Am J Cancer Res 2026;16(2):388-401
www.ajcr.us /ISSN:2156-6976/ajcr0171090

Review Article

Integrin α5β1 in head and neck squamous cell carcinoma: expression, mechanisms, and clinical implications

Bo Wu[1*], Hong-Zhi Ma[2*], Jun-Jun Shang[1], Xue-Ying Zhao[1], Zheng-Yang Wang[1], Li-Li Qiu[1]

[1]Health College, Binzhou Polytechnic, No. 919, Huanghe 12th Road, Bincheng District, Binzhou 256603, Shandong, P. R. China; [2]Second Department of Head and Neck Radiation Oncology, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University/Hunan Cancer Hospital, No. 283 Tongzipo Road, Yuelu District, Changsha 410013, Hunan, P. R. China. [*]Equal contributors.

Received December 28, 2025; Accepted January 25, 2026; Epub February 15, 2026; Published February 28, 2026

Abstract: Head and neck squamous cell carcinoma (HNSCC) represents a significant global health challenge associated with high mortality. A major obstacle in its management is therapeutic resistance, which limits the efficacy of existing treatment modalities. Altered expression of integrins, a family of cell adhesion receptors, has been shown to influence tumor proliferation, migration, and invasion. Among them, integrin α5β1, a member of the RGD (Arg-Gly-Asp)-recognizing integrin subfamily, has emerged as a potentially critical mediator of HNSCC progression and therapeutic resistance, according to a growing body of research. In this review, we assess the evidence regarding the aberrant expression of integrin α5β1 in HNSCC, with a particular focus on common subtypes such as oral squamous cell carcinoma (OSCC), nasopharyngeal carcinoma (NPC), and laryngeal squamous cell carcinoma (LSCC). We then summarize its potential value as a diagnostic and prognostic marker. Furthermore, we discuss the molecular mechanisms that regulate integrin α5β1 and its downstream signaling, especially in the context of therapy resistance. Finally, we outline the potential clinical applications and future research directions related to targeting integrin α5β1. Collectively, this paper aims to synthesize the current knowledge of integrin α5β1 in HNSCC, providing a foundation for the development of personalized, tumor-specific diagnostic tools and targeted therapies.

Keywords: Integrin α5β1, head and neck squamous cell carcinoma, prognostic indicator, therapy resistance, target

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a serious global health issue. According to recent estimates from GLOBOCAN, HNSCC accounts for approximately 890,000 new cases and 450,000 deaths annually [1]. This malignancy arises from the squamous epithelium of the upper aerodigestive tract and includes several subtypes based on anatomical location, the most prevalent of which are oral squamous cell carcinoma (OSCC), nasopharyngeal carcinoma (NPC), and laryngeal squamous cell carcinoma (LSCC). Due to the aggressive nature of HNSCC, a significant number of patients present with locally advanced or metastatic disease at diagnosis [2]. The standard management for HNSCC typically involves a combination of surgery, radiotherapy, chemotherapy, immunotherapy, and targeted therapy. However, treatment outcomes are often compromised by both the aggressive clinical course and the development of therapeutic resistance. Consequently, the five-year overall survival rate for patients with advanced-stage disease remains below 50%. This clinical challenge underscores the urgent need for novel biomarkers and therapeutic targets.

Integrins are a family of transmembrane receptors that play important roles in oncogenesis and cancer progression [3]. Although several integrins (e.g., αvβ3, αvβ5, αvβ8) have been implicated in HNSCC, emerging evidence suggests that integrin α5β1, in particular, shows a consistent association with advanced tumor stage and unfavorable clinical outcomes [4, 5]. Furthermore, studies indicate that integrin α5β1 may promote epithelial-mesenchymal transition (EMT), tumor invasion, and therapeu-

tic resistance [6, 7]. As a transmembrane protein, integrin α5β1 primarily binds to fibronectin in the extracellular matrix (ECM) through its recognition of the RGD (Arg-Gly-Asp) motif. This interaction can trigger downstream signaling cascades, including the focal adhesion kinase (FAK), Src, and PI3K/Akt pathways. In addition to its canonical RGD-dependent interactions, integrin α5β1 can also bind other extracellular ligands through non-RGD-dependent mechanisms. This dual binding capability distinguishes it from some other integrins and may contribute to its diverse functions in HNSCC.

In this review, we first outline the structure, ligands, and biological functions of integrin α5β1. We then examine its aberrant expression in HNSCC and its relevance to prognosis. Moreover, we discuss the regulatory mechanisms governing integrin α5β1 function. Finally, we summarize its potential clinical applications and current limitations. This review aims to establish a conceptual framework that supports future investigations and the therapeutic exploration of integrin α5β1 in HNSCC.

Overview of integrin α5β1

Integrin α5β1 is a member of the RGD-recognizing integrin subfamily, a class of heterodimeric transmembrane receptors. It is composed of an α5 (CD49e) subunit and a β1 (CD29) subunit, which are encoded by the ITGA5 (chromosome 12q11) and ITGB1 (chromosome 10p11.2) genes, respectively. Both gene loci are highly conserved across vertebrates. The structure of the α5β1 heterodimer consists of a β-propeller domain in the α5 subunit that binds non-covalently to the βI domain of the β1 subunit in a Ca^{2+}-dependent manner. The extracellular portion of the receptor contains multiple domains, including the thigh and β-propeller domains of α5 and the PSI, hybrid, βI, and EGF-like domains of β1, which collectively mediate ligand binding [8]. The cytoplasmic tails of both subunits connect to the intracellular cytoskeleton and various signaling molecules, such as focal adhesion kinase (FAK) and Src kinases, enabling bidirectional signal transduction. The binding of ligands to integrin α5β1 is critically dependent on metal ions. For instance, the Asp154 residue in the α5 subunit has a specific affinity for Ca^{2+}, which helps stabilize the metal ion-dependent adhesion site (MIDAS) in the βI domain. Ions such as Mg^{2+} and Mn^{2+} can also synergistically regulate the conformational state of integrin α5β1, thereby modulating its affinity for ligands.

Integrin α5β1 is best known as a classical receptor for proteins containing the RGD motif, with fibronectin being its primary ligand. The RGD-dependent binding of other proteins, such as fibrinogen, to α5β1 can be enhanced under Mn^{2+}-rich conditions, highlighting the conserved role of the RGD motif in this interaction [9]. While these fundamental mechanisms are broadly applicable, their relevance to the HNSCC tumor microenvironment (TME) is an area of active investigation. For example, in some cancer models, FAP^{+} cancer-associated fibroblasts (CAFs) have been shown to secrete fibronectin 1, which binds to integrin α5β1 on macrophages, activating the FAK-AKT-STAT3 pathway and promoting an M2-like immunosuppressive polarization [10]. Although not yet demonstrated directly in HNSCC, such a mechanism could potentially contribute to the immune-evasive TME characteristic of this disease. Beyond matrix proteins, the urokinase receptor (uPAR) can form a ternary complex with its ligand uPA and integrin α5β1, which has been reported to activate ERK/MAPK signaling and influence the balance between tumor dormancy and proliferation in various cancer types [11, 12]. The function of integrin α5β1 is also subject to negative regulation. For instance, Fbln7-C can bind to activated integrin α5β1 and displace the ligand from its binding site, leading to receptor inactivation [13]. Additionally, the metalloproteinase ADAM17 can form a cis-association with integrin α5β1, which is enhanced by the tetraspanin CD9, to maintain the integrin in an inactive state and suppress its-mediated cell adhesion and exosome uptake [14, 15].

