Structure, function and usage of integrin alpha 6 (CD49f): A comprehensive review

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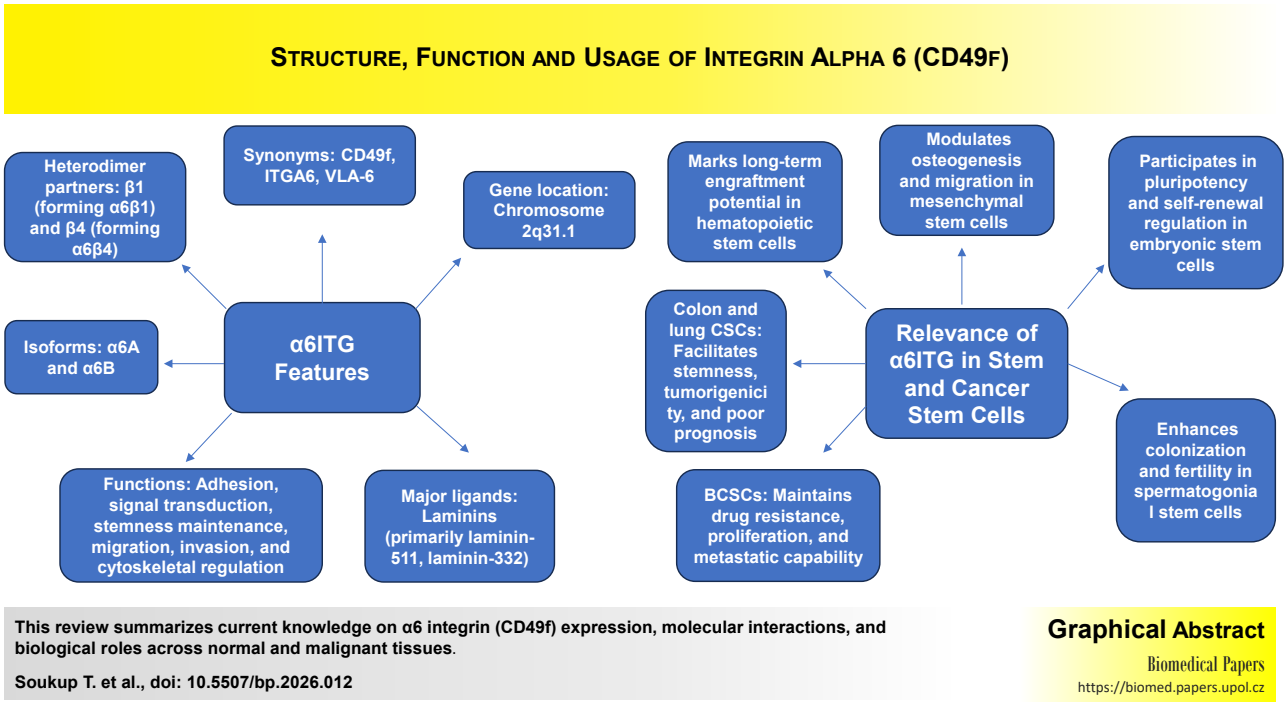
Integrin alpha-6 (α6ITG, CD49f) has long been considered one of the most reliable markers of stemness, yet emerging evidence challenges this view by revealing its broader role in niche accessibility and survival. As a laminin receptor, α6ITG mediates cellular interactions and participates in signal transduction pathways that help maintain cellular phenotype. Its expression allows for the identification and purification of stem cells from heterogeneous populations. Because α6ITG expression is highly sensitive to environmental cues, it also serves as a sensor of culture conditions and cryopreservation stress, with potential use in biobanking and regenerative medicine. This marker holds significant potential; it may be one of the few markers consistently expressed in all stem cells, potentially qualifying it as a common "stemness" marker. Additionally, the therapeutic implications of α6ITG knockdown using antibodies may greatly influence future cancer treatments. Elevated expression in cancer correlates with growth, invasion, and poor prognosis. The aim of this review is to explore the biological and translational importance of α6ITG in stem cell and cancer biology.



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INTRODUCTION

Integrins are a class of transmembrane adhesion receptors that have been thoroughly investigated over the past 35 years. These proteins are known for their roles in mediating cell-cell and cell-matrix interactions. Of these, integrin alpha 6 (α6ITG), identified in the first decade of the 21st century, has garnered special attention due to its diverse functions, particularly in stem and cancer stem cell biology.

