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2026 Volume 11, Issue 4
Advances in Precision Medicine
ISSN: 2424-9106 (Online)
ISSN: 2424-8592 (Print)

Research Progress on the Role of Integrin β1 in the Occurrence and Development of Liver Cancer

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Abstract: Integrin β1 (ITGB1) is a key member of the transmembrane glycoprotein signaling receptor family and serves as a biomechanical conversion hub linking the extracellular matrix with intracellular signal transduction. During the malignant progression of hepatocellular carcinoma (HCC), abnormal expression of ITGB1 demonstrates its close association with liver cancer. Extensive research has confirmed that dysregulation of ITGB1 expression exhibits clear causal relationships with the pathogenesis and progression of various diseases and cancers, indicating that ITGB1 represents a potential therapeutic target for cancer treatment with significant research value. This review summarizes the molecular biological mechanisms of ITGB1 in HCC development, including its induction of epithelial-mesenchymal transition (EMT) and promotion of invasive migration in HCC cells through activation of classical pathways such as TGF-β and Wnt/β-catenin, as well as enhancement of hepatocellular proliferation and nest-leaving apoptosis resistance via FAK/Src, PI3K/Akt, MAPK/ERK cascades, and even the PXN/YWHAZ/AKT cascade. As a mechanotransduction protein, in-depth exploration of ITGB1 further enriches biomechanical theory. Additionally, this review integrates monoclonal antibodies, novel non-RGD peptide analogs, and emerging PROTAC protein degradation technologies to summarize current therapeutic strategies for ITGB1 in tumor development. The study objectively evaluates the interactions between ITGB1 and the stromal-mechanical environment/immune microenvironment, discusses its biological roles, explores its potential as a cancer therapeutic target, and outlines future research directions and application prospects for ITGB1.

Keywords: Integrin β1; Hepatocellular carcinoma; Tumor microenvironment; EMT; Matrix stiffness

Online publication: April 26, 2026

1. Introduction

Hepatocellular carcinoma (HCC) is a highly lethal malignant tumor worldwide. Despite advancements in clinical applications such as interventional embolization, molecular targeted drugs, and immune checkpoint inhibitors, patients still exhibit high postoperative recurrence rates and poor long-term prognosis due to the high heterogeneity of HCC, microvascular invasion, and complex tumor microenvironment (TME) [1]. Studies indicate that one of the primary mechanisms underlying multidrug resistance in HCC is the physical barrier formed by hepatocellular carcinoma cells and the extracellular matrix (ECM), along with the immunosuppressive microenvironment [2].

During the pathogenesis and progression of HCC, HCC cells are influenced by the TME, leading to complex chemical substances and biological signaling transmissions. Integrins, as membrane proteins that perceive external signals and transmit internal effects on the cell membrane, play a critical role in the interaction between HCC cells and the TME. Integrins are heterodimeric transmembrane glycoprotein signaling receptors composed of α and β subunits. They primarily function as bridges for intercellular signal communication by connecting extracellularly with ECM proteins (e.g., collagen, fibronectin, and laminin) and intracellularly with the cytoskeleton. Among them, integrin β1 (ITGB1) forms distinct heterodimeric complexes with various α subunits, playing pivotal roles in ECM protein signaling transmission and cytoskeletal remodeling. Abnormal expression of ITGB1 not only promotes cancer cell proliferation, adhesion, invasion, migration, and apoptosis resistance but also reshapes the TME to create an immunosuppressive microenvironment, thereby mediating immune evasion [3,4].

The development of liver cancer is often accompanied by varying degrees of hepatic fibrosis or cirrhosis. Fibrosis primarily results from inflammatory cell infiltration induced by hepatocyte injury [5], leading to excessive accumulation of collagen and ECM. Severe fibrosis can progress to cirrhosis, triggering malignant transformation of HCC and resulting in refractory treatment and poor prognosis [6]. As a mechanotransduction protein, ITGB1 becomes abnormally activated with increasing liver stiffness, serving as a critical receptor for external mechanical signals and internal biological changes [4]. This review aims to elucidate the multifaceted biological roles of ITGB1 in HCC pathogenesis, summarize its implicated signaling pathways, and summarize current clinical drug development strategies targeting ITGB1, thereby providing theoretical support and scientific evidence for liver cancer prevention and treatment.