In addition to the canonical RGD-dependent interactions, a range of non-RGD-dependent ligands for integrin α5β1 have been identified, primarily in non-HNSCC contexts. These interactions, while not yet fully characterized in HNSCC, suggest additional layers of functional complexity that may be relevant. For example, soluble VEGFR-1 has been shown to promote the adhesion and chemotaxis of endothelial and tumor cells by binding to integrin α5β1 [16]. The EC2 domains of tetraspanins can bind to an allosteric site on integrin α5β1, dis-

Table 1. Ligands and functions of integrin α5β1 in pan-cancer

Category	Ligand	Binding Motif	Functions	Ref.
ECM Proteins	Fibrinogen	RGD	Regulating cell adhesion and migration	[8, 9]
	Fibronectin	RGD	Triggering FAK-AKT-STAT3 signaling and facilitating cell invasion and metastasis	[10, 20]
	Tenascin-C	Non-RGD	Inhibiting cytoskeletal remodeling	[21]
Cell Surface Receptors	uPAR	RGD	Inducing cell adhesion, migration, and intracellular signaling	[11, 12]
	CD44	Non-RGD	Regulating cell adhesion	[22]
	CD9, CD81, and CD151	Non-RGD	Regulating cell adhesion	[17]
	CD154	Non-RGD	Stimulating intracellular signaling and promoting survival of malignant T cells	[18, 23]
Secreted Factors	VEGFR-1	Non-RGD	Stimulating cell adhesion and chemotaxis	[16]
	ANGPT2	Non-RGD	Mediating vascular remodeling and tumor metastasis	[24]
	IGFBP2	Non-RGD	Regulating cell adhesion and migration	[25]
Enzymes/Proteases	ADAM17	RGD	Regulating cell adhesion and mediating the binding and uptake of exosomes	[14, 15]
TGFβ Superfamily	TβRIII	Non-RGD	Regulating integrin α5β1 localization and cell adhesion	[26]
Other ECM Modulators	Fbln7-C	RGD	Regulating cell adhesion and immunological function	[13]

tinct from the RGD-binding site, to modulate its activation [17]. Furthermore, studies using Jurkat T-cell models have demonstrated that soluble CD154 can bind to integrin α5β1, leading to the activation of PI3K/Akt and MAPK signaling pathways and subsequent inhibition of Fas-mediated apoptosis [18, 19]. While these findings originate from immune cell models, they raise the possibility that similar non-canonical interactions could influence the survival and behavior of tumor or immune cells within the HNSCC microenvironment. A summary of key ligands and their functions, derived from pan-cancer studies, is provided in **Table 1**.

Integrin α5β1 in HNSCC

Expression and potential prognostic significance

The aberrant expression of integrin α5β1 has been associated with poor prognosis in HNSCC, although much of the current evidence is derived from transcriptomic analyses and preclinical models rather than prospective clinical validation. In a systematic review of 63 HNSCC transcriptomic studies, the integrin signaling pathway was identified as highly enriched, with ITGA5 emerging as a potential hub gene [27]. Bioinformatic analysis of RNA-seq data also indicated that ITGA5 is highly expressed in HPV-positive HNSCC [28]. A study by Feng et al. conducted a comparative analysis of several integrin subunits in HNSCC, revealing that among ITGA3, ITGA5, and ITGA6, higher expression of ITGA5 showed the strongest correlation with poor clinical outcomes, particularly in patients with advanced-stage tumors [4]. Consistent with these findings, ITGA5 has been incorporated as a component of various multigene prognostic models, such as the neural-related gene risk score (NRGRS), where a higher score is often associated with worse prognosis [29-33].

Similarly, elevated expression of the β1 subunit (ITGB1) has been significantly associated with a high T classification and poor prognosis in some HNSCC cohorts [34, 35]. However, it is important to interpret these findings with caution. The β1 subunit is a promiscuous pairing partner, forming heterodimers with at least twelve different α subunits. Therefore, the prognostic significance of ITGB1 expression may reflect the combined effects of multiple β1-containing integrins (e.g., α3β1, α6β1) and not exclusively the α5β1 heterodimer. Distinguishing the specific contribution of the α5β1 pair

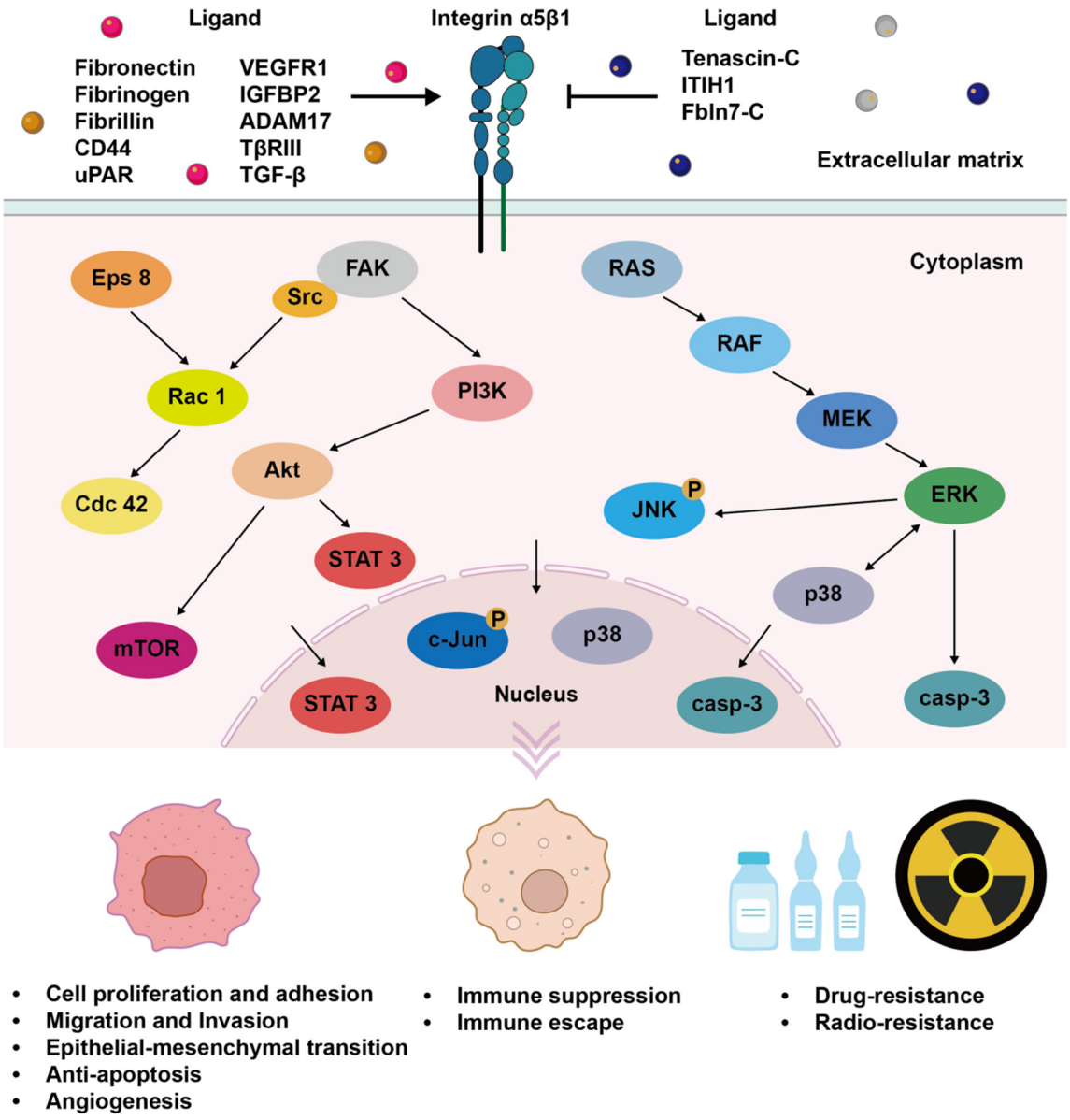

Figure 1. Integrin α5β1-mediated signaling network driving tumor progression and therapeutic resistance. Integrin α5β1 binds to ligands such as fibronectin (FN1) and fibrinogen, activating key signaling pathways including FAK/PI3K/Akt, MAPK/ERK, and mTOR, thereby driving tumor phenotypes and therapy resistance.

from other β1-family integrins remains a key challenge and requires further investigation. Therefore, further analysis is needed to explore the impact of integrin α5β1 on tumor phenotypes and its underlying regulatory mechanisms.

