

The Roles of Integrin $\alpha 5 \beta 1$ in Human Cancer

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Abstract: Cell adhesion to the extracellular matrix has important roles in tissue integrity and human health. Integrins are heterodimeric cell surface receptors that are composed by two non-covalently linked alpha and beta subunits that mainly participate in the interaction of cell-cell adhesion and cell-extracellular matrix and regulate cell motility, adhesion, differentiation, migration, proliferation, etc. In mammals, there have been eighteen α subunits and 8 β subunits and so far 24 distinct types of $\alpha\beta$ integrin heterodimers have been identified in humans. Integrin $\alpha 5 \beta 1$, also known as the fibronectin receptor, is a heterodimer with $\alpha 5$ and $\beta 1$ subunits and has emerged as an essential mediator in many human carcinomas. Integrin $\alpha 5 \beta 1$ alteration is closely linked to the progression of several types of human cancers, including cell proliferation, angiogenesis, tumor metastasis, and cancerogenesis. In this review, we will introduce the functions of integrin $\alpha 5 \beta 1$ in cancer progression and also explore its regulatory mechanisms. Additionally, the potential clinical applications as a target for cancer imaging and therapy are discussed. Collectively, the information reviewed here may increase the understanding of integrin $\alpha 5 \beta 1$ as a potential therapeutic target for cancer.

Keywords: integrin $\alpha 5 \beta 1$, prognostic indicator, tumorigenesis, molecular target

Introduction

Integrins, the family of heterodimeric cell surface receptors that are expressed in most cells including pericytes, endothelial cells, fibroblasts, and tumor cells, which have emerged as important regulators for providing both mechanical engagement of cell to extracellular matrix, and generation of signals that are implicated in various diseases such as autoimmune diseases, deleterious embryonic development, cardiovascular diseases and cancer malignancies.^{1,2} In mammals, eighteen α subunits and 8 β subunits form at least 24 distinct types of $\alpha\beta$ integrin heterodimers, which play as true receptors of tissue and organ-specific ligands.³ Both α and β subunits possess a large extracellular domain, a small cytoplasmic tail, and a transmembrane domain.⁴ The extracellular domains act as the cells sense and respond to the microenvironment cues such as adhesion proteins and growth factors.³ The cytoplasmic tail is linked to the actin cytoskeleton and intracellular signaling pathways such as Src family kinase, focal adhesion kinase (FAK), and mitogen-activated protein kinase (MAPK), as well as protein kinase B (AKT).⁵ Notably, integrins have been received attention as important regulators in mediating the hallmarks that characterize human cancers, including cell proliferation, metastasis, immune evasion, tumor angiogenesis, and resistance to chemotherapy and radiotherapy.

Integrin $\alpha 5 \beta 1$ was firstly reported in the 1992s and was the only known $\alpha 5$ integrin.⁶ Upon binding to the ligand, the cytoplasmic tails of integrin $\alpha 5 \beta 1$ bind to cytoskeleton and then drive reorganization of the cytoskeleton through the

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intracellular signaling pathway, that is, the “outside-in” signaling pathway.^{7,8} Integrin $\alpha 5\beta 1$ -mediated intracellular signals can in turn activate extracellular regions and assist ECM assembly, that is, the “inside-out” signaling pathway.^{9,10} This two-way signaling pathway contributes to various biological activities, such as cell adhesion, migration, and survival.¹¹ And these behaviors can be mediated by arginine-glycine-aspartate (RGD) peptides, specific antibodies, as well as the surface glycosylation.¹² Integrin $\alpha 5\beta 1$ has been defined as a proangiogenic factor involve in regulating tumor angiogenesis by interacting with the Vascular Endothelial Growth Factor Receptor (VEGFR) and angiopoietin-Tie systems.¹³ Moreover, the important roles in tumorigenesis, tumor metastasis, and resistance to chemotherapy and radiotherapy have been highlighted for integrin $\alpha 5\beta 1$.¹⁴ In this review, we focus on the recent findings and important progress to summarize the roles and related mechanisms of integrin $\alpha 5\beta 1$, and discuss the potential strategies targeting integrin $\alpha 5\beta 1$ for improving cancer patient’s outcomes.

Structure, Regulation, Ligands and Functions of Integrin $\alpha 5\beta 1$

Structural Domains of Integrin $\alpha 5\beta 1$

Integrin $\alpha 5\beta 1$, as a member of the integrin family, is a heterodimer composed by two subunits, $\alpha 5$ and $\beta 1$, and both are necessary for complete biological functions.¹⁵ The human integrin alpha 5 gene (*ITGA5*) encodes the $\alpha 5$ subunit and is localized at 12q11. The extracellular domain of $\alpha 5$ subunit has a thigh domain and a β -propeller domain, which is responsible for the recognition of the RGD motifs on the fibronectin and fibrinogen.¹⁶ The integrin beta 1 gene (*ITGB1*) has been proved to reside in chromosome 10p11.2, and the extracellular part of this subunit is made up of a plexin/semaphorin/integrin (PSI) domain, a hybrid domain, a $\beta 1$ domain (with a metal ion-dependent adhesion site [MIDAS] structure), and four EGF like domains.¹⁷ The interactions of integrin $\alpha 5\beta 1$ and its extracellular ligands are dependent on the MIDAS structure and divalent cations.¹⁸ A recent crystal structure of $\alpha 5\beta 1$ integrin has demonstrated that the specific residue (Asp154) could be used to distinguish $\alpha 5$ from other α subunits as its strong preference for fibronectin over other RGD ligands, and also indicated that Ca^{2+} is an important cation for ligand-binding of $\alpha 5\beta 1$ integrin.^{14,16}

Regulation of Integrin $\alpha 5\beta 1$ miRNA Pathways Contribute to Post-Transcriptional Regulation of Integrin $\alpha 5\beta 1$

miRNAs are a class of small endogenous noncoding RNAs and have emerged as important molecules that post-transcriptionally regulate gene expression.¹⁹ The expression of $\alpha 5\beta 1$ integrin is determined by the transcriptional activity of *ITGA5* and *ITGB1* genes. The 3'-untranslated region of the *ITGA5* and *ITGB1* mRNA possess several miRNA target sequences. Recently, some miRNAs were reported to regulate the expression of integrin $\alpha 5\beta 1$ under various pathological conditions. For example, both integrin $\alpha 5$ and $\beta 1$ were directly targeted by miR-17 in ovarian cancer cell lines, and forced expression of miR-17 significantly blocked adhesion and invasion of ovarian cancer cells by inhibiting the expression of integrin $\alpha 5$ and $\beta 1$.²⁰ In addition, miR-23a directly targeted the 3' UTR of High Mobility Group Nucleosomal Binding Domain 2 (*HMG2*) mRNA, which was involved in integrin $\alpha 5\beta 1$ activation. miR-155 might also regulate integrin $\alpha 5\beta 1$ function by control of the expression and chromatin location of the integrin transcription suppressor-Nuclear Factor-I (*NFI*).²¹ In breast cancer cells, miR-149 inhibited cancer cell metastasis by directly targeting GIT ArfGAP 1 (*GIT1*), which was responsible for the lysosome-mediated protein degradation of integrin $\alpha 5\beta 1$.²² Therefore, exploring the network of miRNAs and integrin $\alpha 5\beta 1$ is essential to design strategies for better chemo-therapeutics.