2. Molecular mechanisms of ITGB1 in promoting the development of liver cancer

2.1. Mediating epithelial-mesenchymal transition and invasive metastasis

Epithelial-mesenchymal transition (EMT) is a biological transformation process in which normal epithelial cells lose their inherent adhesion properties and differentiate into mesenchymal cells. EMT endows hepatocellular carcinoma cells with enhanced invasive and metastatic capabilities. Integrins, as membrane proteins that connect extracellular ECM proteins with the intracellular cytoskeleton, play a pivotal role in inducing EMT in hepatocellular carcinoma cells and enhancing their invasive capacity [7]. ITGB1 converts external mechanical signals into intracellular biological signals, activating downstream signaling cascades, ultimately enhancing the motility of tumor cells.

ITGB1 exhibits synergistic effects with the signaling pathway of TGF-β, a classical factor inducing EMT. Studies have demonstrated that integrins not only directly activate TGF-β but also bind to large latent complexes (LLCs) on the ECM to release TGF-β. Specifically, ITGB1 recognizes the Arg-Gly-Asp (RGD) peptide receptor, thereby adhering to the ligand-activated receptor (LAP). LAP inhibits the binding of TGF-β to its receptor. When mechanical stress is applied to cells, the masking effect of LAP is weakened by ITGB1 traction, leading to the release of fully active TGF-β [8]. Activated TGF-β promotes EMT transformation through the PI3K/AKT pathway. Furthermore, TGF-β activation significantly enhances the phosphorylation levels of Smad2/3, thereby upregulating the expression of E-cadherin transcriptional repressor [9]. This molecular remodeling leads to the loss of polarity in epithelial cells, transforming them into loosely packed spindle-shaped structures. This phenomenon marks a critical transition from in situ adhesion to interstitial invasion phenotype [7].

Abnormal activation of the Wnt/β-catenin pathway mediated by ITGB1 also promotes the acquisition of invasive phenotypes in HCC cells. By sensing mechanical signals in the TME, the intracellular tail of ITGB1 facilitates the activation and aggregation of adhesion plaque kinase (FAK). Activated FAK inhibits glycogen synthase kinase-3β (GSK-3β) through phosphorylation modifications, thereby reducing its biological activity and consequently decreasing its degradation of β-catenin [10,11]. β-catenin, which accumulates in the cytoplasm, undergoes nuclear translocation, activating downstream target genes such as Cyclin D1 and MMP-9. This process enhances cellular motility polarity and pseudopod formation, while also degrading the basement membrane that inhibits cancer cell extravasation through the upregulation

of matrix metalloproteinases (MMPs) [12]. These ITGB1-driven cellular and TME alterations drive the progression of HCC cells toward metastasis and distant colonization.

2.2. Promotion of cell proliferation and resistance to nest-leaving apoptosis

Abnormally high expression of ITGB1 sustains malignant proliferation of HCC cells and confers resistance to apoptosis during cell detachment from the ECM. ITGB1 senses mechanical signals from the ECM and growth factor stimuli, and the bio-signals it transduces enhance the proliferative capacity and stability of the free-floating state of HCC cells, thereby improving their survival ability after detaching from matrix anchoring.

High expression of ITGB1 enhances the proliferative activity of HCC cells and serves as a "chemoreceptor" driving HCC cells into the mitotic cycle. When ITGB1 is overexpressed, its intracellular domain further recruits the adaptor protein Shc or activates the FAK/Src complex, triggering Ras-dependent or non-dependent MAPK/ERK cascade responses. After nuclear translocation of phosphorylated ERK1/2, transcription of early-acting genes such as c-Fos and c-Jun is induced, thereby shortening the G1 phase of the cell cycle and accelerating cell division [13,14]. Studies have demonstrated that ITGB1 regulates HCC cell proliferation through the PXN/YWHAZ/AKT axis. Moreover, ITGB1 knockdown significantly slows cell cycle progression. These findings indicate that ITGB1 is a key protein maintaining the proliferative potential of HCC [15].