Integrin α5β1-mediated tumor phenotypes and associated molecular mechanisms

Integrin α5β1 appears to regulate multiple tumor-associated phenotypes in HNSCC by interacting with various receptors and modulating downstream signaling pathways (**Figure 1**). For instance, the urokinase plasminogen activator (uPA) system, which has been linked to tumor progression, includes ITGA5 as a significantly associated gene, and its activity has been shown to promote proliferation, migration, and EMT in HNSCC cells [36]. The RAP1/RAC1 signaling axis, which is involved in regulating the balance between cell-matrix adhesion and migration, has also been shown to function downstream of integrin α5β1 [37]. In

one study, the oncoprotein ACTN1 was found to interact with ITGA5, and this interaction was associated with enhanced proliferative, invasive, and migratory abilities of HNSCC cells; the effects of ACTN1 depletion were reportedly rescued by ITGA5 overexpression in vitro and in vivo [38]. Furthermore, adipocytes have been suggested to enhance resistance to anoikis - a form of programmed cell death - through the overexpression of ITGA5 in HNSCC cells [39].

Several downstream signaling pathways have been implicated in these integrin α5β1-mediated phenotypes. Hypoxia-induced upregulation of TNS4 has been reported to stabilize the integrin α5β1 complex, which in turn leads to FAK phosphorylation and subsequent enhancement of PI3K/Akt and TGF-β signaling [40]. Similarly, the interaction between collagen I and integrin α5β1 has been shown to activate PI3K signaling, thereby suppressing apoptosis and promoting the survival of HNSCC cells under therapeutic stress [41]. The long noncoding RNA LNCOG has also been suggested to promote HNSCC progression by upregulating ITGA5 expression and enhancing ITGA5-mediated FAK/PI3K signaling [42]. In addition to FAK-dependent pathways, integrin α5β1 can interact with uPAR to regulate the ERK/p38 MAPK balance, which may influence the switch between tumor dormancy and proliferation [11]. Collectively, these studies suggest that integrin α5β1 may exert its oncogenic effects through the FAK-dependent activation of multiple downstream pathways, including PI3K/Akt, ERK/MAPK, and TGF-β signaling. However, the precise mechanisms and their context-dependency in HNSCC require further elucidation.

Role in oral squamous cell carcinoma (OSCC)

In OSCC, aberrant expression of integrin α5β1 has been linked to aggressive tumor behavior and poor outcomes. Studies have reported that ITGA5 is highly expressed in OSCC tissues and in cell lines such as HO1-N-1 and SCC-9 [43]. In some patient cohorts, elevated ITGA5 expression levels have been associated with reduced overall survival [44]. Similarly, ITGB1 expression has been reported to be significantly elevated in primary tumors and metastatic lesions compared to normal oral mucosa [45, 46], and its expression has been positively correlated with advanced clinical stage [47]. A systematic review and meta-analysis also suggested that ITGB1 expression is upregulated in oral submucous fibrosis that progresses to OSCC [48]. However, it is crucial to note that because the β1 subunit can form heterodimers with multiple α subunits, the observed correlations between ITGB1 expression and clinical parameters may not be exclusively attributable to the α5β1 integrin and could reflect the broader activity of the β1 integrin family.

Integrin α5β1 has been implicated in several malignant phenotypes of OSCC, including migration, invasion, and EMT. For example, Rac1 activation, which promotes cell migration and invasion, has been shown to be dependent on both integrin α5β1 and αvβ6 in OSCC cells [49]. The process of EMT, a key driver of tumor progression, appears to be a recurrent theme in studies involving integrin α5β1. ITGA5 has been identified as a gene potentially involved in the malignant transformation of oral submucous fibrosis to OSCC, partly through the regulation of EMT [50]. In established OSCC, ITGA5 has also been suggested to promote cell proliferation, migration, and invasion, with associated changes in EMT markers [44]. Rather than a simple linear process, these findings suggest a complex interplay where integrin α5β1 signaling, in response to cues from the tumor microenvironment, contributes to the dynamic cellular changes characteristic of EMT. This is further supported by findings that the RUNX1/miR-429 feedback loop may drive tumor growth and metastasis by targeting ITGB1 and inducing EMT [51].

Mechanistically, these effects appear to be mediated through the activation of downstream signaling cascades. Inhibition of ITGA5 or ITGB1 has been shown to decrease the phosphorylation of key signaling nodes such as FAK, ERK, and MAPK [52]. Specifically, knockdown of ITGA5 has been reported to inhibit the phosphorylation of PI3K, AKT, and ERK [43], as well as c-Jun N-terminal kinase (JNK) [53]. Similarly, PLOD2-mediated activation of ITGB1 was shown to stimulate FAK and Src phosphorylation, leading to increased cell invasion and metastasis [54]. These studies collectively highlight integrin α5β1 as a potential signaling hub in OSCC.

Role in nasopharyngeal carcinoma (NPC)

In NPC, studies have reported the overexpression of both ITGA5 and ITGB1 in tumor tissues and cell lines compared to non-malignant controls, as determined by RNA-seq, RT-qPCR, and immunohistochemistry [55]. However, direct clinical studies correlating the expression of the α5β1 heterodimer with patient prognosis in NPC are currently lacking.

Integrin α5β1 has been shown to mediate various malignant phenotypes in NPC cell models. As a primary fibronectin receptor, it is involved in cell migration and adhesion [56, 57]. Fibronectin-induced migration of NPC cells has been linked to integrin α5β1-mediated Src-Rac1/Cdc42 stimulation, while its effect on proliferation has been associated with HIF-1α/TGF-β1-Akt signaling [58]. Extracellular vesicles modified by the Epstein-Barr virus (EBV) oncoprotein LMP1 have been reported to increase the expression of integrin α5β1 in recipient cells, thereby stimulating adhesion, migration, and invasion through ECM remodeling [59].

The regulation of EMT in NPC has also been linked to integrin α5β1. One study suggested that miR-9-3p acts as an upstream negative regulator, and that integrin α5β1 is a direct modulator of cadherin switching (repressing E-cadherin and inducing N-cadherin) and vimentin upregulation [60]. Other work has shown that inhibition of FN1, ITGA5, and ITGB1 expression suppresses EMT-like changes [61]. Furthermore, the transcription factor E2F7, in collaboration with RUNX1, was found to transactivate ITGA2, ITGA5, and NTRK1, subsequently amplifying Akt signaling [62]. Overall, while these preclinical studies provide a foundation, the regulatory mechanisms and clinical significance of integrin α5β1 in NPC remain insufficiently studied.

Role in laryngeal squamous cell carcinoma (LSCC)

In LSCC, integrin α5β1 has been investigated as a potential regulator of tumor progression and microenvironment remodeling. ITGA5 has been found to be significantly overexpressed in LSCC tissues compared to normal laryngeal tissues at both the mRNA and protein levels [63, 64]. High ITGA5 expression has also been correlated with advanced T stage, lymph node metastasis, and poor prognosis in some patient cohorts. Mechanistically, it has been suggested that ITGA5 promotes LSCC progression through the mTORC1-EFNB2 axis and may also regulate VEGF-C secretion to enhance lymphangiogenesis and metastasis [64, 65].

