activation of intracellular proto-oncogenes and inhibition of apoptosis. Integrins may activate or inhibit the activity of a series of downstream molecules by mediating adhesion of cells to integrin ligands (such as FN), activation of mitogen-like kinase (MAPK) and protein kinase/threonine kinase (PKA/AKT) to inhibit apoptosis and cell immortalization [15-16].

**Promotion of tumor angiogenesis**

Tumor blood vessels provide nutrients for tumor growth

and pathways for tumor cell metastasis. In the angiogenesis stage, depending on the pre-existing vascular expansion, it means that under the action of angiogenic factors, endothelial cells proliferate and migrate to form vascular cords and branch to form a vascular network. During this process, endothelial cells must adhere to each other and the extracellular matrix to form and expand the neovascular. Integrin is a major factor mediating cell-to-extracellular matrix and intercellular adhesion. It plays an indispensable role in tumor angiogenesis [17]. Integrin expressed in the cavity and luminal surface of vascular endothelial cells mediates endothelial cell migration and capillary lumen formation [18-19]. The expression of integrin  $\alpha v\beta 3$  is enhanced in the angiogenesis of lung cancer, colon cancer, pancreatic cancer and breast cancer, indicating that integrin is involved in tumor angiogenesis and metastasis. Antagonists of integrin  $\alpha v\beta 3$  further confirm the important role of integrin in tumor angiogenesis [20]. Various integrin  $\beta 1$  subfamilies are expressed in vascular endothelial cells [21]. Tumor cells bind to integrin on the surface of endothelial cells through the secretion of dysregulin, inhibiting the activation of P53 through MAPK signal transduction system. Or through the influence of the PKC transduction pathway affects signal transduction of the VEGF pathway to promote endothelial cell VEGF expression and angiogenesis. It has been reported that integrin could regulate and promote angiogenesis through the regulation of EGFR and promotion of EphA2 [22].



**Fig. 2 Schematic representation of integrin-related signaling pathways**

**Clinical trials targeting integrins in cancer**

After years of research, integrin-mediated targeted drug therapy has made great progress. Different integrin antagonists can inhibit the tumor cell adhesion, invasion, metastasis to induce tumor and tumor vascular endothelial cells apop-

osis, inhibit tumor angiogenesis and achieve the purpose of treating tumor [23]. The advantage of targeted therapy is that it has high specificity for tumor tissue selection and relatively small side effects. The study has achieved remarkable results in the treatment of tumors by regulating the activity of integrin; synergistic effects with other therapeutic methods

(such as radiotherapy) and chemotherapy drugs have also achieved certain results in cancer treatment<sup>[5]</sup>. There are currently four types of integrin targeted therapeutics: integrin monoclonal antibodies, integrin inhibitors, integrin gene targeting regulation and other treatments mediated by integrins. Integrin antagonists, which are currently studied more frequently in the clinical research, are summarized below.

#### Cilengitide

Due to the specific anti-tumor effect of integrin receptors, Merck in Germany began developing drugs for this receptor in the mid-1980s. After years of research, it has finally found cilengitide which has good performance, specificity and toxicity<sup>[24]</sup>. The structure of cilengitide contains a cyclic RGD structure which binds to integrin  $\alpha v \beta 3$  and  $\alpha v \beta 5$ <sup>[25]</sup>. Cilengitide belongs to a novel anti-angiogenic drug targeting the integrin of vascular endothelial cells. In the preclinical research, cilengitide could target RGD-binding integrins on endothelial cells to inhibit tumor angiogenesis through suppression of the FAK/Src/AKT signaling pathway<sup>[25]</sup>. Cilengitide induces apoptosis in U87 glioma cells by preventing adhesion to vitronectin and tenascin of brain tumor invasion and growth. Because cilengitide inhibits survival pathways, it may enhance antitumor activity in combination with conventional cytotoxic or pro-apoptotic therapies, including radiation. Hence, cilengitide targeting of integrin  $\alpha v \beta 3$  combines with radio-therapy to increase apoptosis in breast cancer and NSCLC xenograft models<sup>[24]</sup>. Clinical studies have shown dual effects of anti-angiogenesis and production inhibition on malignant glioma, brain and central nervous system cancer. Studies have confirmed that cilengitide has good tolerance and good anti-tumor activity when used alone in the treatment of complex glioblastoma<sup>[26]</sup>. Cilengitide can be combined with gemcitabine to treat unresectable advanced pancreatic cancer<sup>[27]</sup>. So far, although cilengitide is the first anticancer drug to enter the phase 3 clinical trial targeting integrin receptors, there are still many problems to be solved. Cilengitide is the most promising integrin inhibitor in clinical research. In patients with glioblastoma multiforme (GBM), cilengitide showed no significant toxicity as a single agent and combined with radiotherapy and temozolomide<sup>[28]</sup>. However, in the standard treatment of GBM, cilengitide failed to achieve good results in phase 3 clinical trials, and further clinical development seems to be very difficult<sup>[29]</sup>.