The aim of this review was to summarize 1. the structural characteristics of α6ITG, its biological functions, involvement in various signaling pathways, its relevance to tissue-specific and cancer stem cells, and 2. explore its translational potential, including its application in stem cell isolation and targeted cancer therapies.

STRUCTURE AND BIOCHEMISTRY OF α6ITG

α6ITG, also known as CD49f, ITGA6, or VLA-6, belongs to the integrin alpha subunit family. It is encoded by the ITGA6 gene located on chromosome 2q31.1 (ref.[1]). Integrins are heterodimeric molecules formed by noncovalent associations between alpha and beta subunits. The α6 subunit pairs with β1 and β4 to form the α6β1 and α6β4 integrins, each exhibiting distinct biological functions[2,3].

The α6 protein consists of 1073 amino acid residues, including a signal peptide, a large extracellular domain, a transmembrane domain, and a cytoplasmic domain[4]. Structurally, it contains a heavy and light chain connected by a disulfide bond. The α6β1 and α6β4 integrins function primarily as laminin receptors, facilitating cell-ECM adhesion and signaling.

Cross-species homology studies show that approximately 90% of human α6 subunit amino acids are conserved in rats and mice, making them a valuable model target in animal studies.

Importantly, alternative splicing of the ITGA6 transcript generates two functionally distinct isoforms: α6A and α6B. The α6B variant lacks 130 nucleotides in the cytoplasmic domain coding region, resulting in a frameshift and the synthesis of a novel C-terminal tail comprising 54 amino acids rich in charged residues[1]. These isoforms display tissue-specific expression and divergent functions. For example, α6B is involved in nephrogenic and nervous system development, whereas α6A is observed in the developing heart, epidermis, and dental tissues[5].

Further, the α6A/α6B expression ratio varies between differentiated and undifferentiated stem cells across different tissues, suggesting functional roles in stem cell maintenance and differentiation[6].

BIOLOGICAL FUNCTION

Function of integrins

Integrins are transmembrane receptors composed of 18 α- and 8 β-subunits that combine to form 24 distinct heterodimers. These receptors are unique for their bidirectional signaling capabilities, with their extracellular domains interacting with the extracellular matrix (ECM) and their cytoplasmic domains activating intracellular signaling pathways[7,8]. Integrins regulate a variety of essential cellular processes, including adhesion and migration, proliferation and survival, as well as differentiation and cytoskeletal organization. Through these functions, integrins play key roles in critical physiological events such as tissue development, angiogenesis, immune response, and hemostasis[9].

Signaling pathways influenced by α6ITG

α6ITG is implicated in several critical signaling cascades that regulate key cellular behaviors. It activates the PI3-K pathway via IRS-1/2, promoting migration, invasion, and motility[10,11]. Through Shc–Grb2–Ras interactions, α6β4 also triggers the MAPK pathway, enabling cells to respond to environmental cues and initiate intracellular signaling via phosphorylation events[12]. Additionally, α6β4 activates RhoA and Rac1 through Rho GTPase signaling, driving cytoskeletal reorganization and migration, particularly in carcinoma cells[13]. α6ITG enhances VEGF translation and tumor survival through the mTOR/4E-BP1 pathway by facilitating the phosphorylation of 4E-BP1, a process regulated by the PI3-K–Akt axis[14]. In breast cancer, α6ITG contributes to radioresistance by promoting Akt and Erk phosphorylation[15]. Moreover, α6β1 integrin interacts with laminin-511 to activate the TAZ/Hippo axis which supports breast cancer stem cell (BCSC) self-renewal[16]. It also forms a complex with EGFR, HER2, and ColXVIII, promoting proliferation, drug resistance, and migration in breast cancer[17]. In glioblastoma stem cells, α6ITG enhances proliferation and stemness by regulating FGFR1 through the transcriptional activators ZEB1 and YAP1 in the ZEB1/YAP1-FGFR1 axis[18]. Collectively, these findings confirm that α6ITG serves as a convergence point for multiple pro-survival and differentiation-associated signaling pathways. Interestingly, CD146 (MCAM), though from a different protein family, influences similar signaling pathways and is also linked to poor prognosis. This convergence suggests that their common interaction with laminins might underlie shared pathway activation, raising questions about whether these markers initiate or merely reflect oncogenic dysregulation.

