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# The mechanism of ITGB4 in tumor migration and invasion

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Integrin  $\beta 4$  (ITGB4) is a transmembrane protein that functions as a mechanosensor, mediating the bidirectional exchange of information between the intracellular and extracellular matrices. ITGB4 plays a critical role in cell adhesion, migration, and signaling. Numerous studies have implicated ITGB4 as a key facilitator of tumor migration and invasion. This review provides a foundational description of the mechanisms by which ITGB4 regulates tumor migration and invasion through pathways involving focal adhesion kinase (FAK), protein kinase B (AKT), and matrix metalloproteinases (MMPs). These mechanisms encompass epithelial-mesenchymal transition (EMT), phosphorylation, and methylation of associated molecules. Additionally, this review explores the role of ITGB4 in the migration and invasion of prevalent clinical tumors, including those of the digestive system, breast, and prostate.

## KEYWORDS

integrin  $\beta 4$  (ITGb4), tumor metastasis, cell adhesion, epithelialmesenchymal transition (EMT), cancer therapy

## 1 Introduction

Cancer poses a significant social, public health, and economic burden. Data from the International Agency for Research on Cancer (IARC) indicate that roughly one in five individuals, both men and women, will develop cancer during their lifetime. Furthermore, approximately one in nine men and one in two women succumb to the disease (1). Metastasis, the spread of cancer cells from the primary tumor to distant organs, is the leading cause of death from cancer. Unlike primary tumors, metastasis represents a systemic disease affecting the entire body (2). Therefore, elucidating the mechanisms underlying tumor metastasis and identifying non-specific targets within the metastatic cascade are crucial for advancing cancer therapy.

Integrins are heterodimeric transmembrane receptors composed of non-covalently associated  $\alpha$  and  $\beta$  subunits. The human genome encodes 18  $\alpha$  and 8  $\beta$  subunits, which can combine to form a repertoire of 24 distinct integrin receptors. Each integrin receptor possesses unique binding specificities and exhibits a distinct tissue distribution (3). These receptors span the plasma membrane and serve as platforms for the assembly of signaling

complexes that physically connect the extracellular matrix to the intracellular cytoskeleton. Notably, integrins exhibit a remarkable capacity for bidirectional signaling across the plasma membrane, mediating both “inside-out” (4) and “outside-in” signaling (5). This bidirectional communication enables human cells to not only respond to changes in their surrounding extracellular environment but also actively influence it (6). It is now understood that integrins primarily mediate cell-matrix interactions and play crucial roles in various cellular processes, including adhesion, proliferation, differentiation, migration, and invasion (7).

Integrin  $\beta 4$  (ITGB4, also known as CD104), a member of the tryptophan-aspartic acid (WD)-40 repeat family, is a tumor-associated antigen (TAA) exhibiting high expression levels in diverse malignant tumors. ITGB4 promotes tumor progression by amplifying distinct signaling pathways (8) and facilitating tumor cell migration and invasion (9, 10). Transcriptome analysis from The Cancer Genome Atlas (TCGA) pinpointed *ITGB4* as a target gene in colorectal cancer, suggesting a critical role in disease development (11). Likewise, in squamous cell carcinoma of the lung, elevated ITGB4 expression is associated with tumorigenesis and progression via modulation of various signaling pathways (12). ITGB4 is widely recognized as a molecule with both prognostic and predictive value in cancer patients (13). Notably, ITGB4 exhibits high expression levels in oral squamous cell carcinoma, gliomas, and pancreatic cancer (14–17). In colon cancer patients, high ITGB4 expression correlates with poor overall survival. Additionally, *ITGB4* serves as a pivotal gene for constructing a predictive risk model for the clinical prognosis of lung adenocarcinoma (18–20). Furthermore, ITGB4 possesses diagnostic value for lung adenocarcinoma, demonstrating a significant correlation with overall survival (21).

ITGB4 has been implicated in promoting the invasive potential of various squamous cell carcinomas, breast cancers, and gastric cancers by activating MAPK and NF- $\kappa$ B signaling pathways (22–25). Mechanistically, ITGB4 engagement with extracellular ligands, such as human leukocyte antigen-1 (HLA-1), triggers the phosphorylation of Src kinase. This phosphorylation event subsequently leads to the activation of focal adhesion kinase (FAK) and downstream PI3K/AKT and Erk signaling pathways, ultimately promoting tumor cell migration (26). Furthermore, epidermal growth factor receptor (EGFR)/Src signaling can mediate the tyrosine phosphorylation of ITGB4, facilitating the recruitment of FAK to ITGB4. FAK activation then stimulates the Akt signaling pathway, thereby promoting tumor cell invasion (27–29). Collectively, these findings highlight the strong correlation between ITGB4 expression and tumor cell migration and invasion.