Importance of Post-Translational Modifications (PTMs) in Regulation of Integrin $\alpha 5\beta 1$

PTMs are made up of methylation, acetylation, phosphorylation, ubiquitination, neddylation, sulphation, sumoylation, prenylation, and glycosylation, which are the fundamental process for regulating the function of proteins, such as subcellular location, DNA-binding affinity, molecular half-life, and interactions with other proteins. N-Glycosylation of protein is considered to be as the most abundant PTM, and nearly 50% all known proteins are glycosylated in eukaryotes.²³ Integrins as the major glycan-carrying proteins, its complete biological functions rely on the N-Glycosylation modifications. Among the 24 human integrins, the functions of N-Glycosylation on integrin $\alpha 5\beta 1$ have been well characterized.^{23,24} Gu and colleagues have identified several individual N-glycan sites in both $\alpha 5$ and $\beta 1$ subunits, which are critical for heterodimerization and biological functions of integrin $\alpha 5\beta 1$.²⁵⁻²⁸ For example, the N-glycan of $\beta 1$ -N343 on the $\beta 1$ domain of $\beta 1$ subunit is linked to integrin $\alpha 5\beta 1$

activation. Loss of this glycan site led to the persistent activation of integrin $\alpha 5\beta 1$;²⁹ The N-glycan sites on the I-like domain of the $\beta 1$ subunit ($\beta 1S4-6$) are important for integrin $\alpha 5\beta 1$ -mediated cell spreading and migration;²⁶ The N-glycosylation on the β -propeller domain of the $\alpha 5$ subunit ($\alpha 5S3-5$) are critical for the heterodimerization, and biological functions of integrin $\alpha 5\beta 1$, as well as the formation of $\alpha 5$ -syndecan-4 complex.^{25,27} The site-11 N-glycosylation on calf domain of $\alpha 5$ subunit is also important for the $\alpha 5$ -EGFR complex formation and the inhibitory effect on EGFR signaling.²⁸ Beyond glycosylation, ubiquitination of $\alpha 5$ subunit also plays an important role for integrin $\alpha 5\beta 1$ -mediated fibroblast migration.³⁰ Therefore, exploring the PTMs of integrin $\alpha 5\beta 1$ is essential to understand the biological function and mechanism of integrin $\alpha 5\beta 1$.

Potential Trafficking Machinery of Integrin $\alpha 5\beta 1$

As transmembrane proteins, the transport of integrins to the cell surface is determined by the integrin trafficking machinery including exocytosis of integrins by vesicles and endocytosis of integrins at the plasma membrane. Integrin trafficking is considered to be an important regulator of cell adhesion and migration. The trafficking of $\alpha 5\beta 1$ integrin is affected by several proteins such as CD151, Ras Homolog Family Member C (RhoC), Cytoskeleton-Associated Protein 4 (CKAP4), PTPRF Interacting Protein Alpha 1 (PPFIA1), Ankyrin-B, protein kinase B, syntaxins 3 and 4, Vesicle-Associated Membrane Protein 2 (VAMP2), Adaptor Protein, phosphotyrosine interacting with ph domain and leucine zipper 1 (APPL1), TGF- β type III receptor (T β RIII), and Neuropilin-2 (NRP-2).³¹⁻⁴¹ For example, CD151 was functionally linked to integrin-mediated cell migration by control of the endocytosis and/or vesicular trafficking of $\alpha 3\beta 1$, $\alpha 5\beta 1$, and $\alpha 6\beta 1$ integrins.³¹ And mutation of the YXX ϕ endocytosis/sorting motif on the C-terminal cytoplasmic domain of CD151 significantly disrupted CD151-mediated cell migration.³¹ In pancreatic carcinoma cells, RhoC over-expression enhanced integrin $\alpha 5\beta 1$ internalization and trafficking, increasing the levels of $\alpha 5\beta 1$ integrin at the cell surface and promoting cell metastasis.³² T β RIII, a ubiquitous co-receptor for TGF- β , inhibited cell motility by control of β -arrestin2 dependent $\alpha 5\beta 1$ internalization and recycling. In addition, T β RIII expression was significantly associated with $\alpha 5$ localization and overall survival in breast cancer patients.⁴⁰

Extracellular Molecules Modulate Integrin $\alpha 5\beta 1$

Extracellular molecules such as growth factor and receptors, cytokine and cytokine receptors, as well as extracellular matrix proteins are crucial regulatory factors affecting the biological activity and function of integrin $\alpha 5\beta 1$. In cancer cells, epidermal growth factor (EGF) treatment could promote the p90RSK-dependent phosphorylation of filamin A (FLNa), which was responsible for the inactivation of integrin $\alpha 5\beta 1$.⁴² In addition, Dudvarski et al reported that epidermal growth factor-like protein 7 (EGFL7) elevated the levels of integrin $\alpha 5\beta 1$ on the cellular surface and then promoted the fibronectin-induced angiogenesis in glioblastoma.⁴³ Interleukin 1 β (IL-1 β), an inflammatory cytokine, not only induced inflammatory but also increased integrin $\alpha 5\beta 1$ -dependent adhesion to fibronectin. Upon IL-1 β treatment, the expression of $\alpha 5$ subunit increased and the active $\beta 1$ subunit were relocated to focal contacts in the transformed human brain microvascular endothelial cells (THBMECs). And using $\alpha 5$ - and $\beta 1$ -specific antibodies could remarkably inhibit the transmigration function under IL-1 β -induced inflammatory conditions.⁴⁴ In basal-like breast cancer cells, CD44 elevated the expression and activity of $\beta 1$ subunit, and also increased the expression of $\alpha 5$ subunit.⁴⁵ In addition, E-cadherin also associated with the expression and transcription activity of $\alpha 5\beta 1$ in ovarian cancer cells. Sawada et al demonstrated that E-cadherin loss could increase $\alpha 5\beta 1$ expression by regulating the FAK1/ERK1/MAPK signaling pathway.⁴⁶ Therefore, better understanding of the associations of extracellular molecules and $\alpha 5\beta 1$ is essential for clinical therapy.