Context-dependent biological roles of α6ITG (α6β4 vs α6β1)

The α6β4 integrin is a principal laminin-binding receptor in stratified epithelia such as the epidermis[19,20]. Genetic studies in knockout mice revealed that α6β4 integrin is essential for epithelial adhesion, particularly in forming hemidesmosomes, the anchoring complexes that tether epithelial cells to the basement membrane[21,22].

Experimental inhibition of α6β4 using blocking antibodies disrupts cell adhesion and induces detachment[23]. Although earlier models proposed α3β1 as the dominant laminin receptor in keratinocytes, it has been shown that α6β4 alone can mediate anchorage in the absence of α3β1 (ref.[24]).

A deficiency in α6 integrin can lead to epidermolysis bullosa, a severe blistering disorder[25]. Additionally, α6β4 plays a role in epithelial cell migration, localizing to filopodia, lamellipodia, and retraction fibers, and enabling actin cytoskeletal remodeling to facilitate movement[26,27]. Thus, α6ITG contributes both to tissue integrity and tumor cell invasiveness.

Beyond its epithelial role, α6β1 integrin is involved in gamete interaction. It was initially discovered on the egg plasma membrane acting as a sperm receptor, working in conjunction with Fertilin[28]. Interestingly, α6β1 is also expressed on sperm, and the presence of the receptor on only one gamete is sufficient for successful fertilization[29].

A recent study demonstrated that 3D alginate hydrogel co-cultures of Sertoli and spermatogonial stem cells in mice enhanced spermatogenesis and upregulated α6 integrin expression, highlighting its role in reproductive biology[30].

These context-dependent roles of α6ITG are reflected in its broad expression across stem, progenitor, and cancer stem cell populations, as discussed below.

CELLS EXPRESSING *α6ITG*

α6ITG is expressed on the surface of a wide range of stem cells and is frequently used as a biomarker for their identification, isolation, and functional analysis. It is currently recognized as a surface marker for over 30 distinct stem cell populations[31], including hematopoietic stem cells (HSCs) (ref.[32]), myometrial stem cells[33], spermatogonial stem cells[34], bone marrow mesenchymal stem cells (BMSCs) and other mesenchymal stem cell (MSC) subtypes[35-37], postnatal liver stem/progenitor-like cells[38], embryonic stem cells (ESCs) (ref.[28,39,40]), prostate stem cells[41,42], and keratinocyte stem cells[43,44].

In addition to stem cells, other differentiated or progenitor cells also express α6ITG, such as club cells in the lung[45] and colonic clonogenic cells[46]. This broader pattern of expression suggests that α6ITG may play important roles beyond stem cell maintenance, contributing to the function and regenerative capacity of certain differentiated cell types.

In the context of oncology, α6ITG expression has been observed in multiple cancer stem cells (CSCs), including breast cancer stem cells[47], prostate cancer stem cells[48,49], glioblastoma stem cells[18], as well as CSCs from colon, lung, and squamous cell carcinomas. This widespread expression across both normal and malignant stem cell types highlights α6ITG's significance as a functional and diagnostic biomarker.

α6ITG and the stem cell niche

Stem cells reside in specialized microenvironments known as niches, where cell-cell and cell-matrix interactions play a vital role in maintaining quiescence, self-renewal and differentiation potential. A unifying element across many niches is the extracellular matrix protein laminin, which interacts directly with α6β4 integrin[50].

In limbal epithelial progenitor cells, α6β4 integrin anchors cells to the basement membrane via interaction with laminin and dystroglycan complexes[51]. Other studies suggest that stem cells can secrete laminins, potentially helping to form or maintain their own microenvironment[31]. As α6ITG is also involved in key signaling cascades, it contributes not only to niche adhesion but also to functional maintenance of stemness.

α6ITG function in specific stem cells

Hematopoietic stem cells (HSCs) can be functionally purified based on α6 integrin (α6ITG) expression, with α6ITG-positive HSCs exhibiting long-term engraftment potential, whereas α6ITG-negative progenitors tend to lose their stemness and favor differentiation[32]. Similarly, in the case of myogenic stem cells, α6ITG expression marks cells in porcine muscle that express MYF5 and exhibit fusion potential, while α6ITG-negative cells fail to form myotubes[33].