#### GLPG0187

GLPG0187 is a broad spectrum integrin receptor antagonist (IRA) which belongs to a non-peptide RGD integrin receptor antagonist capable of targeting integrin  $\alpha v \beta 3$ <sup>[30]</sup>. In preclinical models, GLPG0187 significantly inhibits angiogenesis, osteoclastogenesis and bone loss *in vivo* and *in vitro*<sup>[31]</sup>. Studies have shown that GLPG0187 dose-dependently reduces cell adhesion and cell migration in PC3 and PCa cells with tumor and metastatic potential. In a mouse cancer model, GLPG0187 inhibits the progression of bone and visceral metastases in prostate and breast cancer<sup>[32]</sup>. It is reported that

GLPG0187 could decrease the adhesion and migration of human prostate cancer cells by downregulating the expression of E-cadherin suppressors Snail1, Snail2 and Twist<sup>[31]</sup>. Compared to cilengitide, GLPG0187 is a more potent and broader spectrum of IRA that enhances the anti-tumor efficacy of IRA treatment. Therefore, a clinical Phase I study was initiated to investigate the safety and tolerability of GLPG0187 when administered intravenously in patients with end-stage cancer<sup>[33]</sup>.

#### MK-0429

MK-0429 is a potent orally active molecule that is a non-peptide small molecule inhibitor of integrin  $\alpha v \beta 3$ <sup>[34]</sup>. It has shown that MK-0429 could inhibit osteoclast formation and osteoclast bone resorption in preclinical and clinical studies<sup>[35]</sup>. MK-0429 was tested in a clinical study of men with hormone-refractory prostate cancer and bone metastases. The results showed that twice-daily administration of MK-0429 for 4 weeks significantly reduced the level of urine N-terminus of male type 1 collagen (uNTx)<sup>[34, 36]</sup>. The level of peptide means a reduction in bone turnover. The patient has good tolerance to MK-0429 and the evidence of decreased osteoclast activity indicates the possibility of clinical use for the treatment of prostate cancer. Moreover, studies have shown that MK-0429 is safe and effective in significantly reducing lung melanoma metastasis and highlighting the potential of MK-0429 as a novel therapeutic agent for the prevention of metastatic melanoma<sup>[37]</sup>.

#### CNTO 95

CNTO 95 is a human-derived monoclonal antibody of the integrin  $\alpha V$  subunit<sup>[38]</sup>. The study has showed that CNTO 95 acted on melanoma cells expressing integrin  $\alpha v \beta 3$  and  $\alpha v \beta 5$  to prevent cell adhesion, metastasis, invasion and angiogenesis<sup>[39]</sup>. Previous studies have shown that CNTO 95 inhibits integrin-mediated tumor growth and angiogenesis *in vitro* and *in vivo* on different animal models and in several different types of human tumors, including melanoma, breast, and small cell lung cancers<sup>[38]</sup>. It is reported that CNTO 95 inhibited breast tumor cell invasion and motility and also resulted in the tyrosine dephosphorylation of FAK and paxillin. *In vivo*, CNTO 95 could inhibit tumor growth and reduced metastasis of MDA-MB-231 cells to the lung. These results demonstrate the anti-metastatic properties of CNTO 95. CNTO 95 has shown anti-angiogenic and anti-tumor activities in preclinical models. In addition, a recent phase I clinical trial demonstrated that CNTO 95 was well tolerated and had clinical anti-tumor activity<sup>[39]</sup>. It has been reported that CNTO95 could inhibit the formation of melanocyte xenografts in 80% of mice and 99% of rats. At present, CNTO95 can be tolerated in all patients with malignant solid tumors in phase 1 clinical treatment<sup>[40]</sup>.