Ligands of $\alpha 5\beta 1$

Integrin $\alpha 5\beta 1$ can recognize and adhere to extracellular ligands containing RGD tripeptide motif. Research on the molecular interactions of integrin $\alpha 5\beta 1$ may be essential for interpreting the biological function and underlying mechanisms of $\alpha 5\beta 1$ integrin. Herein, we will discuss the reported ligands and related functions of integrin $\alpha 5\beta 1$, which are summarized in Table 1. Extracellular matrix molecules fibrinogen, fibronectin, and fibrillin-1 could be recognized and bound by integrin $\alpha 5\beta 1$, which have been shown to affect cell adhesion and migration of endothelial and other cells.^{14,47-50} VEGFR-1 was secreted by endothelial cells and then interacted with integrin $\alpha 5\beta 1$, and this interaction was important for angiogenesis.⁵¹ CD97, CD87 and CD154, transmembrane proteins contain RGD peptide, have shown to interact with integrin $\alpha 5\beta 1$ and induce cell

Table 1 Ligands and Related Functions of Integrin $\alpha 5\beta 1$

Ligand	Functions	Reference
Fibronectin	Regulates cell adhesion and migration	[47]
Fibrinogen	Regulates cell adhesion and migration	[48]
Fibrillin	Regulates cell adhesion and migration	[50]
VEGFR1	Affects angiogenesis	[51]
CD97	Mediates migration and angiogenesis	[52]
CD154	Induces intracellular signaling	[53]
CD87 (uPAR)	Induces migration, invasion and angiogenesis	[54]
PHEV	Mediates actin cytoskeletal rearrangement	[55]
25-hydroxycholesterol	Regulates integrin signaling and cell adhesion	[56]
Tubulointerstitial nephritis antigen-like 1	Mediates FN-induced integrin/FAK signaling	[57]
Pregnancy-Specific Glycoprotein 1	Regulate extravillous trophoblasts migration	[58]
Neuropilin-2	Promotes cells extravasation and metastasis	[41]

adhesion, intracellular signaling, and angiogenesis.^{52–54} Recently, other ligands of integrin $\alpha 5\beta 1$ have been identified including Porcine hemagglutinating encephalomyelitis virus (PHEV), 25-hydroxycholesterol, Tubulointerstitial nephritis antigen-like 1 (Tinagl1), Pregnancy-Specific Glycoprotein 1 (PSG1), and Neuropilin-2.^{41,55–58} All of these studies demonstrate that ligand-binding regulation of $\alpha 5\beta 1$ integrin plays an important role for regulating the cellular function, such as cell adhesion, migration, and angiogenesis.

Functions of $\alpha 5\beta 1$

As a transmembrane protein, integrin $\alpha 5\beta 1$ possess different domains include extracellular, transmembrane, and cytoplasmic domain that determines the multiple functions of $\alpha 5\beta 1$. The extracellular and transmembrane domains are responsible for binding to ECM proteins, or other extracellular ligands, and contribute to subsequent signaling pathway function, whereas the cytoplasmic domain can interact with cytoskeleton-associated proteins to affect cell migration, invasion, and proliferation.^{55,59–66} It also reported that integrin $\alpha 5\beta 1$ was involved in anoikis resistance or drug resistance of cancer cells.^{67–70} Besides, $\alpha 5\beta 1$ integrin was strongly associated with cellular senescence.⁷¹ Integrin $\alpha 5\beta 1$ was also linked to the maintenance of bone tissue-forming and the formation of atherogenic inflammation, as well as the function/survival of T cell.^{72–74} The multiple functions of $\alpha 5\beta 1$ integrin indicated that dysregulation of $\alpha 5\beta 1$ integrin could lead to various diseases, particularly cancer. Indeed, the hyperexpression of $\alpha 5\beta 1$ integrin has been shown to promote tumor metastasis in lung cancer and melanoma. However,

$\alpha 5\beta 1$ integrin also act as a tumor-suppressive role in several breast cancer and colon cancer cell lines.¹⁴

Implication of $\alpha 5\beta 1$ in Carcinogenesis

It is well known that integrin $\alpha 5\beta 1$ acts an important role in diverse cancer progression and cancerogenesis, and thus the deregulation of $\alpha 5\beta 1$ integrin is highly associated with a series of malignant tumors. Herein, we will discuss the potential roles and related functions of integrin $\alpha 5\beta 1$ on human cancers in this section (Table 2).

Expression of Integrin $\alpha 5\beta 1$ is Upregulated in Various Types of Cancers

Aberrant upregulation of integrin $\alpha 5\beta 1$ has been implicated in a number of human malignancies and is closely correlated with poor prognosis. Integrin $\alpha 5\beta 1$ expression was slightly expressed in normal brain tissue, but was expressed at significantly high intensity in glioblastoma tissue.⁷⁵ Research demonstrated that activation of $\alpha 5\beta 1$ integrin was linked to the promotion of cell survival, migration, invasion, angiogenesis, and drug-resistance of glioma cells.^{43,63,69,76,77} In addition, $\alpha 5\beta 1$ integrin expression was overexpressed in colon cancer cells, and blockade of cell surface $\alpha 5$ integrin by selective antibody significantly suppressed cell adhesion and induced apoptosis.^{78,79} In MCF-7 human breast carcinoma cells, hyperexpression of integrin $\alpha 5\beta 1$ promoted cell invasion and doxorubicin resistance by enhancing the activity of AKT, mTOR, and ERK1/2 protein kinases.^{68,80,81} Importantly, blocking $\alpha 5\beta 1$ integrin by PHSCN (Pro-His-Ser-Arg-Asn) peptide significantly prevented cell metastasis in preclinical prostate adenocarcinoma models, and parallel progression

Table 2 Functional Roles of Integrin $\alpha 5\beta 1$ Pathway in Different Types of Cancer