In contrast to other integrin  $\beta$  subunits, ITGB4 exclusively partners with the  $\alpha 6$  subunit to form the  $\alpha 6\beta 4$  integrin, a cell adhesion molecule. Notably, within various cancers,  $\alpha 6\beta 4$  integrin undergoes release from hemidesmosomes. In this unbound state,  $\alpha 6\beta 4$  cooperates with growth factor receptors such as EGFR, ErbB-2, and c-Met. This cooperation leads to the amplification of downstream signaling pathways, including PI3K, AKT, MAPK, and Rho family GTPases. These activated pathways ultimately contribute to tumor migration and invasion (30). This study

focused on the interplay between ITGB4 and other messenger RNAs (mRNAs) and molecules during its expression. We aimed to elucidate how ITGB4 interacts with these factors to influence tumor migration and invasion. By deciphering these mechanisms, we sought to provide valuable insights for further research exploring the impact of ITGB4 on cancer metastasis.

## 2 The interaction between ITGB4, FAK and AKT

Focal adhesion kinase is a central cytoplasmic protein tyrosine kinase. Functioning as a signaling hub, FAK integrates signals from various pathways and plays a critical role in promoting tumor cell invasion and migration through both kinase-dependent and -independent mechanisms. ITGB4 acts as an upstream regulator of FAK, influencing its expression and phosphorylation. For example, in ovarian cancer cells, Spectrin beta non-erythrocytic 2 (SPTBN2) may promote tumor migration and invasion by inhibiting the expression of focal adhesion-related proteins and downstream signaling pathways via ITGB4. Notably, overexpression of *ITGB4* reversed the decrease in phosphorylated FAK (p-FAK) induced by *SPTBN2* knockdown, while the combination of *SPTBN2* knockdown and *ITGB4* overexpression had no effect on total FAK protein expression (31). Furthermore, ITGB4 appears to influence FAK phosphorylation in various cancers. Spindle pole component 25 homologue (SPC25) preferentially affects genes associated with ECM-integrin interactions. Upregulation of *ITGB4* partially reverses the decrease in hepatocellular carcinoma cell invasion and migration caused by *SPC25* silencing. Interestingly, both *SPC25* and *ITGB4* knockdown result in reduced phosphorylation of FAK, Phosphoinositide 3-kinase (PI3K), and AKT, all of which play crucial roles in these processes. In lung cancer, KCNFI1, a regulator of epithelial-mesenchymal transition (EMT) and ECM-integrin interactions, positively regulates signaling downstream of ITGB4. Notably, the expression level of ITGB4 affects the phosphorylation of both FAK and AKT (32, 33).

The ITGB4/FAK signaling pathway is critical in regulating a diverse array of downstream molecules and signaling cascades associated with cancer cell metastasis. FAK activation, characterized by phosphorylation, is triggered upon cell adhesion to the extracellular matrix. This activation, in turn, initiates downstream signaling pathways intricately linked to cancer cell metastasis. Notably, the ITGB4/FAK pathway not only influences AKT phosphorylation but also modulates the activity of the FAK/AKT and PI3K/AKT signaling pathways. AKT, a central node within the PI3K/AKT pathway, exerts a profound influence on tumor cell proliferation, metastasis, invasion, and ultimately, patient prognosis (34).

ITGB4 functions as an upstream regulator of FAK, exerting a significant impact on AKT phosphorylation in non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (32, 33). Studies further suggest that ITGB4 can activate the Akt signaling pathway by triggering FAK. These downstream effects of ITGB4 appear to be mediated by factors such as ZNF306 (35).

The interplay between ITGB4 and FAK can culminate in the inactivation of Akt and p38MAPK signaling pathways. Ziyuglycoside II, the primary compound isolated from *Sanguisorba officinalis L.*, has been shown to inhibit the migration and invasion of triple-negative breast cancer (TNBC) cells. This inhibitory effect was mediated through Src/EGFR-dependent inactivation of the ITGB4/FAK signaling pathway, consequently leading to the inactivation of AKT and p38MAPK signaling pathways (36). EGFR has been found to interact with ITGB4 and influence anoikis through the ITGB4/FAK axis. By modulating the AKT pathway, this interaction plays a role in regulating cancer metastasis (28, 37, 38). Moreover, binding of PD-L1 to ITGB4 activates the AKT/GSK3 $\beta$  signaling pathway, thereby impacting the expression of the transcription inhibitor SNAIL and ultimately suppressing anti-tumor immunity (39).