Expression of ITGB1 has also been reported to be significantly upregulated in LSCC tissues [66]. However, as with other HNSCC subtypes, the specific contribution of the α5β1 pair versus other β1-containing integrins is often not delineated. For example, the MIF-CD44-ITGB1 axis has been implicated in promoting metastasis through mechanotransduction-dependent activation of pro-invasive pathways (e.g., FAK/Src and ERK), in coordination with ladinin-1-mediated basement membrane remodeling [67]. Similarly, the laminin 5 γ2 chain has been suggested to promote tumor aggressiveness by enhancing ITGB1-mediated cell-matrix adhesion and downstream FAK/Src signaling [68]. These findings indicate that signaling axes involving the β1 integrin subunit are important in LSCC, but further research is needed to clarify the specific roles of the α5β1 heterodimer in these processes.

Association of integrin α5β1 with therapeutic resistance

Emerging evidence suggests that integrin α5β1 may play a significant role in the resistance of HNSCC to various therapies, including chemotherapy, radiotherapy, and immunotherapy. However, the current body of research is characterized by considerable heterogeneity in experimental models and endpoints, which warrants a critical interpretation of the findings.

Chemotherapy

Cisplatin and taxanes are cornerstone chemotherapeutic agents for HNSCC. Several preclinical studies have implicated integrin α5β1 in resistance to these drugs (**Table 2**). For instance, genetic knockout of ITGA5 was reported to sensitize LSCC cells to cisplatin in both in vitro and in vivo models [65]. In a three-dimensional (3D) spheroid model of NPC, resistance to cisplatin was associated with altered oligosaccharide modifications of integrin α5β1, and a neutralizing antibody against

Table 2. Integrin α5β1-mediated chemoresistance in head and neck squamous cell carcinoma

Drug	Study material	Study level	Resistance mechanism	Key findings	Ref.
Cisplatin	LIU-LSC-1, CDX, PDX, and, 94 LSCC samples	Cell, xenograft, and clinical cohort	ITGA5 driven mTORC1-mediated progression via upregulation of EFNB2	Genetic knockout of ITGA5 sensitized tumors to cisplatin in vitro and in vivo	[65]
Cisplatin	5-8F and 6-10B	Cell	ITGA5 mediated inhibition of ERK phosphorylation and caspase 3 activation	Integrin α5 inhibits apoptosis and mediates intrinsic cisplatin resistance	[69]
Cisplatin	HSC 2 and HSC 2 CR	Cell	Altered oligosaccharide modification of integrin α5β1 enhances adhesion mediated survival signaling	Neutralizing antibody against integrin α5β1 abolished the difference in cisplatin sensitivity between sensitive and resistant cells	[70]
Paclitaxel	MD 1483	Cell	Collagen I binding to integrin α5β1 activates PI3K signaling	Collagen I conferred a survival advantage under chemotherapeutic stress	[41]
Paclitaxel	SUNE-1-Taxol and C666-1-Taxol	Cell	miR 29c downregulation leads to ITGB1 upregulation	Restoration of miR 29c or knockdown of ITGB1 resensitized cells to Taxol	[71]
Docetaxel	56 HNSCC PDCs, 18 immortalized cell lines, 43 PDXs, and 77 OSCC samples	Cell, xenograft, and clinical cohort	High ITGB1 expression drives docetaxel resistance through reduced microtubule engagement	ITGB1 promoted docetaxel resistance in vitro and in PDX models and predicted poor clinical response in a phase 2 trial	[73]
Docetaxel	224 high-risk OSCC patients receiving postoperative chemoradiotherapy	Clinical trial	/	High ITGB1 expression may predict docetaxel resistance	[72]

CDX, cell line-derived xenograft; LSCC, laryngeal squamous cell carcinoma; OSCC, oral squamous cell carcinoma; PDC, patient-derived cell; PDX, patient-derived xenograft.

the receptor reportedly eliminated the sensitivity difference between cisplatin-sensitive and -resistant cells [69, 70]. Similarly, adhesion to ECM components like fibronectin and collagen I, mediated by integrin α5β1, has been shown to confer resistance to paclitaxel by activating PI3K survival signaling [41]. In taxol-resistant NPC cell lines, downregulation of miR-29c was linked to the upregulation of ITGB1, and restoring miR-29c expression or knocking down ITGB1 reportedly restored sensitivity to the drug [71].

While these studies are informative, it is important to critically assess the discrepancies among them. The summarized findings in **Table 2** originate from diverse experimental systems (e.g., 2D monolayer cultures, 3D spheroids, patient-derived xenografts), utilize different definitions of resistance, and measure varied endpoints. The discussion of these mechanisms often remains descriptive, without sufficient analysis of the underlying reasons for this heterogeneity. For example, the specific ECM components present in a 3D model or an in vivo TME provide a context for integrin-mediated survival signaling that is absent in traditional 2D cultures on plastic. The differences in drug mechanisms - DNA damage from cisplatin versus microtubule stabilization from taxanes - likely engage distinct cellular stress responses and, consequently, different integrin-dependent resistance pathways. Thus, rather than viewing integrin α5β1 as a universal driver of chemoresistance, it is more accurate to consider it a context-dependent modulator whose role is influenced by the specific drug, the cellular model, and the composition of the surrounding ECM. Notably, a randomized phase 2 trial involving OSCC patients provided some clinical evidence, suggesting that high ITGB1 expression may predict resistance to docetaxel-based adjuvant chemoradiotherapy, although this finding requires further validation [72].

Radiotherapy, targeted therapy, and immunotherapy

Fewer studies have explored the role of integrin α5β1 in resistance to other therapeutic modalities. Transcriptomic analyses have associated high ITGB1 expression with poor radiotherapeutic outcomes in HNSCC patients [74].

In 3D NPC models, ITGB1 expression was positively associated with radioresistance, and its knockdown was suggested to improve radiosensitivity, potentially via the ECM/ITGB1/FERMT1/Wnt axis [75-77].

Regarding targeted therapy, one study correlated high ITGA5 expression with resistance to PI3K/Akt inhibitors [78]. In the context of immunotherapy, the evidence is almost exclusively based on bioinformatic correlation analyses of bulk tumor transcriptomes. These analyses have suggested that ITGA5 expression is positively associated with the infiltration of certain immune cells (e.g., neutrophils, macrophages) and negatively associated with others (e.g., $CD8^+$ T cells, B cells) [28]. Furthermore, prognostic models incorporating ITGA5 have linked high-risk scores with an immunosuppressive TME and a potentially compromised response to immunotherapy [79, 80].

These findings, while intriguing, must be interpreted with significant caution. A major limitation is that bulk transcriptomic data does not distinguish between the cellular source of ITGA5 expression. Integrin α5β1 is expressed not only by tumor cells but also by stromal cells (e.g., fibroblasts) and various immune cells, where it can have distinct functions. For example, α5β1 on a T cell may mediate its trafficking and activation, while on a tumor cell, it may promote invasion and survival. Therefore, broadly concluding that high ITGA5 expression is linked to an immunosuppressive TME is an oversimplification. Future studies using single-cell spatial transcriptomics are needed to deconvolve the cell-type-specific roles of integrin α5β1 in the HNSCC immune microenvironment and to validate these correlational findings.

Therapeutic targeting of integrin α5β1

Given its association with tumor progression and therapy resistance, integrin α5β1 represents a promising therapeutic target in HNSCC [81]. Several preclinical strategies are being explored to inhibit its function. For example, K34c, an antagonist of integrin α5β1, was reported to suppress both primary tumor growth and metastasis in a model of Cav1-negative HNSCC [82]. Similarly, ATN-161, a peptide inhibitor of integrin α5β1, was shown to enhance the sensitivity of NPC cells to cisplatin [69]. Targeting the β1 subunit with the antibody AIIB2 reportedly sensitized HNSCC cells to ionizing radiation in both 3D cell culture and xenograft models [83].