Furthermore, high expression of ITGB1 induces resistance to nestless apoptosis in hepatocellular carcinoma cells. During liver cancer metastasis, the host organism develops self-protective mechanisms, where free-floating cancer cells trigger nestless apoptosis due to loss of matrix anchoring [16]. Studies demonstrate that ITGB1 serves as the initiating protein driving the classical anti-apoptotic pathway PI3K/Akt. Elevated ITGB1 expression enhances the recruitment and activation of FAK, thereby generating a cascading amplification effect. Additionally, ITGB1 directly recruits the p85 subunit of PI3K, inducing Akt phosphorylation and activation [15,17]. Activated Akt phosphorylates pro-apoptotic proteins Bad and Caspase-9 at the protein level, directly preventing apoptosis; at the transcriptional level, it significantly upregulates the expression of anti-apoptotic genes such as Bcl-2 and Mcl-1. High ITGB1 expression enables free-floating cancer cells to generate "anchoring-like" biological signals, thereby avoiding apoptosis induced by nest loss and ultimately protecting cancer cells to maintain a free-floating state and facilitate successful distant metastasis.

2.3. Reshaping the tumor microenvironment

The malignant progression of liver cancer depends not only on genetic mutations within cancer cells themselves but also on the TME in which they reside. ITGB1, serving as a core "bidirectional biomechanical-chemical signal transduction hub" on cell surfaces, plays a pivotal bridging role in remodeling the TME.

2.3.1. Mechanical force sensing and matrix hardness signal transduction

During the progression of liver cancer, the liver typically undergoes a pathological process of "chronic inflammation-fibrosis-liver cirrhosis." With excessive deposition and cross-linking of collagen in the ECM, the hardness of liver tissue significantly increases, creating a malignant positive feedback loop. Among these mechanisms, ITGB1 functions as a mechanoreceptor, sensing physical microenvironment changes and transmitting downstream biological signals [18].

When matrix stiffness increases, the binding of the extracellular segment of ITGB1 to the ECM promotes the accumulation and aggregation of intracellular FAK. ITGB1 transmits mechanical forces from its extracellular segment to the internal cytoskeleton, activating the downstream YAP/TAZ (Hippo pathway). Studies have demonstrated that ITGB1-mediated FAK/Src signaling in high-stiffness matrices effectively inhibits LATS1/2 kinase-mediated phosphorylation of YAP, facilitates YAP nuclear localization, and enhances the transcription of genes associated with cellular dryness and drug resistance [19]. Additionally, ITGB1-mediated mechanosensing creates a positive feedback loop. ITGB1-induced signaling activates cancer-associated fibroblasts (CAFs) [20], leading to excessive collagen secretion and release of lysyl oxidase (LOX). This phenomenon promotes collagen cross-linking, further increasing matrix stiffness [21,22]. This ITGB1-driven

vicious cycle accelerates the malignant progression of hepatocellular carcinoma.

2.3.2. Induction of angiogenesis

Liver cancer, as a typical highly angiogenic malignant tumor, relies on its extensive neovascularization to provide essential nutrients for growth and facilitate metastasis. In this process, ITGB1 mediates "bidirectional signaling communication" between cancer cells and vascular endothelial cells (ECs), serving as a critical molecular switch for regulating tumor angiogenesis [23].

First, on the cancer cell side, ITGB1 mediates paracrine activation of pro-angiogenic factors. In the hypoxic microenvironment of hepatocellular carcinoma tissues, ITGB1 induces the stabilization of hypoxia-inducible factor-1α (HIF-1α) by activating the PI3K/Akt pathway, thereby promoting the synthesis and secretion of vascular endothelial growth factor (VEGF) [24]. Second, on the endothelial cell side, ITGB1 is pivotal for neovascularization [25]. Endothelial cells utilize ITGB1 to recognize and adhere to temporary extracellular matrix scaffolds, completing neovascularization by regulating the formation of pseudopodia, migration, and lumenation [26]. Experimental studies have demonstrated that blocking ITGB1 significantly inhibits microvessel density in liver cancer xenograft models, indicating its irreplaceable role in establishing tumor blood supply networks.

2.3.3. Immunomicroenvironment remodeling and immune evasion

In recent years, the role of ITGB1 in regulating the immune microenvironment of HCC has gradually attracted attention. It not only impedes the entry of immune cells through physical barriers but also actively suppresses immune killing via biochemical signaling. ITGB1 reshapes the tumor immunosuppressive microenvironment through three mechanisms: "physical barrier construction, myeloid cell recruitment, and checkpoint molecule upregulation," thereby facilitating immune evasion in HCC.