EMT is a well-characterized cellular process during which epithelial cells undergo a phenotypic transformation, losing their epithelial characteristics and acquiring mesenchymal cell properties. This transition alters the adhesion molecules expressed on the cell surface, enabling cells to adopt migratory and invasive behaviors. EMT is demonstrably linked to tumor cell migration. A hallmark of EMT is the downregulation of the epithelial marker E-cadherin and the concomitant upregulation of the mesenchymal marker vimentin (40, 41). Notably, overexpression of ITGB4 has been shown to induce EMT by upregulating the transcription factor Slug. This upregulation leads to a loss of E-cadherin expression and the acquisition of a mesenchymal phenotype characterized by enhanced migratory and invasive capabilities (42). Conversely, the knockdown of ITGB4 in clear cell renal cell carcinoma (ccRCC) cells results in decreased expression of N-cadherin, vimentin, and the EMT-related transcription factor ZEB1 while simultaneously increasing E-cadherin expression (43).

Reciprocally, AKT can also function as an upstream regulator of ITGB4 expression, as evidenced by studies on NSCLC cells harboring pp53-R273H mutations. In these cells, AKT activation leads to a downregulation of ITGB4, thereby impacting their migratory and invasive phenotypes (44). This intricate interplay between ITGB4 and AKT highlights their critical roles in tumor cell migration and invasion. This interplay is further influenced by epidermal growth factor (EGF), various transcription factors, and drug monomers.

### 3 ITGB4 regulates the expression of MMPs

Matrix metalloproteinases (MMPs) are a family of proteases that play a critical role in shaping the extracellular matrix (ECM). Their expression is tightly regulated at the transcriptional level, and they are implicated in various cellular processes, including cell migration, invasion, angiogenesis, apoptosis, and inflammation (45). MMPs play a pivotal role in tumor progression, particularly in tumor migration and invasion, by facilitating the breakdown of histological barriers that normally restrict tumor cell movement. Studies have shown that nerve growth factor (NGF) promotes corneal epithelial migration by inducing the expression of MMP-9 (46). Furthermore, elevated expression of both MMP15 and ITGB4 has been observed in colorectal cancer patients following radical surgery. This finding

suggests that ITGB4 may be involved in tumor progression by regulating MMPs (47). Supporting this notion, studies in ovarian cancer cells have demonstrated a positive correlation between the expression levels of ITGB4 and MMP2, MMP7, and MMP9 (31).

The mechanisms by which ITGB4 interacts with FAK, AKT and MMP to promote tumor migration and invasion are described in Table 1

## 4 The effect of ITGB4 on the migration and invasion of different tumors

The influence of ITGB4 on tumor migration and invasion extends beyond canonical signaling pathways. For instance, ITGB4 can interact with enzymes like 12-lipoxygenase (12-LOX), impacting tumor metastasis. Stimulation of ITGB4 triggers the recruitment of 12-LOX to the cell membrane, leading to its activation and subsequent production of 12(S)-HETE. This metabolite, in turn, regulates both angiogenesis and cell migration (49).

## 5 ITGB4 regulates the migration and invasion of digestive system related tumors

The multifaceted role of ITGB4 in tumor migration and invasion is further highlighted by its diverse effects across different cancer types. In esophageal cancer, the splice variant ITGB4E exhibits an inhibitory effect on esophageal squamous cell migration, while other variants appear to promote cell migration (50). Similarly, in gastric cancer, MPS-1 plays a regulatory role in invasion and migration by influencing ITGB4 expression (51). In colorectal cancer (CRC), Transcobalamin 1 (TCN1) disrupts the cytoskeletal network through modulation of ITGB4 signaling. Notably, *TCN1* knockdown exhibits a synergistic effect with ITGB4-mediated inactivation of Ki-67 and PCNA, further promoting CRC progression (52). Another study identified the transcriptional inhibitor CBX8 as a repressor of the ITGB4 promoter. Knockdown of *CBX8* leads to derepression and increased ITGB4 protein expression. This, in turn, reduces active RhoA, leading to actin rearrangements and enhanced CRC metastasis (53). Additionally, the microRNA miR-21 has been shown to regulate the colorectal cancer invasion-metastasis cascade by targeting ITGB4 (54). The influence of ITGB4 extends to hepatocellular carcinoma as well. In this context, ITGB4 overexpression downregulates the epithelial markers E-cadherin and N-cadherin, while simultaneously upregulating vimentin, p-AKT, Slug, Sox2, and Nanog in Bel-7402 or SMMC-77721 cells. These changes collectively induce epithelial-to-mesenchymal transition (EMT), promoting hepatocellular carcinoma invasion (48). Furthermore, ITGB4 functions as a laminin receptor, regulating bile duct cancer cell migration (55). In pancreatic ductal adenocarcinoma, ITGB4 promotes vimentin expression, induces EMT, and regulates migration and invasion (56).