#### Volociximab

Volociximab is a first-in-class chimeric monoclonal antibody that targets integrin  $\alpha 5 \beta 1$ <sup>[41]</sup>. Preclinical studies have shown the ability of volociximab to inhibit tumor neoangiogenesis and migration. The phase 1 clinical trial of volociximab

combined with carboplatin and paclitaxel showed significant therapeutic effects on non-small-cell lung cancer (NSCLC), and the three drugs were generally well tolerated [42]. The phase 2 clinical trial of volociximab in combination with gemcitabine for the treatment of pancreatic cancer showed a significant increase in the median time to worsen the subject's condition. In another phase 2 clinical trial of metastatic renal cell carcinoma, the median time to progression of the subject was extended to 4 months, and 35% of subjects were 5.8 to 22 months. Volociximab has been well tolerated in combination with chemotherapy [43-44]. The efficacy data of volociximab has come from non-randomized clinical trials. These results are preliminary and require random studies to validate the efficacy of volociximab. Future research should address several issues beyond efficacy, such as how to combine volociximab therapy with other chemotherapy and biologics, and the role of volociximab in maintenance therapy. And inhibition of integrin  $\alpha 5\beta 1$  in tumor cells by volociximab has any significant anti-tumor effect so that overcoming the resistance to cytotoxic chemotherapy [44]. It has shown promising activity in different types of cancer.

**Etaracizumab**

Etaracizumab is an IgG1 humanized monoclonal antibody that is an antibody to the conformational epitope of integrin  $\alpha v\beta 3$  and is present on the surface of certain types of invasive tumor cells, angiogenic endothelial cells and mature cells [45]. Integrin  $\alpha v\beta 3$  is highly expressed in certain malignancies, such as melanoma, advanced glioma and renal cell carcinoma, and a limited number of cell types, such as endothelial cells [46-47]. Studies have shown that etaracizumab can induce anti-tumor activity *in vitro* and *in vivo*, including inhi-

bition of angiogenesis, direct inhibition of melanoma tumor growth and cell-mediated cytotoxicity of melanoma cells independent of anti-angiogenic activity [48]. Besides, it is reported that integrin  $\alpha v\beta 3$  in ovarian cancer prompted proliferation and invasion and etaracizumab can inhibit tumor growth in an orthotopic mouse model of advanced ovarian cancer. Response to therapy is variable and is enhanced by dependence of the cancer cells on the Akt pathway [47]. The phase 2 clinical trial of etaracizumab, which is currently undergoing etaracizumab treatment of highly metastatic melanoma, can also directly act on tumor cells and inhibit bone damage by inhibiting the adhesion of osteoclasts to achieve an effective reduction of bone metastasis [48].

**ATN-161**

ATN-161 is a pentapeptide containing no RGD sequence derived from the fibronectin synergistic region. It targets for integrin  $\alpha 5\beta 1$  and now is in phase 2 clinical stage [49]. *In vitro* tests, it has been reported that ATN-161 could inhibit breast cancer growth and metastasis [50]. It is reported that the inhibition of integrin and MAPK by ATN-161 in MDA-MB-231 tumor cells *in vitro* was insufficient by itself to affect the proliferation or migration of these cells. Moreover, ATN-161 has significant effects on the proliferation of MDA-MB-231 tumors *in vivo* [49]. ATN-161 has shown to inhibit tumor growth and metastasis and extend survival in multiple animal tumor models. In the mouse model of liver metastasis from colon cancer, it was found that the combination of ATN-161 with 5-Fu significantly reduced tumor burden and liver metastasis compared with other monotherapy [51]. In the Phase 1 clinical trial, ATN-161 was excellent in anti-tumor effect, tolerance and safety [52]. Currently, ATN-161 is in Phase 2 clinical research.