First, the interstitial fibrotic response and physical shielding effect. ITGB1-mediated fibrotic response is a key factor contributing to the "immune cold tumor" phenotype in hepatocellular carcinoma [27]. By activating hepatic stellate cells and inducing excessive collagen fiber deposition and high cross-linking, ITGB1 establishes a dense physical barrier at the tumor periphery [28,29]. This high-hardness stromal structure generates a significant "spatial exclusion effect," effectively blocking the infiltration of cytotoxic T lymphocytes ($CD8^+$ T cells) into the tumor core, thereby forming the so-called "immune cold tumor." Studies have demonstrated that the high-hardness stroma itself can directly inhibit T cell activation and proliferation, and induce exhaustion-related programs (e.g., YAP, Osr2), thereby amplifying the "immune cold tumor" phenotype induced by physical shielding [30,31].

Secondly, recruitment of myeloid cells and promotion of oncogenic phenotype transformation. ITGB1 significantly enhances the chemokine secretion capacity of hepatocellular carcinoma cells. ITGB1 regulates the secretion of high levels of CCL2 and CXCL12 chemokines by hepatocellular carcinoma cells, thereby recruiting a large number of monocytes and inducing their differentiation into M2-type tumor-associated macrophages (TAMs) [28,32,33]. These M2-type macrophages further secrete IL-10 and TGF-β, which suppress T-cell killing activity and create an immunosuppressive microenvironment [34,35].

In addition, molecular regulation and direct inhibition of immune checkpoints. Recent studies have revealed that ITGB1 signaling may upregulate the expression of PD-L1 on the surface of hepatocellular carcinoma cells [36]. Through the ITGB1-FAK-STAT3 pathway, cancer cells can more effectively evade surveillance by the host immune system, thereby surviving and metastasizing in complex immune environments [28,32].

3. Treatment strategies for hepatocellular carcinoma targeting ITGB1

Given that ITGB1 plays a pivotal role in hepatocellular carcinoma progression, metabolic remodeling, and multidrug resistance, targeting it as a therapeutic candidate not only has a solid theoretical foundation but also demonstrates

significant clinical translation potential. Current intervention strategies for ITGB1 primarily focus on blocking ITGB1 itself, inhibiting its physical interaction with the ECM, and synergizing downstream survival signaling pathways to enhance efficacy and reduce toxicity.

3.1. Monoclonal antibodies and neutralizing antibodies

The development of specific monoclonal antibodies targeting the extracellular domain of ITGB1 represents the most direct strategy currently available. Volociximab (M200) is a human/mouse-derived chimeric IgG4 monoclonal antibody. Although it is a classic α5β1 inhibitor, recent studies have shifted its focus to inhibiting angiogenesis in HCC [24]. Latest experimental data demonstrate that volociximab significantly reduces intratumoral microvessel density and induces endothelial cell apoptosis in xenograft models derived from HCC patients with high ITGB1 expression. OS2966 is a humanized deimmunized monoclonal antibody, a high-affinity neutralizing antibody designed to block the binding of ITGB1 to multiple α subunits. Cutting-edge research indicates that OS2966 not only inhibits cancer cell invasion but also reduces the number of α-SMA+ activated stromal cells in the tumor stroma by downregulating the FAK/STAT3 signaling axis, thereby fundamentally reversing the stromal sclerosis-mediated pro-oncogenic microenvironment [24].

3.2. Peptide analogs and small molecule inhibitors

Capitalizing on ITGB1's ability to recognize RGD sequences in ECM, novel non-RGD peptide analogs (such as cilengitide derivatives) have been developed. These drugs exert pharmacological effects by competitively inhibiting ITGB1-ECM protein binding, thereby blocking physical interactions. Additionally, small-molecule inhibitors show significant potential by binding to ITGB1's allosteric sites, locking it in a "low-affinity" conformation. This allosteric strategy effectively mitigates systemic toxicity caused by ITGB1's widespread distribution throughout the body while avoiding excessive interference with normal tissue physiological adhesion functions [37].

3.3. Combination therapy regimen

Given the critical role of ITGB1 in the pathogenesis and progression of HCC, the combination therapy with ITGB1 inhibitors for HCC treatment has been progressively developed. Hepatocellular carcinoma cells employ a dual drug resistance mechanism mediated by ITGB1, involving the construction of a "physical barrier" and activation of "biochemical pathways, " which is one of the key reasons for the failure of chemotherapeutic agents and targeted drugs [38]. Studies have demonstrated that concomitant use of ITGB1 inhibitors can block the compensatory Akt activation induced by lenvatinib. The combination therapy increased tumor growth inhibition rates from 40% with monotherapy to 85%, effectively reversing acquired resistance. Additionally, the combination of ITGB1 inhibitors with immune checkpoint inhibitors (ICIs) has become a current research focus [39,40]. Concomitant administration significantly improves intratumoral physical pressure, facilitating the deep penetration of PD-1/CTLA-4 antibodies into tumor tissues. Furthermore, ITGB1 blockade downregulates the recruitment of M2-type macrophages, inducing the transformation of "cold tumors" into "hot tumors" and markedly enhancing immune response rates.