In addition to direct inhibition, indirect modulation of integrin α5β1 expression and signaling is also being investigated. The CBP/β-catenin Wnt antagonist ICG-001 was found to induce the overexpression of miR-134, which in turn targets ITGB1, thereby inhibiting lung metastasis of NPC cells [84]. The tumor suppressor gene CHL1 has been shown to competitively bind to ITGB1, disrupting the ITGB1-Merlin interaction, inhibiting PI3K/Akt signaling, and inducing a mesenchymal-to-epithelial transition (MET) [85].

Furthermore, the development of nano-delivery systems that specifically target integrin α5β1 offers a promising avenue for enhancing therapeutic efficacy and reducing off-target toxicity [86, 87]. One study developed a TME-responsive nanocarrier system designed to target integrin α5β1 for the delivery of doxorubicin, reporting enhanced antitumor efficacy both in vivo and in vitro [88]. While most of these advanced nano-delivery platforms are being developed in the context of other tumor types, the principles are broadly applicable [89-91]. These systems hold significant potential for translation to HNSCC for both targeted therapy and molecular imaging. However, it is important to note that these approaches remain in the preclinical stage of development, and no specific drugs targeting integrin α5β1 have yet been approved for clinical use in HNSCC.

Limitations of current research

While significant progress has been made in understanding the role of integrin α5β1 in HNSCC, the current body of research has several important limitations that must be acknowledged. A primary limitation is the heavy reliance on preclinical models, correlational studies, and retrospective analyses. Many of the strong mechanistic conclusions suggested in the literature are derived from in vitro cell culture systems or bioinformatic analyses of bulk tumor tissue, which may not accurately reflect the complex biology of human tumors. There is a notable scarcity of prospective clinical studies designed to validate the prognostic and predictive significance of integrin α5β1 expression in HNSCC patients.

Second, a recurring issue is the lack of specificity in attributing functional roles to the α5β1 heterodimer. The β1 subunit is shared among numerous integrin receptors, and many studies measure the expression or function of ITGB1 without adequately distinguishing the specific contribution of the α5 subunit. This makes it difficult to ascertain whether the observed effects are unique to α5β1 or are a more general consequence of β1-integrin signaling. Future studies employing more specific tools, such as α5-subunit-blocking antibodies or genetic knockouts, are required to dissect its precise role.

Third, the relevance of many mechanistic findings to the specific context of HNSCC is not always clear. A considerable portion of the literature on integrin α5β1 ligands and signaling pathways is derived from pan-cancer or non-cancer models. The extent to which these mechanisms can be extrapolated to the unique tumor microenvironment of HNSCC subtypes (OSCC, NPC, LSCC) has not been systematically addressed.

Finally, with regard to immunotherapy, conclusions are almost entirely based on computational analyses of bulk transcriptomic data. These studies are unable to resolve the cell-type-specific expression and function of integrin α5β1, which is critical for understanding its role in modulating the immune response. Acknowledging these limitations is crucial for guiding future research and for maintaining a critical perspective on the potential clinical translation of targeting integrin α5β1.

Conclusion

In conclusion, integrin α5β1 is increasingly recognized as a significant factor in the pathobiology of HNSCC. The available evidence, though largely preclinical, suggests that its aberrant expression is associated with aggressive tumor phenotypes, poor clinical outcomes, and resistance to conventional therapies. It appears to exert its influence by modulating key signaling pathways, including the FAK/PI3K/Akt and ERK/MAPK axes, thereby promoting cell proliferation, survival, invasion, and EMT. The potential to target integrin α5β1 directly with inhibitors or indirectly through nano-delivery systems offers promising therapeutic avenues that warrant further exploration. As our understanding of the complex, context-dependent roles of integrin α5β1 in the HNSCC microenvironment deepens - particularly through the use of advanced, spatially-resolved single-cell technologies - the path toward its successful clinical translation will become clearer.

Disclosure of conflict of interest

None.

Address correspondence to: Li-Li Qiu, Health College, Binzhou Polytechnic, No. 919, Huanghe 12th Road, Bincheng District, Binzhou 256603, Shandong, P. R. China. E-mail: qiulili@bzpt.edu.cn

References

[1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024; 74: 229-263.

[2] Johnson DE, Burtness B, Leemans CR, Lui VWY, Bauman JE and Grandis JR. Head and neck squamous cell carcinoma. Nat Rev Dis Primers 2020; 6: 92.

[3] Li S, Sampson C, Liu C, Piao HL and Liu HX. Integrin signaling in cancer: bidirectional mechanisms and therapeutic opportunities. Cell Commun Signal 2023; 21: 266.

[4] Feng C, Jin X, Han Y, Guo R, Zou J, Li Y and Wang Y. Expression and prognostic analyses of ITGA3, ITGA5, and ITGA6 in head and neck squamous cell carcinoma. Med Sci Monit 2020; 26: e926800.

[5] Vallina C, López-Pintor RM, González-Serrano J, de Vicente JC, Hernández G and Lorz C. Genes involved in the epithelial-mesenchymal transition in oral cancer: a systematic review. Oral Oncol 2021; 117: 105310.

[6] Kisoda S, Shao W, Fujiwara N, Mouri Y, Tsunematsu T, Jin S, Arakaki R, Ishimaru N and Kudo Y. Prognostic value of partial EMT-related genes in head and neck squamous cell carcinoma by a bioinformatic analysis. Oral Dis 2020; 26: 1149-1156.

[7] Steglich A, Vehlow A, Eke I and Cordes N. α integrin targeting for radiosensitization of three-dimensionally grown human head and neck squamous cell carcinoma cells. Cancer Lett 2015; 357: 542-8.

[8] Suehiro K, Gailit J and Plow EF. Fibrinogen is a ligand for integrin alpha5beta1 on endothelial cells. J Biol Chem 1997; 272: 5360-5366.

[9] Laurent-Issartel C, Landras A, Agniel R, Giffard F, Blanc-Fournier C, Da Silva Cruz E, Habes C,

Leroy-Dudal J, Carreiras F and Kellouche S. Ascites microenvironment conditions the peritoneal pre-metastatic niche to promote the implantation of ovarian tumor spheroids: Involvement of fibrinogen/fibrin and αV and α5β1 integrins. Exp Cell Res 2024; 441: 114155.

[10] Chen W, Jiang M, Zou X, Chen Z, Shen L, Hu J, Kong M, Huang J, Ni C and Xia W. Fibroblast Activation Protein (FAP)(+) cancer-associated fibroblasts induce macrophage M2-like polarization via the Fibronectin 1-integrin α5β1 axis in breast cancer. Oncogene 2025; 44: 2396-2412.

[11] Tarui T, Andronicos N, Czekay RP, Mazar AP, Bdeir K, Parry GC, Kuo A, Loskutoff DJ, Cines DB and Takada Y. Critical role of integrin alpha 5 beta 1 in urokinase (uPA)/urokinase receptor (uPAR, CD87) signaling. J Biol Chem 2003; 278: 29863-29872.

[12] Aguirre-Ghiso JA, Estrada Y, Liu D and Ossowski L. ERK(MAPK) activity as a determinant of tumor growth and dormancy; regulation by p38(SAPK). Cancer Res 2003; 63: 1684-1695.

[13] Kumar P, Kumar Rai S and Sarangi PP. An in-silico study reveals that a C-terminal fragment of the adhesion protein Fibulin7 (Fbln7-C) regulates the activation of integrin α5β1 through dynamics of VWA and the hybrid domain in the β1 subunit. J Biomol Struct Dyn 2024; 1-20.

[14] Cardeñes B, Clares I, Toribio V, Pascual L, López-Martín S, Torres-Gomez A, Sainz de la Cuesta R, Lafuente EM, López-Cabrera M, Yáñez-Mó M and Cabañas C. Cellular integrin α5β1 and exosomal ADAM17 mediate the binding and uptake of exosomes produced by colorectal carcinoma cells. Int J Mol Sci 2021; 22: 9938.