In myometrial stem cells, α6ITG expression identifies clonogenic cells capable of uterine remodeling during pregnancy, especially under hypoxic conditions[52]. For spermatogonial stem cells (SSCs), α6ITG-positive cells demonstrate enhanced colonization and self-renewal capacity in murine models[34]. Bone marrow mesenchymal stem cells (BMSCs) also exhibit a role for α6ITG, where the α6A isoform proves more efficient than α6B in promoting osteogenic differentiation[37]; however, inflammatory stimuli such as TNF-α can reduce α6ITG expression, altering migration and adhesion patterns. This observation supports the hypothesis that stress-induced environmental changes may play a role in directing stem cell fate, potentially favoring differentiation pathways that align with the mechanical or biochemical stimuli encountered by the cell.

Table 1. Structural and functional summary of α6 integrin (CD49f).

Feature	Details
Synonyms	CD49f, ITGA6, VLA-6
Gene location	Chromosome 2q31.1
Heterodimer partners	β1 (forming α6β1) and β4 (forming α6β4)
Isoforms	α6A and α6B (via alternative splicing); differ in cytoplasmic tail and function
Major ligands	Laminins (primarily laminin-511, laminin-332)
Functions	Adhesion, signal transduction, stemness maintenance, migration, invasion, and cytoskeletal regulation
Expression conservation	~90% conserved amino acid sequence in rats and mice

In dental pulp stem cells (hDPSCs), knockdown of α6ITG leads to a reduction in stemness markers such as CD105 and STRO-1, while promoting odontogenic differentiation[53]. Postnatal liver progenitor cells are similarly marked by α6ITG expression, allowing for improved colony-forming assays compared to other markers like CD13 or CD133 (ref.[38]).

Furthermore, in the broader context of embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs), laminin–α6 integrin interactions significantly promote MSC osteogenesis through signaling pathways involving FAK/ERK, Wnt5a, and BMP. Laminin fragments such as iMatrix-511 enhance odontogenic gene expression through α6β1 binding. Collectively, these examples underscore that α6ITG's function extends well beyond its use as a surface marker for cell sorting; it plays active biological roles in stem cell survival, lineage specification, and regenerative potential.

Cancer stem cells expressing α6ITG

Just as in healthy tissues, α6ITG is also prominently expressed in cancer stem cells (CSCs) from a variety of tumor types, including breast CSCs (ref.[47]), prostate CSCs (ref.[48,49]), glioblastoma stem cells[18,54-56], squamous cell carcinoma CSCs (ref.[57,58]), colon CSCs (ref.[59]), lung adenocarcinoma CSCs (ref.[60]), and HPV-positive head and neck squamous cell carcinoma (HNSCC) (ref.[61]). Because α6ITG is also found in normal stem cells, its role in CSC biology is an area of active research aimed at distinguishing its driver versus passenger roles in tumorigenesis.

Notably, in acute lymphoblastic leukemia (ALL), CD49f is expressed across most subtypes and facilitates cellular retention within the meningeal niche of the central nervous system, contributing to disease relapse. This supports the idea that CD49f may act less as a stemness determinant and more as a niche access factor essential for survival[62].

α6ITG AS A STEM CELL-ASSOCIATED MARKER

Stemness markers are molecular indicators used to enrich cell populations with enhanced self-renewal capacity, multipotency, and high proliferative potential, rather than to define stem cell identity per se. Common markers include CD44, CD133, ALDH1, CD24, EpCAM, Sox-2, Nanog, and c-Myc. Of these, α6ITG, stands out due to its consistent association with multipotent phenotypes and pluripotency-associated transcriptional networks, including context-dependent modulation of p53 signaling, a key differentiation and apoptosis regulator[63]. Its expression is modulated by Oct-4 and Sox-2, which bind to the α6ITG promoter region, affirming its relevance to both embryonic and adult stem cells. Moreover, α6ITG is directly regulated by hypoxia-inducible factors (HIFs) (ref.[64]) and Y-box binding protein-1 (YB-1) (ref.[65]). Importantly, these regulatory relationships indicate that α6ITG functions as a downstream component of stemness-associated transcriptional networks, rather than as a master regulator of stem cell identity.