Netrin-1, a guidance cue molecule, exhibits anti-tumorigenic properties in pancreatic ductal adenocarcinoma. Overexpression of

TABLE 1 ITGB4 works with different molecules to regulate tumor migration and invasion.

Molecule	Model	Function of ITGB4	Machine	Phenotype	Reference
FAK/AKT	SPTBN2-knockdown A2780 cells	Reverse SPTBN2 knockout	Reverse decline in p-FAK expression	Reverse the decrease of p-FAK expression level	(31)
	A549, H23 and H2122 cells nude mouse	Downstream of KCNF1	Decreased phosphorylation of FAK	Reduce xenotransplantation in mice	(32)
	Hepatocellular carcinoma cells and tissues	Downstream of SPC25	Decreased phosphorylation of FAK/PI3K/AKT	Promotes hepatocellular carcinoma metastasis	(33)
	ccRCC tissue and cells	Enhancing the EMT process and facilitating metastasis	N6-methylamine modification of ITGB4 mRNA	Inhibit the metastasis of clear cell renal cell carcinoma	(43)
	HCC tissue and cells	ZKSCAN3 binds directly to the ITGB4 promoter	Triggers FAK to activate the AKT signaling pathway	Promotes hepatocellular carcinoma metastasis	(35)
	MDA-MB-231 cells	-	Src/EGFR effect ITGB4/FAK regulates Akt and p38MAPK pathways	Inhibition of aggressive phenotype of triple-negative breast cancer cells	(36)
	HCC tissue and cells	Increased susceptibility to anoikis	ITGB4-EGFR triggers FAK to activate the AKT signaling pathway	Promotes lung metastasis of hepatocellular carcinoma	(28)
	ESCC tissue and cells	ITGB4/FAK/Grb2 pathway	phosphorylation of FAK and AKPde	Regulation of esophageal squamous cell carcinoma metastasis	(38)
	-	ITGB4 directly bind PD-L1	Activate the AKT/GSK3β signaling pathway	Promotes lymph node metastasis of cervical cancer	(39)
	HCC tissue and cells	-	Regulates SLUG expression and AKT/Sox2-Nanog	Promotes hepatocellular cancer cell invasion and EMT	(48)
	ovarian cance cells	p53 <sup>R248</sup> induced cell adhesion	Activate the PI3K/Akt Pathway	Promote the adhesion of mesothelial cells	(42)
	H1299 cells HEK 293T cells	NEU1 silencing increases ITGB4 protein and mRNA expression	p53-R273H activates AKT signaling to promote NEU1 transcription	Promote cancer cell migration	(44)
	MMPs	Ovarian cells	Focal adhesion and ECM receptor signaling pathways mediated by SPTBN2/ITGB4	The decline in MMP2, MMP7 and MMP9 levels was reversed	Regulates the proliferation, invasion and migration of endometrial ovarian cancer cells

netrin-1 has been shown to impede the growth of pancreatic ductal adenocarcinoma cells by downregulating *ITGB4* expression. Mechanistically, netrin-1 signaling through the UNC5B/FAK axis stimulates nitric oxide production. This, in turn, promotes the PP2A-mediated inhibition of the MEK/ERK pathway, ultimately leading to a reduction in the recruitment of phosphorylated c-Jun to *ITGB4* promoters (57). The MEK/ERK pathway is a well-established signaling cascade implicated in various cellular processes, including gene expression, cell proliferation, and behaviors that influence tumor progression (58, 59). Activation of MEK rapidly triggers the phosphorylation of downstream ERK 1/2. These phosphorylated ERKs then activate transcription factors, kinases, and other signaling molecules, ultimately influencing tumor migration and invasion. Interestingly, studies have shown that phosphorylated *ITGB4* at the Y1510 site can regulate the MEK1-ERK1/2 signaling cascade. Therefore, modulation of *ITGB4* expression or its phosphorylation at Y1510 represents a potential novel therapeutic approach for pancreatic cancer (60). Furthermore, the MEK/ERK pathway can also regulate integrin  $\alpha\beta4$  expression. KRAS mutations, frequently observed in pancreatic cancer, have been shown to regulate the expression of integrin  $\alpha\beta4$  through the MEK/ERK pathway, thereby altering the migratory and invasive potential of tumor cells (61). Recepteur d'origine nantais (RON) receptor tyrosine kinases have been implicated in promoting the aggressive behavior of pancreatic cancer cells. These kinases disrupt the interaction between plectin and *ITGB4*, thereby

stimulating cell migration. This disruption of the plectin-*ITGB4* interaction is dependent on PI3K activity and RON signaling (62).