Cancer Type	Experimental Model	Function	References
Glioblastoma	Cell culture, Animal model	Promotes angiogenesis	[43]
Glioma	Cell culture	Drives migration	[63]
Glioblastoma	Cell culture	Increases resistance to temozolomide	[69]
Glioblastoma	Cell culture	Promotes cell proliferation	[76]
Glioblastoma	Cell culture	Resists apoptosis	[77]
Colorectal cancer	Cell culture	Promotes cell adhesion	[78]
Colorectal cancer	Cell culture	Promotes cancer resistance	[94]
Colon cancer	Cell culture	Regulates cell differentiation	[79]
Colon cancer	Cell culture, Animal model	Inhibits tumor metastasis	[108]
Colon cancer	Cell culture	Suppresses cell proliferation	[109]
Colon cancer	Cell culture	Inhibits cell apoptosis	[110]
Breast cancer	Cell culture	Promotes resistance to doxorubicin	[68]
Breast cancer	Cell culture	Regulates cell apoptosis and drug resistance	[80]
Breast cancer	Cell culture	Facilitates cell invasion	[81]
Prostate cancer	Cell culture, Animal model	Promotes tumor metastasis	[82]
Melanoma	Cell culture, animal model, clinical settings	Promotes tumor metastasis	[3]
Melanoma	Cell culture, animal model	Promotes tumor metastasis	[83]
Uveal melanoma	Cell culture	Inhibits tumorigenic properties	[114]
Lung cancer	Immunohistochemical analysis	Correlates with lymph node metastasis	[85]
Cervical cancer	Immunohistochemical analysis	Correlates with poor histologic differentiation and lymph node metastasis	[86]
Bulky squamous cervical cancer	Immunohistochemical analysis	Correlates with negative chemotherapy response and recurrence	[87]
Epithelial ovarian cancer	Cell culture, animal model	Inhibits tumor growth	[89]
Ewing sarcoma	Cell culture, animal model	Promotion tumor progression	[90]
Acute lymphoblastic leukemia	Cell culture	Facilitates cell adhesion and invasion	[91]
Basal Cell Carcinoma	Cell culture, animal model	Promotes cell invasion	[92]
Multiple myeloma	Cell culture	Facilitates cell adhesion and drug resistance	[93]
Osteosarcoma	Cell culture, animal model	Facilitates tumor metastasis	[95]
Squamous carcinoma	Immunohistochemical analysis	Promotes carcinogenesis	[96]
Head and neck squamous cell carcinoma	Cell culture	Increases EMT and metastasis	[97]
Mesothelioma	Cell culture, animal model	Promotes cell invasion	[98]
Pancreatic ductal adenocarcinoma	Cell culture, animal model	Promotes cell migration	[32]
Gastric cancer	Immunohistochemical analysis	Facilitates gastric carcinogenesis	[99]
Cholangiocarcinoma	Cell culture	Promotes cell invasion	[100]
Epidermoid carcinoma	Cell culture	Promotes cell proliferation	[101]
Epidermoid carcinoma	Cell culture, animal model	Facilitates tumor growth	[104]
Chondrosarcoma	Cell culture	Promotes cell motility	[102]
Neuroblastoma	Cell culture	Promotes cell motility	[103]
Motile carcinoma	Cell culture	Regulates cell adhesion	[105]
Rectal cancer	Immunohistochemical analysis	Functions as a predictive marker	[106]
Transitional carcinoma	Cell culture	Increases cell adhesion	[107]

Phase I clinical trial.⁸² Besides, integrin $\alpha 5\beta 1$ was upregulated in some primary and metastatic melanoma cells and positively linked to liver metastasis in melanoma.^{3,83} In node-negative non-small cell lung cancer (NSCLC), the expression of $\alpha 5\beta 1$ integrin was highly expressed in 50.0% (44/88) node-negative

NSCLC patients and significantly associated with the differentiation status and age of the patients.⁸⁴ Notably, another study demonstrated that $\alpha 5\beta 1$ integrin expression was more frequent in NSCLC with lymph node metastasis.⁸⁵ Integrin $\alpha 5\beta 1$ was also overexpressed in 84.6% (143/169) cervical

cancer samples, and high $\alpha 5\beta 1$ integrin expression was closely linked to poor histologic differentiation, lymph node metastasis, negative chemotherapy response, and recurrence in cervical cancer.^{86,87} Researchers also showed that the $\alpha 5$ and $\beta 1$ integrin subunits were significantly increased in ovarian cancer compared with the normal tissue, and inhibition of the expression of integrin $\alpha 5$ and $\beta 1$ may be improved the prognosis of ovarian cancer patients.^{88,89} Patients with $\alpha 5\beta 1$ integrin hyperexpression tended to have poor overall survival in ewing sarcoma, leukemia, basal cell carcinoma, multiple myeloma, colorectal cancer, osteosarcoma, squamous carcinoma, head and neck squamous cell carcinoma, mesothelioma, pancreatic carcinoma, gastric cancer, cholangiocarcinoma, epidermoid carcinoma, chondrosarcoma, neuroblastoma, epidermoid carcinoma, motile carcinoma, rectal cancer, and transitional carcinoma.^{32,81,90–107}

Integrin $\alpha 5\beta 1$ as a Tumor Suppressor in Several Types of Cancer Cell Lines

Integrin $\alpha 5\beta 1$ as a classic cell surface receptor has been reported as a tumor suppressor due to overexpressing $\alpha 5\beta 1$ integrin in tumor cells are less tumorigenic than its corresponding parent cells. In colon cancer cell line, HT29, $\alpha 5\beta 1$ integrin overexpression showed a strong inhibitory function on lung colonization and metastasis.¹⁰⁸ And de novo expression of $\alpha 5$ integrin subunit was linked to suppress cell growth arrest and retard the tumorigenic growth of HT29 cells.¹⁰⁹ However, another study demonstrated that upregulation of the $\alpha 5$ integrin subunit suppressed apoptosis triggered by serum deprivation in HT29 cells.¹¹⁰ Then, further research demonstrated that integrin $\alpha 5\beta 1$ level was significantly elevated in the poorly differentiated colon cancer cell lines and was positively associated the tumorigenic capacity. Therefore, the different roles of $\alpha 5\beta 1$ integrin in colon cancer cells might be related to the differentiation status.¹¹¹ Besides, loss of $\alpha 5\beta 1$ integrin at the cell surface of the uveal melanoma cells was positively associated with the high tumorigenicity and aggressiveness.^{112–114}

Deregulation of Integrin $\alpha 5\beta 1$ Exerts Dramatic Effects on Diverse Cellular Functions