[15] Machado-Pineda Y, Cardeñes B, Reyes R, López-Martín S, Toribio V, Sánchez-Organero P, Suarez H, Grötzinger J, Lorenzen I, Yáñez-Mó M and Cabañas C. CD9 controls integrin α5β1-mediated cell adhesion by modulating its association with the metalloproteinase ADAM17. Front Immunol 2018; 9: 2474.

[16] Atzori MG, Ceci C, Ruffini F, Scimeca M, Cicconi R, Mattei M, Lacal PM and Graziani G. The Anti-Vascular Endothelial Growth Factor Receptor 1 (VEGFR-1) D16F7 monoclonal antibody inhibits melanoma adhesion to soluble VEGFR-1 and tissue invasion in response to placenta growth factor. Cancers (Basel) 2022; 14: 5578.

[17] Takada YK and Takada Y. The EC2 domains of tetraspanins CD9, CD81, and CD151 bind to the allosteric site of integrins (site 2) and activate integrins αvβ3, α5β1 and α4β1 in a biphasic manner. bioRxiv 2025.

[18] Bachsais M, Naddaf N, Yacoub D, Salti S, Alaaeddine N, Aoudjit F, Hassan GS and Mourad W. The interaction of CD154 with the α5β1 integrin inhibits Fas-induced T cell death. PLoS One 2016; 11: e0158987.

[19] Bachsais M, Salti S, Zaoui K, Hassan GS, Aoudjit F and Mourad W. CD154 inhibits death of T cells via a Cis interaction with the α5β1 integrin. PLoS One 2020; 15: e0235753.

[20] Sil H, Sen T and Chatterjee A. Fibronectin-integrin (alpha5beta1) modulates migration and invasion of murine melanoma cell line B16F10 by involving MMP-9. Oncol Res 2011; 19: 335-348.

[21] Jachetti E, Caputo S, Mazzoleni S, Brambillasca CS, Parigi SM, Grioni M, Piras IS, Restuccia U, Calcinotto A, Freschi M, Bachi A, Galli R and Bellone M. Tenascin-C protects cancer stem-like cells from immune surveillance by arresting T-cell activation. Cancer Res 2015; 75: 2095-2108.

[22] McFarlane S, McFarlane C, Montgomery N, Hill A and Waugh DJ. CD44-mediated activation of α5β1-integrin, cortactin and paxillin signaling underpins adhesion of basal-like breast cancer cells to endothelium and fibronectin-enriched matrices. Oncotarget 2015; 6: 36762-36773.

[23] Alturaihi H, Hassan GS, Al-Zoobi L, Salti S, Darif Y, Yacoub D, El Akoum S, Oudghiri M, Merhi Y and Mourad W. Interaction of CD154 with different receptors and its role in bidirectional signals. Eur J Immunol 2015; 45: 592-602.

[24] Kapiainen E, Kihlström MK, Pietilä R, Kaakinen M, Ronkainen VP, Tu H, Heikkinen A, Devarajan R, Miinalainen I, Laitakari A, Ansarizadeh M, Zhang Q, Wei GH, Ruddock L, Pihlajaniemi T, Elamaa H and Eklund L. The Amino-Terminal oligomerization domain of angiopoietin-2 affects vascular remodeling, mammary gland tumor growth, and lung metastasis in mice. Cancer Res 2021; 81: 129-143.

[25] Mendes KN, Wang GK, Fuller GN and Zhang W. JNK mediates insulin-like growth factor binding protein 2/integrin alpha5-dependent glioma cell migration. Int J Oncol 2010; 37: 143-153.

[26] Mythreye K, Knelson EH, Gatza CE, Gatza ML and Blobe GC. TβRIII/β-arrestin2 regulates integrin α5β1 trafficking, function, and localization in epithelial cells. Oncogene 2013; 32: 1416-1427.

[27] Yu YH, Kuo HK and Chang KW. The evolving transcriptome of head and neck squamous cell carcinoma: a systematic review. PLoS One 2008; 3: e3215.

[28] Zhou Q, Yuan O, Cui H, Hu T, Xiao GG, Wei J, Zhang H and Wu C. Bioinformatic analysis identifies HPV-related tumor microenviron-

ment remodeling prognostic biomarkers in head and neck squamous cell carcinoma. Front Cell Infect Microbiol 2022; 12: 1007950.
[29] Tao ZY, Yang WF, Zhu WY, Wang LL, Li KY, Guan XY and Su YX. A neural-related gene risk score for head and neck squamous cell carcinoma. Oral Dis 2024; 30: 477-491.
[30] Wang X and Wang Z. A novel basement membrane-related gene signature for predicting prognosis of HNSCC. Medicine (Baltimore) 2025; 104: e41316.
[31] Zhu L, Wang Y, Yuan X, Ma Y, Zhang T, Zhou F and Yu G. Effects of immune inflammation in head and neck squamous cell carcinoma: Tumor microenvironment, drug resistance, and clinical outcomes. Front Genet 2022; 13: 1085700.
[32] Li Z, Cai H, Zheng J, Chen X, Liu G, Lv Y, Ye H and Cai G. Mitochondrial-related genes markers that predict survival in patients with head and neck squamous cell carcinoma affect immunomodulation through hypoxia, glycolysis, and angiogenesis pathways. Aging (Albany NY) 2023; 15: 10347-10369.
[33] You Y, Du Z, Xu G, Tian Z, Xiao M and Wang Y. Identification of exosome-related genes associated with prognosis and immune infiltration features in head-neck squamous cell carcinoma. Biomolecules 2023; 13: 958.
[34] Koukourakis MI, Giatromanolaki A, Tsakmaki V, Danielidis V and Sivridis E. Cancer stem cell phenotype relates to radio-chemotherapy outcome in locally advanced squamous cell head-neck cancer. Br J Cancer 2012; 106: 846-853.
[35] Routila E, Salminen S, Mahran R, Toriseva M, Irjala H, Haapio E, Kytö E, Ventelä S, Pettersson K, Routila J, Gidwani K and Leivo J. Evaluation of integrin glycovariants as biomarkers of metastasis, invasion, and therapy stratification in head and neck squamous cell carcinoma. Cancer Med 2025; 14: e70717.
[36] Chen G, Sun J, Xie M, Yu S, Tang Q and Chen L. PLAU promotes cell proliferation and epithelial-mesenchymal transition in head and neck squamous cell carcinoma. Front Genet 2021; 12: 651882.
[37] Liu M, Banerjee R, Rossa C Jr and D'Silva NJ. RAP1-RAC1 signaling has an important role in adhesion and migration in HNSCC. J Dent Res 2020; 99: 959-968.
[38] Wang R, Gao Y and Zhang H. ACTN1 interacts with ITGA5 to promote cell proliferation, invasion and epithelial-mesenchymal transformation in head and neck squamous cell carcinoma. Iran J Basic Med Sci 2023; 26: 200-207.
[39] He Y, Shi Y, Li X, Wang R, Wang L, Li H, Zhu S, He S and Fang J. Adipocytes promoted anoikis resistance of head and neck cancer cells via overexpressed ITGA5. Eur J Med Res 2025; 30: 989.
[40] Zhao X, Mai Z, Liu L, Lu Y, Cui L and Yu J. Hypoxia-driven TNS4 fosters HNSCC tumorigenesis by stabilizing integrin α5β1 complex and triggering FAK-mediated Akt and TGFβ signaling pathways. Int J Biol Sci 2024; 20: 231-248.
[41] Cohen E, Tendler T, Lu H, Hansen CK, Kertsman J, Barrios J and Wieder R. Collagen I provides a survival advantage to MD-1483 head and neck squamous cell carcinoma cells through phosphoinositol 3-kinase signaling. Anticancer Res 2013; 33: 379-386.
[42] Li J, Wu T, Song K, Zhu L, Wang Y, Chen T and Wang X. Integrative network analysis reveals subtype-specific long non-coding RNA regulatory mechanisms in head and neck squamous cell carcinoma. Comput Struct Biotechnol J 2023; 21: 535-549.
[43] Fan QC, Tian H, Wang Y and Liu XB. Integrin-α5 promoted the progression of oral squamous cell carcinoma and modulated PI3K/AKT signaling pathway. Arch Oral Biol 2019; 101: 85-91.
[44] Deng Y, Wan Q and Yan W. Integrin α5/ITGA5 promotes the proliferation, migration, invasion and progression of oral squamous carcinoma by epithelial-mesenchymal transition. Cancer Manag Res 2019; 11: 9609-9620.
[45] Park SY, Lee SK, Lim M, Kim B, Hwang BO, Cho ES, Zhang X, Chun KS, Chung WY and Song NY. Direct contact with platelets induces podoplanin expression and invasion in human oral squamous cell carcinoma cells. Biomol Ther (Seoul) 2022; 30: 284-290.
[46] Veeravarmal V, Austin RD, Nagini S and Nassar MHM. Expression of β1integrin in normal epithelium, oral submucous fibrosis and oral squamous cell carcinoma. Pathol Res Pract 2018; 214: 273-280.
[47] Lin HC, Wu CL, Chen YL, Huang JS, Wong TY and Yuan K. High-level β1-integrin expression in a subpopulation of highly tumorigenic oral cancer cells. Clin Oral Investig 2014; 18: 1277-1284.
[48] Mohapatra D, Panda S, Mohanty N, Panda S, Lewkowicz N and Lapinska B. Comparison of immunohistochemical markers in oral submucous fibrosis and oral submucous fibrosis transformed to oral squamous cell carcinoma-a systematic review and meta-analysis. Int J Mol Sci 2023; 24: 11771.
[49] Yap LF, Jenei V, Robinson CM, Moutasim K, Benn TM, Threadgold SP, Lopes V, Wei W, Thomas GJ and Paterson IC. Upregulation of Eps8 in oral squamous cell carcinoma promotes cell migration and invasion through integrin-dependent Rac1 activation. Oncogene 2009; 28: 2524-2534.
[50] Shetty SS, Ram Padam KS, Sharma M, Kudva A, Patel P and Radhakrishnan R. Novel transcripts of EMT driving the malignant transfor-