**Table 2 Integrin antagonists under clinical investigation**

Drug Name	Company	Target	Disease	Trial Stage
Cilengitide [24]	EMD pharm. Merck KGaA	Integrin $\alpha v\beta 1/\alpha v\beta 5$	Renal cell carcinoma, colon cancer, glioma, melanoma, refractory advanced solid tumours, AML	Clinical Phase 3
GLPG0187 [30]	Galapagos SASU	Integrin $\alpha v\beta 1/\alpha v\beta 3/\alpha v\beta 5/\alpha v\beta 6/\alpha v\beta 8/\alpha 5\beta 1$	Advanced solid tumours	Clinical Phase 1
CNTO 95 [38]	Centocor	Integrin $\alpha V$	Refractory advanced solid tumours	Clinical Phase 2
Volociximab [41]	Protein design labs	Integrin $\alpha 5\beta 1$	Renal cell carcinoma, melanoma, NSCLC, pancreatic cancer	Clinical Phase 2
Etaracizumab [45]	Medimmune Inc.	Integrin $\alpha v\beta 3$	Melanoma, prostate/colon/ thyroid cancer	Clinical Phase 2
ATN-161 [49]	Attenuon, LLC	Integrin $\alpha 5\beta 1$	Advanced solid tumours	Clinical Phase 2

**Application of natural products in inhibiting integrin**

Numerous studies have suggested that natural product drugs play an important role in cancer treatment. Some natural drug extracts have exerted good drug activity in inhibiting integrin activity, inhibiting tumor adhesion, invasion and metastasis, and promoting tumor cell apoptosis. Moreover, natural products have good advantages in cytotoxicity. Natural products have great potential in the treatment of cancers that target integrin.

**Gleditsia sinensis**

The *Gleditsia sinensis* (GS) is the fruit of the bean agaric, which is tasteful, warm and slightly toxic. It is a traditional Chinese herbal medicine. It is one of the commonly used drugs for treating various cancers such as lung cancer and breast cancer [53]. It is listed as an anti-cancer Chinese herbal medicine. Studies have shown that GS has anti-tumor activity against a variety of cancers, such as gastric cancer, lung cancer, colon cancer and prostate cancer (PCa) [54]. GS can affect the expression of integrin  $\alpha 2\beta 1$  and have a regulatory effect on migration and adhesion of PCa cells. Recent studies have

shown that GS inhibits collagen-mediated migration and adhesion of PC3 cells by inhibiting the expression of integrin  $\alpha 2\beta 1$  [23]. Inhibition of integrin  $\alpha 2\beta 1$  leads to a decrease in FAK activity. In the integrin/FAK pathway, FAK phosphorylation activates Src family kinases and other related signaling pathways, thereby regulating cell migration and invasion. In the xenograft tumor model, the tumor suppressive effect was significantly increased after administration of GS to mice as compared with the control group. Studies have found that GS can significantly inhibit collagen that is able to induce migration and adhesion of PC3 and PCa cells by activating integrin  $\alpha 2\beta 1$  [54].

#### D-Pinitol

D-pinitol is a plant-derived chemical that is an active ingredient in soy foods and beans. Mature and dry soybean seeds contain about 1% D-pinitol and D-pinitol is capable of acting as permeates in plants by improving tolerance to drought or heat stress [55]. D-pinitol has a variety of physiological activities, such as insulin sensitization, hypoglycemia, anti-tumor, immune regulation, anti-inflammatory and anti-edema. D-pinitol can be applied to medicines, health care raw materials and dietary supplements. The study has found that D-pinitol has anti-lung, bladder and breast cancer effects. D-pinitol is capable of inhibiting cell migration and invasion of PC3 and DU145 PCa cell lines which are androgen-independent [56]. Moreover, studies have shown that D-pinitol could reduce the expression of integrin  $\alpha v\beta 3$ , thereby inhibiting invasion and metastasis. D-pinitol can regulate the expression of integrin  $\alpha v\beta 3$  through two signaling pathways. First, D-pinitol inhibits the FAK/c-Src kinase phosphorylation pathway and exhibits a dose-dependent inhibition in cell movement and invasion. Second, D-pinitol reduces p65 phosphorylation in the NF- $\kappa$ B signaling pathway which in turn regulates cell invasion and metastasis [57]. In conclusion, the anti-invasion and metastatic ability of D-pinitol in PCa cells is exerted by regulating the expression level of integrin  $\alpha v\beta 3$  on the surface of tumor cells [56].