Role of Integrin $\alpha 5\beta 1$ in Angiogenesis

Angiogenesis is a crucial physiological and pathological process for the development of new blood vessels, which was responsible for the tissue repair and fertility, embryonic

development, chronic inflammation, tumor growth and metastasis.¹¹⁵ Basic and clinical studies demonstrated that inhibition of angiogenesis could suppress tumor metastasis and progression. Most studies implicate integrins, which are critical modulators of tumor angiogenesis. Among the integrin family, αv , $\alpha 2$, $\alpha 3$, $\alpha 4$, $\alpha 5$, $\beta 1$ or $\beta 2$ integrin subunits have been demonstrated to be associated with vasculo- and angiogenesis during development.^{5,14,65} Research found that loss of fibronectin, the major ligand for $\alpha 5\beta 1$ integrin, led to angiogenesis abnormalities and embryonic death at E9.5 in mice.¹¹⁶ Genetic ablation studies have indicated that $\beta 1$ -integrin-null endothelial cells displayed vascular remodeling effects resulting from adhesion and migration alteration, suggesting the $\beta 1$ integrin family clearly played an important role in angiogenesis.^{14,117} Integrins $\alpha 5$ and αv have been considered as key modulators of endothelial cells and vascular smooth muscle cell (vSMC) function. Interestingly, endothelial cell-specific knockout of either integrin $\alpha 5$ and αv do not have obvious angiogenesis defects during embryonic development.¹¹⁸ Researchers found that vSMC-specific knockout of both $\alpha 5$ and αv integrin led to the formation of large aneurysms within the brachiocephalic/carotid arteries and cardiovascular defects, as well as late embryonic lethality.¹¹⁹ These studies indicate that specific integrins are important during the vascular development, and the compensation mechanisms by other integrins are essential for normal angiogenesis.

In most quiescent endothelium, integrin $\alpha 5\beta 1$ was limited to very low levels, but its expression was significantly upregulated in tumor vasculature or neovessels.^{120,121} Integrin $\alpha 5\beta 1$ participated in regulating angiogenesis by interacting with diverse partners such as CD97, angiopoietin-2 (Ang-2), CD87, VEGFR1, and endostatin.^{51,54,122–124} Integrin $\alpha 5\beta 1$ levels in endothelial cells were induced in response to several angiogenic factor stimuli, such as IL-8, bFGF, EGFL7, Del-1 or TNF α , but not by VEGF.^{43,120,125} Besides, HoxD3 acts as a homeobox gene controlled the expression of integrin $\alpha 5$ by directly binding to the promoter of the $\alpha 5$ subunits.¹²⁶ Therefore, integrin $\alpha 5\beta 1$ plays an important role in angiogenesis, and blocking $\alpha 5$ and $\beta 1$ integrin subunits by specific monoclonal antibodies or small peptides has become a potential strategy for anti-angiogenesis therapy.^{127–130}

Integrin $\alpha 5\beta 1$ Regulates the Migration and Invasion of Tumor Cells

The ability of cancer cells to invade locally and further form distant metastasis is partly determined by integrin-mediated attachment to ECM. Integrin $\alpha 5\beta 1$ function as a critical

regulator for tumor cell migration and invasion by affecting cytoskeleton rearrangement, cell adhesion, and the production of matrix metalloproteinase (MMP). Some studies have demonstrated that integrin $\alpha 5\beta 1$ enhanced keratinocyte adhesion to fibronectin, and promoted invasion and metastasis via activating various signaling pathways.^{11,131} Besides, fibronectin binding to integrin $\alpha 5\beta 1$ led to the direct association of $\alpha 5$ integrin with c-Met, which was upstream of Src and FAK. Integrin $\alpha 5\beta 1$ promoted tumor cells invasion and metastasis via activating the c-Met/FAK/Src-dependent signaling pathway.¹³² Research also found that integrin $\alpha 5\beta 1$ promoted invasiveness and metastasis by regulating the expression and/or activity of MMPs.¹³³ In breast cancer, cells with high integrin $\alpha 5\beta 1$ expression elevated a 3-fold invasive capacity compared with cells exhibiting low $\alpha 5\beta 1$ levels.⁸¹ Integrin $\alpha 5\beta 1$ could direct recruit MMP2 collagenase on the surface of breast carcinoma cells, and then regulating cell invasion by control of the levels of MMP2.¹³⁴ Moreover, MMP-2/ $\alpha 5\beta 1$ binding has pivotal role in regulating tumor metastasis by inducing $\alpha 5\beta 1$ -mediated IL-6/STAT3 signaling pathway.¹³⁵ In murine cell line B16F10, integrin $\alpha 5\beta 1$ and fibronectin interaction facilitated cell invasion by inducing the activity, mRNA, and protein expression of MMP9. Blocking the $\alpha 5$ integrin receptor by specific antibody remarkably abrogated the fibronectin-induced MMP9 response.¹³⁶ Moreover, ADAM Metallopeptidase Domain 17 (ADAM17) was reported to directly interacted with integrin $\alpha 5\beta 1$, and this interaction might take place on the same cell or on different cell, with the function to affect cell-cell adhesion and migration.^{137,138} In addition, Rab-coupling protein (RCP)-driven endocytic recycling of $\alpha 5\beta 1$ integrin also promoted invasion of cancer cells, which was associated with actin cytoskeleton arrangement.⁷ The effects of integrin $\alpha 5\beta 1$ on the cell adhesion, migration, and invasion of tumor cells indicate that it may be used as the biomarker for the metastasis of tumors.

Integrin $\alpha 5\beta 1$ Mediates the Proliferation of Tumor Cells

Mounting studies have implicated that integrin $\alpha 5\beta 1$ contributed to tumor cell proliferation in vitro and tumor growth in vivo. It has been demonstrated that $\alpha 5\beta 1$ integrin possessed the ability of enhancing cell proliferation depending on the fibroblasts, which are some of the major cells in neoplasm tissues and affect cancer progression. High L1 cell adhesion molecule (L1CAM) levels in fibroblasts promoted cancer cell proliferation by targeting integrin

$\alpha 5\beta 1$.¹³⁹ In addition, interaction of myofibroblasts and soluble fibronectin facilitated the $\alpha 5\beta 1$ integrin-dependent tumor growth in the hepatocellular carcinoma.¹⁴⁰