In summary, the multifaceted influence of *ITGB4* on a diverse array of downstream signaling molecules underscores its critical role in promoting tumor migration and invasion across a spectrum of cancers.

The role of *ITGB4* in digestive system tumor migration and invasion are described in Table 2.

## 6 *ITGB4* regulates the migration and invasion of breast cancer

Caveolin-1 (P132L), a frequently occurring mutation in breast cancer, has been shown to selectively enhance the expression of *ITGB4*. *ITGB4* is a well-characterized signaling molecule linked to tumor cell migration and invasion (63). Notably, overexpression of *ITGB4* in triple-negative breast cancer cells has been implicated in the transfer of *ITGB4* protein to cancer-associated fibroblasts (CAFs) via exosomes. This transfer, in turn, induces BNIP3L-dependent mitochondrial dysfunction and lactate production in CAFs. Co-culture assays revealed that the level of *ITGB4* expression directly correlated with enhanced breast cancer cell proliferation, EMT, and invasion. Conversely, the knockdown of *ITGB4* or inhibition of exosome production in MDA-MB-231 cells, or blockade of c-Jun or AMPK

TABLE 2 ITGB4 regulates the migration and invasion of digestive system related tumors.

Molecule	Model	Regulation of ITGB4	Machine	Phenotype	Reference
ITGB4E	OE21 cells	-	-	Slow down esophageal squamous cell migration	(50)
MPS-1	gastric adenocarcinoma cells	Negatively correlated with MPS-1	Changes in RNA and protein expression of ITGB4	Regulates the invasion and migration of gastric cancer cells	(51)
CBX8	CRC tissue and cells	Negatively correlated with CBX8	increase expression of the ITGB4 protein	Facilitates CRC migration, intrusion, and migration	(53)
miR-21	CRC cells	Target gene of miR-21; Regulating EMT	Regulate ITGB4 expression	miR-21 is overexpressed lines with high metastasis potential and EMT characteristics	(54)
Slug	HCC tissue and cells	-	Regulates SLug expression and AKT/Sox2-Nanog in hepatocellular carcinoma	Promotes hepatocellular cancer cell invasion and EMT	(48)
Laminin	Cholangiocarcinoma cells	As downstream signaling molecules for laminin	Affected distribution of ITGB4	Induced migration process	(55)
-	Pancreatic cancer tissue CFPAC-1 cells	Up regulating and promoting EMT	-	High expression of ITGB4	(56)
Netrin-1	AsPC-1 cells	The target of netrin-1	UNC5B/FAK stimulate nitric oxide production, to promotes PP2A-mediated inhibition of the MEK/ERK and reduces recruitment of ITGB4 promoters by phosphorylated c-Jun	Inhibit the growth of xenografted PDAC cells	(57)
RON	PDAC tissue and paracancerous tissue	-	RON binds to lectins and ITGB4, leading to disruption of lectin- ITGB4 interactions	Regulates the migration of pancreatic cancer cells	(62)

phosphorylation in CAFs, significantly suppressed ITGB4-mediated mitochondrial autophagy and glycolysis in CAFs (9). Similar to ITGB4, Rac1 functions as a key regulator of the cytoskeleton. Both proteins represent promising therapeutic targets for disrupting the ability of cancer cells to reattach and establish themselves in new locations (reconnection ability or RA). Intriguingly, sustained Rac1 activity can prevent the lysosomal degradation of  $\beta 4$  integrins, highlighting a potential mechanism for its role in cancer progression (64).

SPARC acts as a downstream effector molecule that amplifies ITGB4-mediated invasion in breast cancer. However, the miR-29a microRNA directly targets SPARC, inhibiting this invasive process. Interestingly, breast cancer cells with low ITGB4 expression exhibit a concomitant decrease in miR-29a levels (65). TMEM268 is a transmembrane protein that interacts directly with the  $\beta 4$  subunit of integrin. Knockdown of TMEM268 promotes the ubiquitin-mediated degradation of ITGB4, ultimately leading to cytoskeletal remodeling (36).

The role of ITGB4 in breast cancer migration and invasion are described in Table 3.