mation of oral submucous fibrosis. Sci Rep 2025; 15: 3294.
[51] Lu X, Yang Y, Chen J, Zhao T and Zhao X. RUNX1/miR-429 feedback loop promotes growth, metastasis, and epithelial-mesenchymal transition in oral squamous cell carcinoma by targeting ITGB1. Naunyn Schmiedebergs Arch Pharmacol 2024; 397: 5289-5302.
[52] Kusayama M, Wada K, Nagata M, Ishimoto S, Takahashi H, Yoneda M, Nakajima A, Okura M, Kogo M and Kamisaki Y. Critical role of aquaporin 3 on growth of human esophageal and oral squamous cell carcinoma. Cancer Sci 2011; 102: 1128-1136.
[53] Kurihara M, Kirita T, Sasahira T, Ohmori H, Matsushima S, Yamamoto K, Bosserhoff AK and Kuniyasu H. Protumoral roles of melanoma inhibitory activity 2 in oral squamous cell carcinoma. Br J Cancer 2013; 108: 1460-1469.
[54] Saito K, Mitsui A, Sumardika IW, Yokoyama Y, Sakaguchi M and Kondo E. PLOD2-driven IL-6/STAT3 signaling promotes the invasion and metastasis of oral squamous cell carcinoma via activation of integrin β1. Int J Oncol 2021; 58: 29.
[55] Yen YC, Hsiao JR, Jiang SS, Chang JS, Wang SH, Shen YY, Chen CH, Chang IS, Chang JY and Chen YW. Insulin-like growth factor-independent insulin-like growth factor binding protein 3 promotes cell migration and lymph node metastasis of oral squamous cell carcinoma cells by requirement of integrin β1. Oncotarget 2015; 6: 41837-41855.
[56] Morris MA, Dawson CW, Laverick L, Davis AM, Dudman JP, Raveenthiraraj S, Ahmad Z, Yap LF and Young LS. The Epstein-Barr virus encoded LMP1 oncoprotein modulates cell adhesion via regulation of activin A/TGFβ and β1 integrin signalling. Sci Rep 2016; 6: 19533.
[57] Wasil LR and Shair KH. Epstein-Barr virus LMP1 induces focal adhesions and epithelial cell migration through effects on integrin-α5 and N-cadherin. Oncogenesis 2015; 4: e171.
[58] Wang WY, Twu CW, Liu YC, Lin HH, Chen CJ and Lin JC. Fibronectin promotes nasopharyngeal cancer cell motility and proliferation. Biomed Pharmacother 2019; 109: 1772-1784.
[59] Nkosi D, Sun L, Duke LC and Meckes DG Jr. Epstein-Barr virus LMP1 manipulates the content and functions of extracellular vesicles to enhance metastatic potential of recipient cells. PLoS Pathog 2020; 16: e1009023.
[60] Ding Y, Pan Y, Liu S, Jiang F and Jiao J. Elevation of MiR-9-3p suppresses the epithelial-mesenchymal transition of nasopharyngeal carcinoma cells via down-regulating FN1, ITGB1 and ITGAV. Cancer Biol Ther 2017; 18: 414-424.
[61] Tao L, Wei Z, Wang Y and Xiang P. CEACAM6 inhibits proliferation and migration of nasopharyngeal carcinoma cells by suppressing epithelial-mesenchymal transition. Nan Fang Yi Ke Da Xue Xue Bao 2025; 45: 566-576.
[62] Zheng ZQ, Huang ZH, Liang YL, Zheng WH, Xu C, Li ZX, Liu N, Yang PY, Li YQ, Ma J, Sun Y, Tang LL and Wei D. VIRMA promotes nasopharyngeal carcinoma, tumorigenesis, and metastasis by upregulation of E2F7 in an m6A-dependent manner. J Biol Chem 2023; 299: 104677.
[63] Zhou C, Shen Y, Wei Z, Shen Z, Tang M, Shen Y and Deng H. ITGA5 is an independent prognostic biomarker and potential therapeutic target for laryngeal squamous cell carcinoma. J Clin Lab Anal 2022; 36: e24228.
[64] Wang X, Huang J, You R, Hou D, Liu J, Wu L, Yao M, Yang F and Huang H. Downregulation of ITGA5 inhibits lymphangiogenesis and cell migration and invasion in male laryngeal squamous cell carcinoma. Protoplasma 2023; 260: 1569-1580.
[65] Li D, Sun A, Zhang L, Ding Z, Yi F, Yang X, Wang Z, Chen X, Liu W, Liu S, Shen H, Miao M, Zhang L, Liu P, Liu Y, Su S, Huang H, Huang C, Hu Z, Zhang H, Zha X and Liu Y. Elevated ITGA5 facilitates hyperactivated mTORC1-mediated progression of laryngeal squamous cell carcinoma via upregulation of EFNB2. Theranostics 2022; 12: 7431-7449.
[66] Feng L, Wang R, Lian M, Ma H, He N, Liu H, Wang H and Fang J. Integrated analysis of long noncoding RNA and mRNA expression profile in advanced laryngeal squamous cell carcinoma. PLoS One 2016; 11: e0169232.
[67] Klobučar M, Sedić M, Gehrig P, Grossmann J, Bilić M, Kovač-Bilić L, Pavelić K and Kraljević Pavelić S. Basement membrane protein ladinin-1 and the MIF-CD44-β1 integrin signaling axis are implicated in laryngeal cancer metastasis. Biochim Biophys Acta 2016; 1862: 1938-1954.
[68] Yin C, Ma B, Zhang X, Lan L, Ren G, Xu J and Wang J. Overexpression of Laminin 5γ2 chain correlates with tumor cell proliferation, invasion, and poor prognosis in laryngeal squamous cell carcinoma. J Oncol 2022; 2022: 7248064.
[69] Ngaokrajang U, Janvilisri T, Sae-Ueng U, Prungsak A and Kiatwuthinon P. Integrin α5 mediates intrinsic cisplatin resistance in three-dimensional nasopharyngeal carcinoma spheroids via the inhibition of phosphorylated ERK /caspase-3 induced apoptosis. Exp Cell Res 2021; 406: 112765.