Integrin $\alpha 5\beta 1$ was also considered to be an important regulator for cell cycle-associated proteins. p53 is a universal tumor suppressor implicated in cell cycle arrest, apoptosis, and DNA repair. Research found that the expression of $\alpha 5$ integrin subunit was negatively associated with p53 activity, and depletion of the $\alpha 5$ integrin subunit could increase p53 activity.⁶⁹ Interestingly, re-activation of p53 by Nutlin-3, a p53-reactivating compound, significantly inhibited the mRNA and protein expression of $\alpha 5$ integrin subunit.¹⁴¹ Thus, the crosstalk between $\alpha 5\beta 1$ integrin and p53 was crucial for tumor growth, and some antagonists of $\alpha 5\beta 1$ integrin have been applied by modulating the integrin $\alpha 5\beta 1$ /p53 pathway.^{77,142} Of note, the integrin $\alpha 5\beta 1$ -ERK pathway was also involved in the regulation of cancer cell proliferation.¹⁰⁴ Antibodies that block the integrin $\alpha 5\beta 1$ negated the proliferative effect of integrin $\alpha 5\beta 1$ in malignancy cells.¹⁴³

Role of Integrin $\alpha 5\beta 1$ in Chemoresistance and Radioresistance

Resistance to chemotherapy and radiotherapy is a unique hallmark of neoplasm and is responsible for tumor recurrence and patient relapse.¹⁴⁴ Cell adhesion to ECM components is a critical determinant of chemotherapeutic response of human cancers, such as myeloma. For example, Integrin $\alpha 5\beta 1$ promoted K562 chronic myelogenous leukemia (CML) cells bind to fibronectin, and this binding was resistant to apoptosis induced by chemotherapeutic drugs and γ -irradiation.¹⁴⁵ Besides, fibronectin/integrin $\alpha 5\beta 1$ binding elevated the efficiency of 2-D colony formation, and provided resistance to paclitaxel-mediated apoptosis.¹⁴⁶ Research has demonstrated that integrin $\alpha 5\beta 1$ protected high-grade glioma cells from temozolomide-induced apoptosis by interfering with the p53 pathway in glioma.⁶⁹ In epithelial ovarian carcinomas, overexpression of integrin $\alpha 5$ was a strong risk factor for drugs resistance.¹⁴⁷ Integrin $\alpha 5\beta 1$ also contributed to cell adhesion and drug resistance of multiple myeloma cells through activating the FAK/STAT3/AKT pathways.⁹³ In MCF-7 human breast carcinoma cells, hyperexpression of integrin $\alpha 5\beta 1$ promoted the doxorubicin resistance in an ERK-dependent manner. Besides, silencing of integrin $\alpha 5\beta 1$ significantly inhibited the activity of kinases AKT and ERK in MCF-7 doxorubicin-resistant cells.⁸⁰

The Signaling Pathways Involved in Integrin $\alpha 5\beta 1$ -Mediated Tumor Progression

Integrin $\alpha 5\beta 1$ functions as a cell surface receptor, and ligation of integrin $\alpha 5\beta 1$ activates several crucial signaling pathways that are critical in carcinogenesis/tumor progression, such as FAK signaling, Wnt/ β -catenin signaling, NF- κ B signaling, Yes-associated protein (YAP) signaling, and ERK signaling. Interpreting the molecular mechanism of integrin $\alpha 5\beta 1$ in these pathways may provide a better understanding of carcinogenesis/tumor progression.

Regulation FAK Pathway by Integrin $\alpha 5\beta 1$

Due to lack of intrinsic tyrosine kinase activity, integrins transduce extracellular cues to intracellular signaling pathways require non-receptor tyrosine kinases such as FAK.^{148,149} Research demonstrated that fibronectin-integrin $\alpha 5\beta 1$ complex facilitated the auto-phosphorylation of the Tyr 379 residue on FAK. Subsequently, the tyrosine kinase Src bound to phosphorylated FAK through its SH2 domain, and induced phosphorylation of FAK at Tyr 925 residue, which then promoted the formation of FAK-Grb2-SOS complex. Ultimately, this complex contributed to cell proliferation, metastasis, and tumorigenesis of cancer cells by activating Ras GTPase and inducing the MAPK/ERK signaling pathway.^{150,151} Indeed, integrin $\alpha 5\beta 1$ -FAK signaling pathway contributed to cell metastasis and cancer progression of several malignant neoplasms, and some specific monoclonal antibody or integrin $\alpha 5\beta 1$ inhibitor could significantly negate these accelerative effects.^{57,152–154}

Regulation Wnt/ β -Catenin Pathway

Wnt/ β -catenin pathway is critical to facilitate tumor progression, such as cell proliferation, cell cycle, cell metastasis, differentiation, and apoptosis. In pancreatic cancer, integrin $\alpha 5\beta 1$ mediated the adhesion of pancreatic adenocarcinoma cells on fibronectin under serum-free conditions, resulting in the increasing of β -catenin localization throughout the cell.¹⁵⁵ In hepatocellular carcinoma, overexpression of CD147 competitively bound to integrin $\beta 1$ that interrupted the fibronectin/integrin $\beta 1$ interaction, which is responsible for E-cadherin degradation and β -catenin nuclear translocation.¹⁵⁶ In glioma cells, overexpression and activation of $\alpha 5\beta 1$ integrin by fibronectin facilitated the transactivation of β -catenin gene targets and induced an increase in cell migration.⁶³ In addition, other high-affinity peptide such as cyclized CRRETAWAC also promoted integrin $\alpha 5\beta 1$ -mediated Wnt/ β -catenin transcriptional activity.¹⁵⁷

Regulation of NF- κ B Signaling

NF- κ B transcription factors and their regulated genes have been recognized as critical mediators involved in tumor initiation, cell proliferation, survival, metastasis, angiogenesis, and resistance to chemotherapy and radiotherapy.¹⁵⁸ Fibronectin/integrin $\alpha 5\beta 1$ interaction was responsible for inducing the expression of the p65 component of NF- κ B and enhancing the DNA-binding activity of NF- κ B in human bronchial epithelial cells.¹⁵⁹ Upon fibrinogen binding, integrin $\alpha 5\beta 1$ and $\alpha v\beta 3$ promoted the activation of NF- κ B and increased the expression of NF- κ B-mediated inflammatory chemokines in endothelial cells. And these effects were inhibited by blockage of the integrin $\alpha 5\beta 1$ and $\alpha v\beta 3$ with the GRGDS peptide.¹⁶⁰ Besides, lunasin, a naturally occurring 43-amino acid peptide isolated from soybean, direct binding with integrin $\alpha 5\beta 1$ and inhibiting the NF- κ B signaling in colon cancer cells.¹⁵²