## 7 ITGB4 regulates the migration and invasion of prostate cancer

ITGB4 has emerged as a critical driver of metastatic tumor cell migration and invasion in prostate cancer, as evidenced by studies using DU145 cells (68). ZEB1, a well-characterized regulator of EMT, interacts with the promoters of laminin  $\alpha 2$  (LAMC2) and ITGB4, thereby influencing their expression levels (69). Interestingly, ITGB4 promoter methylation levels exhibit variation across prostate cancer cell

lines representing distinct disease stages, including local tumors, lymph node metastases, and bone metastases (70). Estrogen receptor-regulated microRNA-182-5p (miR-182-5p) has been shown to promote proliferation, invasion, migration, and inhibit apoptosis in prostate cancer cells. This oncogenic effect is mediated through ARRDC3/ITGB4 signaling (71). Parathyroid hormone-related peptide (PTHrP) also contributes to prostate cancer growth and metastasis by regulating ITGB4 levels through transcriptional and post-translational pathways, including association with the NF- $\kappa$ B signaling pathway (72).

Proteomic analysis of exosomes isolated from body fluids has revealed upregulation of *ITGB4*. This finding suggests that ITGB4 may serve as a potential biomarker for prostate cancer progression and taxane resistance. Furthermore, the knockout of *ITGB4* in PC-3R cells significantly weakened their migratory and invasive capabilities, further highlighting the crucial role of ITGB4 in these processes (73).

The role of ITGB4 in prostate cancer migration and invasion are described in Table 4.

## 8 ITGB4 regulates the migration and invasion of other tumors

Quantitative real-time PCR analysis has identified a high ITGB4/JUP ratio as a significant factor promoting distant metastasis in oral cancer (74). This finding suggests that the relative expression level of ITGB4 compared to JUP may be a valuable prognostic indicator. Vimentin, an intermediate filament protein, has been shown to play a novel role in regulating cell motility by destabilizing adhesions mediated by  $\beta 4$  integrin. Interestingly, the knockdown of vimentin in

TABLE 3 ITGB4 regulates the migration and invasion of breast cancer.

Molecule	Model	Function of ITGB4	Machine	Phenotype	Reference
Caveolin-1(P132L)	Met-1 cells WT mouse	-	Up regulated ITGB4 expression	Cell migration, invasion and metastasis increased significantly	(63)
-	-	Induce BNIP3L dependent mitochondrial and lactate production in CAFs	Overexpression of ITGB4 and provided to cancer-associated fibroblasts (CAF) through exosomes	Promote the proliferation, invasion and EMT of breast cancer cells	(9)
Rac1	-	Affect reconnection ability	Rac1 activity regulates integrin levels in mammary epithelial cells	Regulates the ability of breast cancer cells to reattach	(66)
SPARC	breast cancer cells	Inhibition of miR-29a	Regulating SPARC	Facilitated invasion	(67)
Ziyuglycoside II	MDA-MB-231 cells	-	Src/EGFR effect ITGB4/FAK regulates Akt and p38MAPK pathways	Inhibition of aggressive phenotype of triple-negative breast cancer cells	(36)

oral cancer cells enhances the mechanical binding function of ITGB4 (75). This finding suggests a potential therapeutic strategy targeting the interaction between vimentin and ITGB4 to regulate cell motility and metastasis. Micropeptides that inhibit the actin cytoskeleton (MIACs) have been demonstrated to regulate interactions between the cytoskeletal protein SEPT2 and ITGB4. By suppressing the actin cytoskeleton, MIACs ultimately inhibit tumor growth and metastasis in head and neck squamous cell carcinoma (76).

In nasopharyngeal carcinoma, latent membrane protein 2A (LMP2A) competes with tyrosine kinase (ySyk) to bind ITGB4, promoting cell migration and invasion (77). Conversely, inhibition of LMP2A expression or miR-182-5p reduction leads to decreased migration and invasion, highlighting the potential regulatory role of these factors. Moreover, a meta-analysis of ccRCC identified ITGB4 as a target gene regulated by microRNA-204 (miR-204), further emphasizing the importance of ITGB4 in the context of cancer progression (78).

ITGB4 emerges as a key player with diverse regulatory mechanisms across different cancers. In brain cancer, mutations in the isocitrate dehydrogenase 1 (IDH1) gene, particularly IDH1<sup>R132H/WT</sup>, promote cell migration and inhibit proliferation by upregulating ITGB4, suggesting altered molecular targets and pathways (79). Ovarian cancer highlights

another regulatory mechanism, where mutant p53 promotes peritoneal metastasis by upregulating ITGB4 and activating the AKT pathway to enhance adhesion between cancer cells and mesothelial cells (42). Hypochlorous acid (HOCl) affects the oxidative modification of glucose-regulated protein 78 (GRP78) and GRP78 ATPase activity to regulate autophagy. ZBM-H acts as a probe for HOCl and can bind directly to GRP78 in the presence or absence of ATP. The interaction between GRP78 and annexin A7 (ANXA7) was facilitated after the use of ZBM-H, which was accompanied by an increased phosphorylation of ITGB4, which in turn regulated lung cancer cell behavior (80). In NSCLC, ZBM-H activates GRP78 ATPase, reduces ITGB4 protein levels, inhibits A549 cell migration, and suppresses EMT processes (81).