Comparative transcriptomics and commonality across stem cell types

Attempts to identify universal stemness genes across various stem cell types have consistently highlighted α6ITG. In a study examining five distinct stem cell types – human fetal hematopoietic stem cells (HSCs), murine fetal and adult HSCs, neural stem cells, and embryonic stem cells – 283 common gene signatures were reported[66]. Another analysis comparing embryonic stem cells (ESCs), neural stem cells, and HSCs found 230 shared genes[40]. Similarly, a third study comparing ESCs, neural stem cells, and retinal progenitor cells identified 385 commonly expressed genes[67]. When these three datasets were cross compared, α6ITG emerged as the one of the few recurrently expressed genes across all examined stem cell types.

Importantly, shared transcriptional expression does not imply a universal functional role in maintaining stemness, but may instead reflect common biological requirements such as survival, adhesion, and interaction with laminin-rich microenvironments.

Marker specificity and conceptual limitations

Several limitations exist in defining a universal stemness marker. Variability in isolation methods may yield impure or adapted cell populations, while in vitro culture conditions can alter gene expression and induce artifactual marker profiles[68]. Additionally, many markers, including α6ITG, are also expressed in non-stem cell types,

Table 2. Key signaling pathways involving α6 integrin.

Pathway	Mechanism	Biological impact
PI3-K/Akt	IRS-1/2-dependent activation	Promotes invasion, migration, motility
MAPK/ERK	Shc–Grb2–Ras complex	Supports proliferation and environmental responsiveness
Rho GTPase	Activates RhoA and Rac1	Regulates migration and cytoskeletal remodeling
mTOR/4E-BP1	Via Akt phosphorylation	Enhances VEGF translation and cell survival
TAZ/Hippo	Laminin-511 interaction with α6Bβ1	Maintains breast cancer stemness
EGFR/HER2/ColXVIII	Complex formation	Promotes resistance and metastatic behavior
ZEB1/YAP1–FGFR1	Transcriptional upregulation in glioblastoma stem cells	Enhances stemness and proliferation

Table 3. Expression of α6ITG (CD49f) in cancer stem cells and its functional and clinical associations.

Cancer type	CSC localization / context	Functional role of α6ITG	Key signaling pathways / interactions	Biological / clinical relevance
Glioblastoma	Perivascular niches	Promotes CSC proliferation, survival, and tumor sphere formation	FGFR1 regulation via ZEB1/YAP1 axis	Knockdown reduces tumor growth and recurrence after therapy
Head and neck squamous cell carcinoma (HNSCC)	HPV tumor subpopulations	Enhances invasion, therapy resistance, and CSC maintenance	Laminin-mediated adhesion; cooperation with oncogenic pathways	High α6ITG expression correlates with poor prognosis and aggressiveness
Breast cancer	Basal-like and HER2 CSC fractions	Maintains stemness, migration, and drug resistance	Complexes with EGFR, HER2, ColXVIII; PI3K/AKT and MAPK/ERK activation	Targeting α6ITG restores sensitivity to HER2 inhibitors
Triple-negative breast cancer (TNBC)	CSC-enriched populations	Supports colony formation and self-renewal	Conformational regulation of α6ITG	Pranlukast disrupts CSC properties without cytotoxicity
Hepatocellular carcinoma (HCC)	Tumor-initiating cell populations	Drives migration, proliferation, and tumor growth	Laminin–integrin signaling	α6ITG inhibition suppresses tumor growth in xenograft models
Prostate cancer	Invasive and perineural niches	Promotes collective invasion and metastatic behavior	α6β4–laminin-332 interaction; integrin internalization	DNA aptamers targeting α6β4 reduce invasion and metastasis
Colon cancer	Tumor-initiating CSC populations	Enhances stemness and tumorigenicity	Laminin-dependent signaling	High α6ITG expression enriches for initiating cells
Acute lymphoblastic leukemia (ALL)	Meningeal niche	Facilitates niche retention and survival	Adhesion-mediated niche access	Associated with CNS relapse rather than intrinsic stemness

Table 4. Stem and cancer stem cells expressing α6 integrin.