Activation of YAP by Integrin $\alpha 5\beta 1$

YAP, the crucial transcriptional regulator of the Hippo pathway, is involved in modulating organ size, tissue homeostasis and repair, and tumorigenesis.¹⁶¹ Hyperactivation of YAP is associated with the malignant behavior of neoplasm, such as high proliferation, invasion into the surrounding normal tissue, vascularization, and drug resistance.¹⁶² Recent studies demonstrated that activation of integrin $\alpha 5\beta 1$ by the ligand fibronectin significantly increased the phosphorylation of YAP at Tyr357 and induced YAP nuclear translocation via the tyrosine kinase c-Abl in ECs. In contrast, blockage of integrin $\alpha 5\beta 1$ with ATN161 or inhibition of c-Abl with bosutinib markedly reduced the levels of integrin $\alpha 5\beta 1$ and p-YAP^{Y357}.¹⁶³ Beyond YAP phosphorylation, the dephosphorylation of YAP (S127) was also regulated by the $\alpha 5$ integrin subunits.¹⁶⁴ In Ewing sarcoma cells, integrin $\alpha 5\beta 1$ signaling was associated with YAP dephosphorylation and nuclear translocation, and this signaling pathway significantly promoted tumor progression.⁹⁰

Integrin $\alpha 5\beta 1$ Regulates ERK Signaling Pathway

ERK signaling pathway is hyperactivated in a variety of cancers, which execute programmes related to cell cycle, differentiation, migration and invasion, and apoptosis. Fibronectin and integrin $\alpha 5\beta 1$ binding enhanced Hela cell proliferation by increasing the phosphorylation of ERK at Thr 202 and Tyr 204 residues and then activating the ERK pathway.¹⁴⁸ uPAR (CD87), an urokinase receptor frequently upregulated in several types of tumors, bound to integrin $\alpha 5\beta 1$ and then persistently activated the ERK

signaling.¹⁶⁵ Using site-directed mutagenesis, two single amino acid mutants of the uPAR (S245A and H249A) were respectively identified that fail to facilitate integrin $\alpha 5\beta 1$ -mediated ERK signaling.^{104,166} Moreover, disruption of uPAR/integrin $\alpha 5\beta 1$ interaction by using specific small molecules significantly inhibited ERK activity and tumor progression.^{104,167}

Translational Implications of Integrin $\alpha 5\beta 1$ in Cancer

Integrin $\alpha 5\beta 1$ as a Target for Imaging

Although integrin $\alpha 5\beta 1$ is limited to very low levels in quiescent endothelial cells, it is significantly upregulated in tumor vasculature or neovessels.^{120,121} And $\alpha 5\beta 1$ integrin is strongly correlated with tumor angiogenesis, suggesting it may be a potential predictive target. So far, several imaging probes for $\alpha 5\beta 1$ have been described for tumor molecular imaging. Stefanie et al firstly developed the $\alpha 5\beta 1$ -selective antagonists labeled with $^{68}\text{Ga}^{3+}$ for PET (positron emission tomography) imaging and could verify different patterns of integrin $\alpha 5\beta 1$ expression in tumors.¹⁶⁸ D'Alessandria et al then successfully developed a ^{68}Ga -labelled $\alpha 5\beta 1$ -selective peptidomimetic named FR366, which showed good image quality for PET imaging.¹⁶⁹ Through sequential N-methylation analysis, Tobias et al discovered a most potent and selective $\alpha 5\beta 1$ -integrin ligand peptide, c(phg-isoDGR-(NMe)k), which was applied for PET imaging by trimerized with the chelator TRAP and labeled with ^{68}Ga .¹⁷⁰ In addition, there have been several $\alpha 5\beta 1$ -specific probes such as $^{99\text{m}}\text{Tc}$ -HisoDGR, $^{99\text{m}}\text{Tc}$ -AB-3PisoDGR2, and $^{99\text{m}}\text{Tc}$ -3PisoDGR were developed for SPECT (single-photon emission computed tomography) imaging.^{171,172} Recently, RNA aptamers have received attention as promising tools for clinical applications due to their smaller size, lack of immunogenicity and toxicity, temperature stability, ease of chemical modification, and lower cost of production.^{173,174} Fechter and colleagues successfully identified and developed RNA aptamers, aptamer H02, is efficient to distinguish GBM tumor tissues from patient-derived tumor xenografts. This new, original, and powerful aptamer tool may be open roads for $\alpha 5\beta 1$ -specific clinical therapy.¹⁷⁵

Integrin $\alpha 5\beta 1$ as a Target for Therapy

Integrin $\alpha 5\beta 1$ has become a potential target for cancer therapy, and several specific $\alpha 5\beta 1$ integrin antagonists have been developed and used in preclinical or clinical

studies. These antagonists are mainly presented as anti-angiogenic agents due to the pro-angiogenic function of integrin $\alpha 5\beta 1$, and they mainly consisted by specific antibodies and small peptides.

A series of blocking antibodies was developed to target the interaction between integrin $\alpha 5\beta 1$ and fibronectin. IIA1, an integrin $\alpha 5\beta 1$ function-blocking murine antibody, was generated and used to inhibit in vitro angiogenesis, cell adhesion, invasion, and survival of tumor cells.^{46,130,176} Notably, Ramakrishnan and colleagues firstly developed a chimeric human IgG4 version of IIA1 antibody, volociximab, with similar affinity for $\alpha 5\beta 1$ integrin and similar activity by inhibition of fibronectin binding than IIA1.¹³⁰ Volociximab as a potential anti-angiogenic drug and has been shown to be effective, safe, and tolerable in phase I b studies in patients with non-small-cell lung cancer, and in Phase II studies in patients with epithelial ovarian or primary peritoneal cancer.¹⁷⁷⁻¹⁷⁹ The MINT1526A is a function-blocking anti- $\alpha 5\beta 1$ monoclonal antibody, has been used in anti-angiogenic therapy combining $\alpha 5\beta 1$ and VEGF inhibition, and has been shown to be well tolerated and safe in phase I study.¹⁸⁰ Recently, a bispecific antibody (BsA $\alpha 5\beta 1/\alpha v$) simultaneously targeting the degradation of αv and $\alpha 5\beta 1$ integrins. And this combinatorial strategy was superior to monospecific antibodies in abrogating cell adhesion, migration, survival in prostate cancer cells.¹⁸¹