The role of ITGB4 in other tumors migration and invasion are described in Table 5

## 9 Conclusions

ITGB4 exhibits high expression levels in numerous tumors, making it a potential tumor marker. Furthermore, methylation and genetic alterations within the *ITGB4* gene hold significant promise for

TABLE 4 ITGB4 regulates the migration and invasion of prostate cancer.

Molecule	Model	Function of ITGB4	Machine	Phenotype	Reference
-	DU145 cells nude mouse	Increased protein expression	Up regulated LAMC2 and ITGB4 mRNA and protein	The migration and invasion of metastatic DU145-LN cells increased	(68)
ZEB1	TEM4-18 cells	-	coordinately regulates laminin-332 and ITGB4 expression	Changes the invasive phenotype of prostate cancer cells	(69)
-	PC-3 cells LNCaP cells 22Rv1 cells	Differential methylation of different regions of the promoter	-	Different methylation regions represent different transfer modes	(70)
miR-182-5p	Prostate cancer tissue cells C4-2 cells PC-3 cells	-	miR-182-5p promotes PCa by affecting ITGB4 expression through ARRDC3	Promote the proliferation, invasion and migration of prostate cancer cells, and inhibit apoptosis	(71)
PTHrP	-	Positively correlated with PTHrP	PTHrP regulates the expression level of ITGB4	Enhance CaP growth and metastasis <i>in vivo</i>	(72)
-	PC-3R cells	-	ITGB4 and vinculin (VCL) in exosomes are upregulated	Regulates migration and invasion of PC-3R cells	(73)

TABLE 5 ITGB4 regulates the migration and invasion of other tumors.

Molecule	Model	Function of ITGB4	Machine	Phenotype	Reference
-	Oral squamous cell carcinoma	A high ITGB4/JUP ratio was found to be a major factor in distant metastasis	-	Risk for local and blood-borne transmission of oral squamous cell carcinoma	(74)
vimentin	AW13516 cells	Linking vimentin intermediate filament proteins	Destabilize ITGB4 mediated binder interactions	Regulates cell adhesion	(75)
MIAC	CAL27cells nude mouse	-	MIAC interacts directly with AQP2, regulating SEPT2/ITGB4	Inhibit tumor growth and metastasis to inhibit actin cytoskeleton	(76)
LMP2A	-	LMP2A competes with tyrosine kinase to bind ITGB4	Syk interacts with ITGB4	Enhanced cell migration and invasion	(77)
-	ccRCC and paracancerous tissue	regulated by has-miR-204	-	Correlated with focal adhesion of ccRCC	(78)
IDH1 <sup>R132H/WT</sup>	SVG-10B1cells U87 cells U373cells	Up regulation	-	Promote cell migration	(79)
p53 <sup>R248</sup>	ovarian cancer cells	Participating in p53 <sup>R248</sup> induced cell adhesion	Activate the PI3K/Akt pathway	Promote the adhesion of ovarian cancer cells to mesothelial cells	(42)
ZBM-H	A549 cells	ITGB4 phosphorylation	increased phosphorylation of ITGB4	-	(80)
GRP78 ATPase	A549 cells	To regulate the selective autophagy and degradation of ITGB4	Reduces ITGB4 protein levels in cells. Induce autophagy to negatively regulate ITGB4 protein levels	Regulating cell migration	(81)

The mechanism of ITGB4 in tumor migration and invasion are described in Figure 1.