#### Tanshinone IIA

Tanshinone IIA is one of the active ingredients of traditional Chinese medicine for promoting blood circulation and removing phlegm. It has obvious anti-inflammatory and anti-oxidation effects. In recent years, its anti-tumor activity has also been reported [58]. The mechanism involves inducing apoptosis and differentiation, regulating cell cycle and affecting the expression of tumor-related genes and telomerase activity [59]. Tanshinone IIA can effectively inhibit the growth of human gastric cancer cells in a time and dose-dependent manner. Tanshinone IIA may inhibit the proliferation of tumor cells by reducing the expression of integrin $\beta 1$  and MMP-7 mRNA in human gastric cancer cells [60].

#### Amygdalin

Amygdalin is one of the active constituents of traditional Chinese medicine bitter almond. It belongs to the class of hydroglycosides and is widely found in the seeds of *Rosaceae*

plants [61]. It has been found that amygdalin has inhibitory activity against a variety of tumors. Amygdalin plays an anti-bladder cancer effect by blocking tumor cells in the S phase or G0/G1 phase and regulating the expression levels of integrin  $\beta 1/4$ . By regulating the activity of Akt, RICTOR and other related signaling pathways and the expression of integrin and cadherin E, amygdalin effectively inhibits the proliferation, migration and invasion of tumor cells *in vitro* [62]. Meanwhile, amygdalin achieves anti-cancer effects by down-regulating cell cycle-related factors. Amygdalin can significantly inhibit the proliferation of human lung cancer H1299 cells *in vitro* and downregulate the expression levels of MMP-2/9, integrin  $\beta 1/4$  protein. And the invasion and migration ability of tumor cells are significantly decreased [63]. Compared with traditional chemotherapy, amygdalin has a lower toxicity and lower incidence of drug resistance [64]. So, it has a wider application prospect in clinical practice.

#### Celestrol

Celestrol, also known as South snake vine, is derived from the root bark of the traditional Chinese medicine *Tripterygium wilfordii*. It is one of the active ingredients of the preparations such as *Tripterygium wilfordii* for the treatment of rheumatoid diseases. At the same time, celestrol has an anti-tumor effect which can effectively inhibit the proliferation and induce apoptosis of various tumor cells [65-67]. Studies have shown that celestrol could inhibit the expression of integrin  $\beta 1/CD29$  in HUVECs cells to inhibit cell adhesion and migration [68]. In the study of lung cancer, it has been found that celestrol could effectively inhibit the adhesion of 95D cells. Celestrol can reduce the expression of integrin  $\beta 3$ ,  $\beta 4$  and  $\alpha v$  to inhibit adhesion, migration and invasion of tumor cells [69]. In addition, it has been found that celestrol could inhibit the adhesion, migration and invasion of lung cancer cells by decreasing the phosphorylation of Akt, C-Raf, GSK-3 $\beta$  and PDK1. In H1299 cells, the integrin family plays an important role in the metastasis of lung cancer [70].

#### Curcumin

Curcumin is a phenolic pigment extracted from the rhizome of the herbaceous turmeric (*Curcuma longa*) which has wide pharmacological effects such as anti-inflammatory, anti-oxidation and anti-tumor [71]. Because of its wide anti-cancer spectrum and small side effects, the National Cancer Institute has listed curcumin as the third-generation cancer chemopreventive drug and it has entered the clinical trial stage [72]. Curcumin inhibits the growth of cell lines of various tumors such as glioma, breast cancer, lung cancer, leukemia, kidney cancer and rhabdomyosarcoma *in vitro* [73]. It is reported that integrin  $\beta 1$  is highly expressed in human B cell lymphoma cell line Raji cells and is lowly expressed in normal human lymph nodes and peripheral blood lymphocytes. Integrin  $\beta 1$  plays different roles in different types of lymphoma. Curcumin can significantly inhibit the expression of integrin  $\beta 1$  [74]. Curcumin shows promise to become a new drug for inhibiting the invasion and metastasis of lymphoma [75]. Furthermore,

curcumin was reported to suppress IL-1 $\beta$ -induced high expression of integrin  $\beta$ 1 in human chondrocytes. Meanwhile, study has showed that curcumin inhibited RCP (Rab coupling protein) induced recycling of integrin  $\beta$ 1, thereby suppressed activation of FAK and the EGFR/Slug signaling pathway and ovarian cancer cell invasion. The mechanism of reduced recycling of RCP-induced integrin  $\beta$ 1 by curcumin may be caused by downregulation of RCP, Rab11 and Rab25. Curcumin effectively reduced the expression of RCP-induced Rab11 and Rab25 [72].