Integrins $\alpha 5\beta 1$ can recognize the RGD motif of fibronectin and then directly bind to it. Recent years, many studies focus on the design antagonists with enhanced selectivity of $\alpha 5\beta 1$ integrin. Some antagonists have been developed and used in preclinical or clinical studies, such as SJ749 and JSM6427, and ATN-161.^{120,142,182,183} Among them, ATN-161 (Ac-PHSCN-NH2), a competitive inhibitor of the FN- $\alpha 5\beta 1$ interactions firstly developed by Attenuon LLC (San Diego, CA, USA), have moved to Phase II clinical trails.¹⁴

Although many preclinical studies supported the anti-angiogenic therapies of blocking antibody and small molecule, early clinical responses have been disappointing. Most $\alpha 5\beta 1$ integrin inhibitors and antibodies were clinical investigations in phases 1 or 2 that have not progressed through phases 3, revealed no treatment benefit.¹⁸⁴ Murphy and colleagues revealed that FN and the FN receptors, $\alpha 5$ and αv , were dispensable for tumor angiogenesis through a series of genetic tools and pre-clinical models (transplant models and *RIP1-Tag2* model of pancreatic cancer), suggesting that the antagonism of antibodies or small molecules on tumor angiogenesis may occur through a dominant-negative effect, rather than a simple

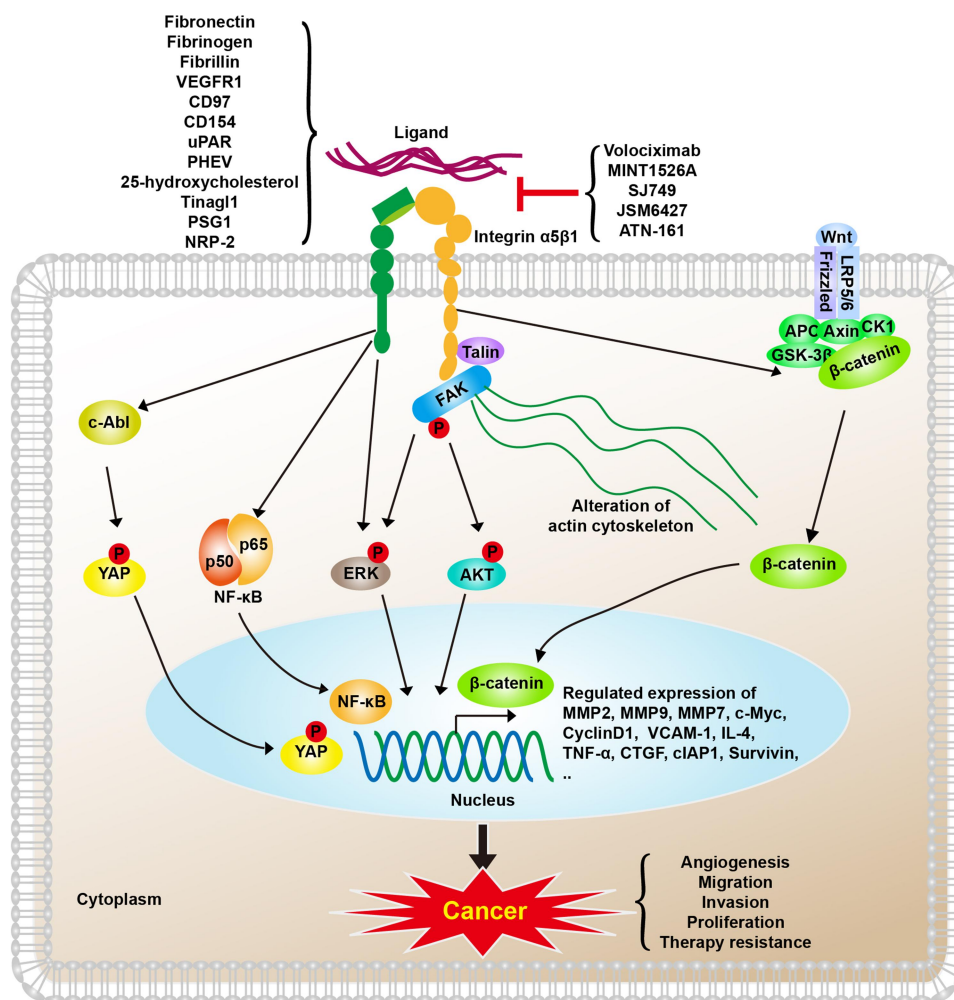


Figure 1 A schematic model by which integrin $\alpha 5\beta 1$ /ligand binding contributes to cancer progression through regulating several crucial signaling pathways such as FAK signaling, Wnt/ β -catenin signaling, NF- κ B signaling, YAP signaling, and ERK signaling.

block of the FN-integrin $\alpha 5\beta 1$ binding.¹⁸⁴ And they also found that tumor growth was not affected by the absence of FN and its integrin receptors.¹⁸⁴ In addition, they revealed the potential compensatory mechanism that several RGD-containing extracellular matrix proteins, such as fibrillins, collagens, and nidogens, might be important in compensating for the loss of FN.¹⁸⁴ Therefore, further in vivo genetic studies were necessary to resolve the targeting difficulties.

Conclusion

In this review, we briefly illustrate our understanding on the structure, regulation, ligands and biological functions of integrin $\alpha 5\beta 1$, and reveal the roles of integrin $\alpha 5\beta 1$ in various tumors. The dysregulation of $\alpha 5\beta 1$ integrin significantly relates to the development and progression of many neoplasms and can be used as a valuable indicator

of poor prognosis. Functionally, integrin $\alpha 5\beta 1$ can recognize and adhere to extracellular ligands containing RGD tripeptide motif, and this integrin $\alpha 5\beta 1$ /ligand binding modulates diverse cellular progression by activation of several classic oncogenic signaling pathways, such as FAK signaling, Wnt/ β -catenin signaling, NF- κ B signaling, YAP signaling, and ERK signaling (Figure 1). The important role of integrin $\alpha 5\beta 1$ in the tumor angiogenesis is that provides the potential predictive possibility for tumor molecular imaging, such as PET, SPECT, and RNA aptamers. Moreover, several specific $\alpha 5\beta 1$ integrin antagonists have been developed and/or used in preclinical or clinical studies. Considering the pivotal cellular role of the integrin $\alpha 5\beta 1$, it is reasonable to assume that advances in integrin $\alpha 5\beta 1$ research will facilitate the development of molecular diagnosing and therapy of tumors in the future.

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Disclosure

The authors declare no conflicts of interest.

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