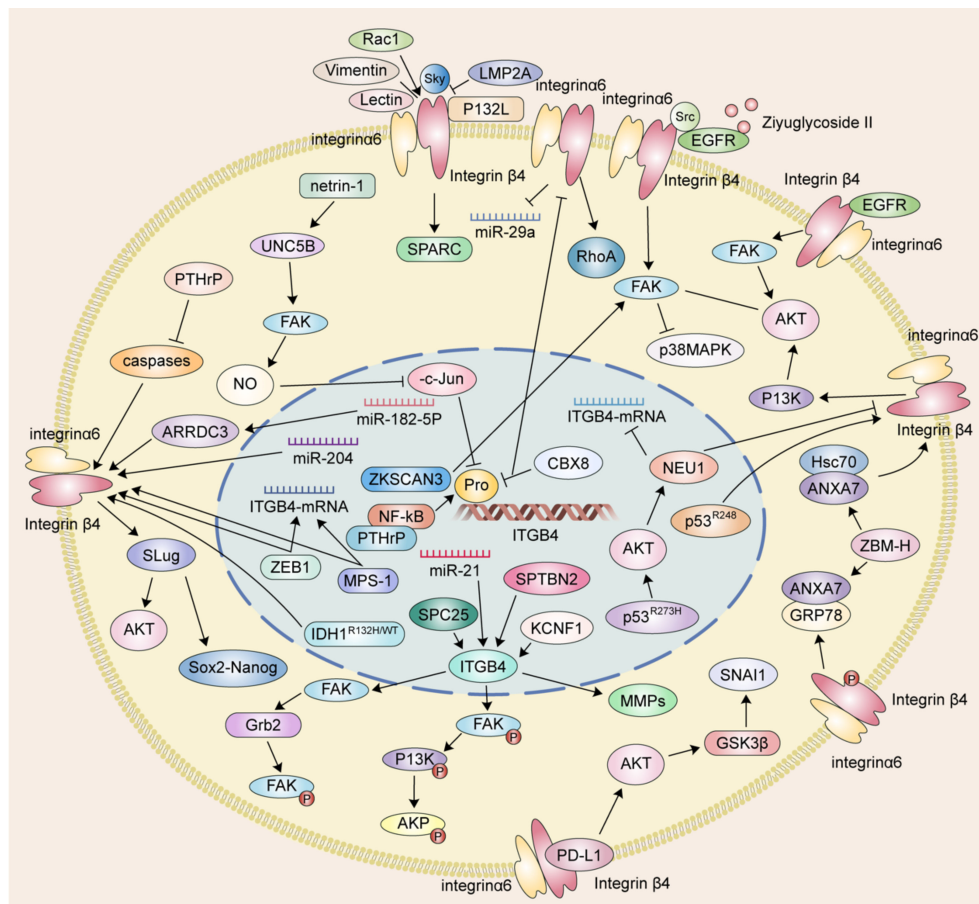


FIGURE 1 The mechanism of ITGB4 in tumor migration and invasion.

tumor diagnosis and treatment development (19, 82). Notably, the function of ITGB4 varies across different tumor types. In hepatocellular carcinoma and prostate cancer, ITGB4 expression is associated with tumor-associated fibroblasts. Conversely, in breast and lung cancers, ITGB4 correlates with the level of immune cell infiltration, suggesting potential roles in NA metabolism and protein processing within its functional mechanism (83). In gliomas, ITGB4 demonstrates high expression and serves as a reliable prognostic indicator for low-grade tumors, as confirmed by both bioinformatic analysis and tissue sample comparison (84). Integrins play a critical role in regulating various hallmarks of cancer, including tumor metastasis, immune evasion, and metabolic reprogramming. This has led to the exploration of integrin-targeted immunotherapy and other integrin inhibitors in preclinical and clinical studies (85). Interestingly, recent research suggests that ITGB4 may serve as a targeted immune site for CSCs (86). Furthermore, studies have revealed a novel signaling pathway in TNBC. TNFAIP2 promotes the proliferation and migration of TNBC cells by activating RAC1. ITGB4, through TNFAIP2 and IQGAP1, further activates RAC1, conferring resistance to DNA damage-induced cell death in TNBC. This ITGB4/TNFAIP2/IQGAP1/RAC1 signaling axis presents a potential therapeutic target to overcome DNA damage resistance in TNBC (87).

While research has confirmed the differential expression of upstream and downstream molecular pathways associated with ITGB4, a significant knowledge gap remains regarding its role in tumor biology, particularly its function as a cell adhesion molecule. Further studies are warranted to elucidate the precise molecular mechanisms by which ITGB4, a critical molecule in tumor progression and a potential target for therapeutic intervention, contributes to tumor development and metastasis.

## Author contributions

GH: Conceptualization, Writing – original draft, Writing – review & editing. MZ: Conceptualization, Writing – original draft, Writing – review & editing. DL: Conceptualization, Writing – original draft,

Writing – review & editing. JL: Data curation, Formal analysis, Writing – original draft. QT: Data curation, Formal analysis, Writing – original draft. CX: Data curation, Formal analysis, Writing – original draft. FL: Supervision, Writing – original draft, Writing – review & editing. RC: Supervision, Writing – original draft, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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