#### Ginsenoside

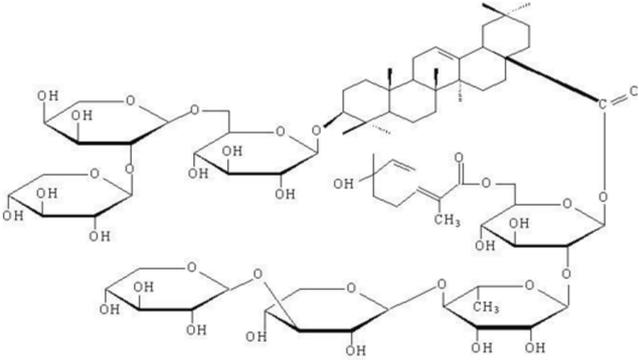
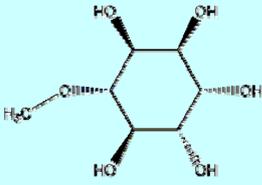
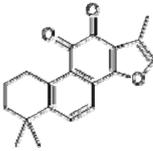
Ginsenoside 20(R)-Rg3 is a tetracyclic triterpenoid polyglycol diol saponin monomer isolated and purified from *Ginseng* [76]. It has been reported that it could induce apoptosis, inhibit the proliferation, invasion and metastasis of a variety of tumor cells. "Shenyi Capsule" which uses ginsenoside 20 (R)-Rg3 as the main component has been successfully launched and is widely used in clinical practice [77]. Pharmacokinetic studies have found that oral bioavailability of ginsenoside Rg3 is very low. Therefore, many scholars have modified or optimized them to enhance their water solubility, prolong their residence time and improve bioavailability. HRG is a new monomeric compound obtained which is structurally modified by ginsenosides [78]. HRG as a new monomeric compound can inhibit the proliferation of liver cancer cells and cause S phase arrest of lung cancer cells [79]. Meanwhile, it can inhibit the migration and invasion of liver cancer cells and downregulate the expression of integrin  $\alpha$ v $\beta$ 3 [80].

It exerts an anti-hepatocarcinal effect by many pathways *in vitro*.

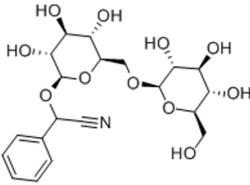
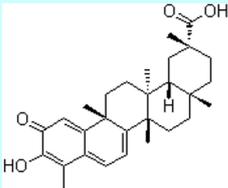
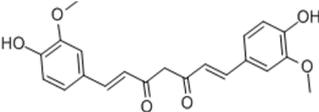
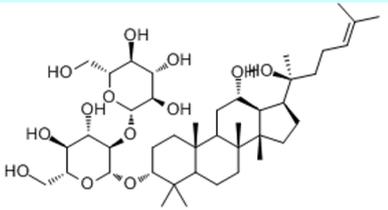
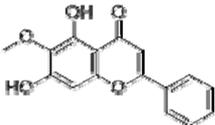
#### Oroxylin A

*Scutellariae radix* is a dry root of the genus *Astragalus* in the Labiatae family. It is a commonly used traditional Chinese medicine in the clinic [81]. Experimental studies have shown that in addition to the traditional biological activities of anti-inflammatory, anti-viral, liver-protecting and abortion, *Astragalus* has a strong anti-tumor effect [82]. The active ingredient of *Astragalus membranaceus* are flavonoids, which contain oroxylin A. In the study of tumors, oroxylin A has anti-proliferation, promotion of apoptosis, inhibition of invasion and metastasis and other biological activities [83]. It has been reported that oroxylin A can reverse the resistance of human HCC BEL7402 cell line to 5-Fu by inhibiting PI3K/AKT and NF- $\kappa$ B pathways, suggesting that oroxylin A may have the potential to reverse resistance [84]. In the study of cell adhesion mediated-drug resistance (CAM-DR) model, oroxylin A significantly increased paclitaxel-induced tumor cell apoptosis. Oroxylin A can not only inhibit the PI3K/AKT pathway, but also significantly inhibit the expression levels of integrin  $\beta$ 1. Adhesion of HepG2 cells to FN increased the expression of integrin  $\beta$ 1 and activated the PI3K/AKT pathway to exhibit resistance to the chemotherapeutic agent paclitaxel [85]. Oroxylin A can reverse CAM-DR and its mechanism is related to inhibition of the expression of integrin  $\beta$ 1 and its signal transduction pathway. Oroxylin A may be a promising CAM-DR reversal agent to tumor chemotherapy.