[70] Nakahara S, Miyoshi E, Noda K, Ihara S, Gu J, Honke K, Inohara H, Kubo T and Taniguchi N. Involvement of oligosaccharide changes in alpha5beta1 integrin in a cisplatin-resistant human squamous cell carcinoma cell line. Mol Cancer Ther 2003; 2: 1207-1214.

[71] Huang L, Hu C, Chao H, Wang R, Lu H, Li H and Chen H. miR-29c regulates resistance to paclitaxel in nasopharyngeal cancer by targeting ITGB1. Exp Cell Res 2019; 378: 1-10.

[72] Jiang W, Chen L, Li R, Li J, Dou S, Ye L, He Y, Tian Z, Yao Y and Zhu G. Postoperative radiotherapy with docetaxel versus cisplatin for high-risk oral squamous cell carcinoma: a randomized phase II trial with exploratory analysis of ITGB1 as a potential predictive biomarker. BMC Med 2024; 22: 314.

[73] Gu Z, Yao Y, Yang G, Zhu G, Tian Z, Wang R, Wu Q, Wang Y, Wu Y, Chen L, Wang C, Gao J, Kang X, Zhang J, Wang L, Duan S, Zhao Z, Zhang Z and Sun S. Pharmacogenomic landscape of head and neck squamous cell carcinoma informs precision oncology therapy. Sci Transl Med 2022; 14: eabo5987.

[74] You GR, Cheng AJ, Lee LY, Huang YC, Liu H, Chen YJ and Chang JT. Prognostic signature associated with radioresistance in head and neck cancer via transcriptomic and bioinformatic analyses. BMC Cancer 2019; 19: 64.

[75] Fang Y, Liang S, Gao J, Wang Z, Li C, Wang R and Yu W. Extracellular matrix stiffness mediates radiosensitivity in a 3D nasopharyngeal carcinoma model. Cancer Cell Int 2022; 22: 364.

[76] Li X, Zhao H, Jiang E, Liu P, Chen Y, Wang Y, Li J, Wu Y, Liu Z and Shang Z. ITGB1/FERMT1 mechanoactivation enhances CD44 characteristic stemness in oral squamous cell carcinoma via ubiquitin-dependent CK1α degradation. Oncogene 2025; 44: 1530-1544.

[77] Park SJ, Min HJ, Yoon C, Kim SH, Kim JH and Lee SY. Integrin β1 regulates the perineural invasion and radioresistance of oral squamous carcinoma cells by modulating cancer cell stemness. Cell Signal 2023; 110: 110808.

[78] Liu J, Wang Y, Chen X, Chen X and Zhang M. ITGA5 is associated with prognosis marker and immunosuppression in head and neck squamous cell carcinoma. Diagn Pathol 2024; 19: 134.

[79] Ye S, Huang L, Ma L, Xu L, Liu L, Li J, Zhang Y, Gao B, Ji Y, Zheng Z and Guo H. NOTCH gene pattern predicts prognosis, immune infiltration, and drug response in Head and Neck squamous cell carcinoma. J Stomatol Oral Maxillofac Surg 2025; 126: 102582.

[80] Liu L and Liu Q. Characterization of macrophages in head and neck squamous cell carcinoma and development of MRG-based risk signature. Sci Rep 2024; 14: 9914.

[81] Kumar P, Sharma P, Singh D, Mishra N and Sarangi PP. Unraveling the molecular basis for effective regulation of integrin α5β1 for enhanced therapeutic interventions. Biochem Biophys Res Commun 2024; 734: 150627.

[82] Jung AC, Ray AM, Ramolu L, Macabre C, Simon F, Noulet F, Blandin AF, Renner G, Lehmann M, Choulier L, Kessler H, Abecassis J, Dontenwill M and Martin S. Caveolin-1-negative head and neck squamous cell carcinoma primary tumors display increased epithelial to mesenchymal transition and prometastatic properties. Oncotarget 2015; 6: 41884-41901.

[83] Eke I, Zscheppang K, Dickreuter E, Hickmann L, Mazzeo E, Unger K, Krause M and Cordes N. Simultaneous β1 integrin-EGFR targeting and radiosensitization of human head and neck cancer. J Natl Cancer Inst 2015; 107: dju419.

[84] Chen L, Chiang YC, Chan LS, Chau WY, Lung ML, Kahn M, Lo KW, Mak NK and Lung HL. The CBP/β-Catenin antagonist, ICG-001, inhibits tumor metastasis via blocking of the miR-134/ITGB1 axis-mediated cell adhesion in Nasopharyngeal carcinoma. Cancers (Basel) 2022; 14: 3125.

[85] Chen J, Jiang C, Fu L, Zhu CL, Xiang YQ, Jiang LX, Chen Q, Liu WM, Chen JN, Zhang LY, Liu M, Chen C, Tang H, Wang B, Tsao SW, Kwong DL and Guan XY. CHL1 suppresses tumor growth and metastasis in nasopharyngeal carcinoma by repressing PI3K/AKT signaling pathway via interaction with Integrin β1 and Merlin. Int J Biol Sci 2019; 15: 1802-1815.

[86] Nishimura R and Kanchanawong P. Nanoscale mechano-adaption of integrin-based cell adhesions: new tools and techniques lead the way. Curr Opin Cell Biol 2025; 94: 102509.

[87] Lorenzoni S, Rodríguez-Nogales C and Blanco-Prieto MJ. Targeting tumor microenvironment with RGD-functionalized nanoparticles for precision cancer therapy. Cancer Lett 2025; 614: 217536.

[88] Han W, Ke J, Guo F, Meng F, Li H and Wang L. Construction and antitumor properties of a targeted nano-drug carrier system responsive to the tumor microenvironment. Int J Pharm 2021; 608: 121066.

[89] Zhang S, Ma X, Wu J, Shen J, Shi Y, Wang X, Xie L, Sun X, Wu Y, Tian H, Gao X, Chen X, Huang H, Chen L, Song X, Hu Q, Zhang H, Wang F, Jin ZH, Zhang MR, Wang R and Hu K. Enhanced radiotheranostic targeting of integrin α5β1 with PEGylation-enabled peptide multidisplay platform (PEGibody): a strategy for prolonged tumor retention with fast blood clearance. Acta Pharm Sin B 2025; 15: 692-706.

[90] Alfano M, Alchera E, Sacchi A, Gori A, Quilici G, Locatelli I, Venegoni C, Lucianò R, Gasparri AM, Colombo B, Taiè G, Jose J, Armanetti P, Menichetti L, Musco G, Salonia A, Corti A and Curnis F. A simple and robust nanosystem for photoacoustic imaging of bladder cancer based on α5β1-targeted gold nanorods. J Nanobiotechnology 2023; 21: 301.

[91] Han M, Liang J, Wang K, Si Q, Zhu C, Zhao Y, Khan NAK, Abdullah ALB, Shau-Hwai AT, Li YM, Zhou Z, Jiang C, Liao J, Tay YJ, Qin W and Jiang Q. Integrin A5B1-mediated endocytosis of polystyrene nanoplastics: Implications for human lung disease and therapeutic targets. Sci Total Environ 2024; 953: 176017.