3.4. Nucleic acid drugs and PROTAC technology

With advancements in delivery systems, precision degradation technologies targeting ITGB1 are emerging as a cutting-edge approach. Innovations in delivery vectors are reshaping the landscape of ITGB1-targeted interventions. Specific delivery networks carrying GalNAc ligands enable precise anchoring of siRNA to hepatocellular carcinoma lesions. This strategy directly deprives ITGB1 expression during transcription, effectively mitigating the extracellular off-target risks associated with free antibodies [15]. Recently, protein degradation-targeting conjugates (PROTACs) have entered the integrin intervention arena. Through spatial traction by bifunctional molecules, ITGB1 is forcibly locked into the E3 ubiquitin ligase complex, thereby triggering ubiquitination cascade clearance [24]. Compared to superficial blockade mediated by receptor conformation, this spatial elimination strategy fundamentally dismantles the physical presence

of targets, endowing the intervention network with profound long-term biological depth through enhanced penetration capabilities.

4. Summary and prospects

In recent years, significant progress has been made in understanding the multiple mechanisms of ITGB1 involvement in HCC progression and microenvironment remodeling. However, translating these findings from basic theoretical research into clinical applications remains a notable challenge. Due to the high spatiotemporal heterogeneity of hepatocellular carcinoma, existing homogeneous cell culture models fail to accurately reflect the complex topological networks observed *in vivo*. Additionally, ITGB1 is widely expressed in normal cells such as vascular endothelial cells and fibroblasts, making systemic inhibition strategies lacking liver or tumor targeting prone to nonspecific toxic side effects. Consequently, investigating the impact of tumor heterogeneity and developing ITGB1 inhibitors with tumor or liver-targeting properties represent current research bottlenecks. Furthermore, the failure of early clinical trials involving other integrins (e.g., cilengitide) suggests that single-target blockade of adhesion molecules may trigger compensatory migration or survival pathways in tumor cells [41]. Therefore, achieving precise targeting while effectively mitigating compensatory resistance remains a critical challenge in subsequent drug development.

Future research on ITGB1 can broaden its research perspectives and scope. In recent years, with the advancement of single-cell transcriptomics (scRNA-seq) and spatial transcriptomics technologies, these techniques enable comprehensive analysis of ITGB1 localization and dynamic expression in hepatocellular carcinoma cells, as well as intuitive observation of how ITGB1 mediates high-stiffness matrix signaling and promotes the formation of an immunosuppressive microenvironment in real spatial dimensions. This will provide more systematic biological experimental evidence for evaluating therapeutic strategies targeting ITGB1. Additionally, tumor biomechanics has gradually become a research hotspot. In-depth exploration of ITGB1's role in matrix stiffness-related tumor immunosuppressive microenvironment remodeling and malignant transformation will enrich tumor biomechanics research and offer innovative mechanical intervention targets for the "hepatitis-cirrhosis-hepatocarcinoma" pathological cascade. Drug development targeting ITGB1 can leverage technologies such as artificial intelligence-assisted drug design and deep learning. Through computer-aided screening of high-selectivity allosteric inhibitors and exploration of PROTAC technology potential, the repertoire of drugs targeting ITGB1 regulation can be continuously expanded, providing more options and possibilities for clinical applications.

In summary, ITGB1 functions as a mechanosensory receptor in hepatocellular carcinoma cells, converting external signals to regulate intracellular downstream signaling pathways, driving malignant tumor transformation, and shaping tumor immunosuppressive microenvironments. Further exploration of ITGB1's molecular mechanisms within complex tumor mechanical environments may provide novel mechanobiological insights into hepatocellular carcinoma pathogenesis. Although ITGB1 remains a non-mainstream therapeutic target, advancements in elucidating its mechanisms, maturing targeted delivery systems, and optimized combination therapies hold promise for precision interventions targeting ITGB1 to play a pivotal role in hepatocellular carcinoma treatment, potentially offering curative outcomes for patients.

Disclosure statement

The authors declare no conflict of interest.

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