**Table 3** Natural medicines targeting integrin under investigation

Compounds	Chemical structure	Target	Disease
Gleditsia sinensis [53]		Integrin $\alpha$ 2 $\beta$ 1	Inhibiting adhesion and migration in prostate cancer
D-pinitol [55]		Integrin $\alpha$ v $\beta$ 3	Inhibiting metastasis, invasion and migration in prostate cancer
Tanshinone IIA [58]		Integrin $\beta$ 1	Inhibiting proliferation in gastric cancer

Continued

Compounds	Chemical Structure	Target	Disease
Amygdalin <sup>[61]</sup>		Integrin $\beta 1/4$	Inhibiting proliferation, invasion and migration in bladder cancer and human lung cancer
Celastrol <sup>[65]</sup>		Integrin $\alpha v\beta 3/\alpha v\beta 4$	Inhibiting adhesion, invasion and migration in human lung cancer
Curcumin <sup>[71]</sup>		Integrin $\beta 1$	Inhibiting invasion and migration in lymphoma
Ginsenoside <sup>[76]</sup>		Integrin $\alpha v\beta 3$	Inhibiting proliferation, invasion and migration in human hepatocellular carcinoma
Oroxylin A <sup>[85]</sup>		Integrin $\beta 1$	Reversing the resistance of human hepatocellular carcinoma BEL7402/5-Fu and HepG2/paclitaxel

## Conclusions

As a bridge between cells and cells as well as cells and extracellular matrix, integrin plays an important role in tumor cell transformation, growth, invasion, migration, apoptosis and tumor angiogenesis<sup>[5]</sup>. Meaningfully, integrin can be used as a tumor treatment target to prevent tumor development. However, due to the wide varieties and complex functions of integrin, the exact mechanism of biological action on cells needs further research. There are many integrin inhibitors in clinical research. However, due to the short research time of such drugs, a large amount of basic research is needed to help reduce risks. For example, cilengitide, an integrin inhibitor developed by Merck, is in phase 3 clinical trials to treat deteriorative and recurrent gliomas. Treatment aims at patients with methylated 6-methylguanine-DNA methyltransferase (MGMT). However, it has been found that patients with methylated MGMT are not sensitive to cilengitide. The reason may be that deteriorative and recurrent gliomas are very difficult to treat. Merck's risk of choosing this disease for Phase 3 clinical is also very large. Merck is currently conducting Phase 2 clinical trials of cilengitide in other cancer patients: cilengitide alone for early diagnosis of glioma patients, who

are unmethylated MGMT; A phase 1/2 clinical trial of cilengitide in the treatment of non-small cell lung cancer. The Phase 3 clinical research of cilengitide has failed<sup>[3]</sup>. This result is disappointing, but it does not mean that integrin inhibitors have no future. On the contrary, there is a certain positive significance. Because some scientists have also begun studying and exploiting natural products of traditional Chinese medicine. At present, some natural products targeting integrins have exhibited satisfactory preclinical research potential. Future natural products are promising as clinical integrin targeted inhibitors or adjuvant therapeutic drugs. In addition, different treatment methods and drugs have their own advantages and disadvantages. In future, research should be paid attention to the selection of suitable objects, clinical application methods and combined treatment (such as traditional treatments combined with integrin-targeted drugs) for tumors. Synergies and mechanisms of different integrin-target drugs will provide a theoretical basis for the further development of new anti-tumor drugs and well-designed tumor treatment programs.

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published by correspondence author or first author. The cumulative impact factor is 100, the maximum number of citations per article is 156 and the total number of citations is more than 500.