Cell Type	Tissue / Source	Function or Relevance
Hematopoietic stem cells (HSCs)	Bone marrow	Marks long-term engraftment potential
Mesenchymal stem cells (MSCs)	Bone marrow, dental pulp	Modulates osteogenesis and migration
Embryonic stem cells (ESCs)	Blastocysts	Participates in pluripotency and self-renewal regulation
Spermatogonial stem cells (SSCs)	Testis	Enhances colonization and fertility
Myometrial stem cells	Uterus	Contributes to uterine remodeling during pregnancy
Keratinocyte stem cells	Skin	Involved in adhesion and epidermal renewal
Glioblastoma stem cells (GSCs)	Brain tumor	Promotes survival, therapy resistance, and recurrence
Breast cancer stem cells (BCSCs)	Mammary carcinoma	Maintains drug resistance, proliferation, and metastatic capability
Prostate cancer stem cells	Prostate tumors	Supports invasion and perineural spread
Colon and lung CSCs	Colorectal and lung cancers	Facilitates stemness, tumorigenicity, and poor prognosis

complicating their specificity. Accordingly, α6ITG should not be interpreted a definitive determinant of stemness. Instead, it functions as a biologically relevant enrichment marker that identifies cells capable of maintaining stem cell like behavior under appropriate microenvironmental conditions.

α6ITG EXPRESSION IN CULTIVATION AND CRYOPRESERVATION

The expression of α6ITG is highly sensitive to environmental conditions, making it a useful marker for evaluating stem cell maintenance during in vitro culture and cryopreservation.

Expression dynamics in culture

In many cell types, α6 integrin (α6ITG) expression decreases with extended in vitro passaging. For example, in bone marrow mesenchymal stem cells (BMSCs), α6ITG levels dropped from 95.2% to 48.7%, despite the retention of clonogenicity and differentiation potential[37]. Conversely, other studies have shown that overnight culture can increase α6ITG expression, such as in freshly purified hematopoietic stem/progenitor cells, indicating context-dependent regulation[39]. These differences may stem from several factors, including culture substrate and extracellular matrix (ECM) composition, cytokine supplementation, oxygen concentration, and passage number. This variability highlights the need to carefully interpret α6ITG levels in cultured cells, as they may not fully reflect the in vivo stemness status.

Role in cryopreservation

Cryopreservation is essential for biobanking and clinical applications, and the expression of α6 integrin (α6ITG) has been investigated as a marker for post-thaw stemness retention. Studies show that cryopreserved hematopoietic stem cells (HSCs) maintain their engraftment and regenerative capacity comparable to fresh cells[39]. Furthermore, α6ITG can serve as a quality control parameter for assessing cell viability and pluripotency after thawing.

Enhancing α6ITG expression in vitro

To improve stem cell yields and quality, researchers have tested small molecules that can upregulate α6ITG expression. For example, "c7," an analog of the p38-MAPK inhibitor SB203580, significantly increased the α6ITG cell population from 1.1% to 6.0% after 11 days in culture[69]. Such methods may support more efficient cell expansion, sorting, and stemness maintenance, particularly for therapeutic applications.

Conclusion of section

α6ITG plays a dual role in culture: it acts both as a functional protein in adhesion and signaling, and as a diagnostic marker of stem cell quality. Its dynamic expression in response to environmental factors must be accounted for in both basic and translational research.

DISCUSSION

Clinical applications and translational potential

The broad expression of α6ITG in both healthy and malignant stem cell populations makes it a promising target for clinical translation.

Regenerative medicine

In regenerative therapies, α6 integrin (α6ITG) serves as a reliable surface marker for isolating functionally competent stem cells, including hematopoietic stem cells[31], myogenic progenitors[33], mesenchymal stem cells (MSCs) (ref.[35-37]), and epithelial progenitors[19,20]. Its application in fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) facilitates the selection of highly clonogenic populations[70]. These sorted cells demonstrate improved grafting efficiency, making α6ITG particularly valuable in autologous transplants, tissue engineering, and stem cell therapy protocols.

Oncology

In cancer, α6 integrin (α6ITG) is increasingly recognized as a diagnostic marker and therapeutic target. It is elevated in breast, prostate[48], glioblastoma[18], and hepatocellular cancer stem cells[71], where it plays a critical role in tumor initiation, treatment resistance, and metastatic progression. Therapeutic strategies targeting α6ITG include monoclonal antibodies, aptamers and DNA-based inhibitors, and small molecule inhibitors[17,55]. These approaches have demonstrated preclinical efficacy in reducing tumor growth and metastasis. Moreover, modulation of α6ITG may enhance the effects of standard therapies such as radiation and chemotherapy by disrupting cancer stem cell (CSC) survival pathways.

Emerging directions

Innovative α6ITG-targeted platforms are currently under development for drug delivery, including siRNA- or microRNA-conjugated vectors and toxin delivery systems[72]. These vectors may enable the selective elimination of cancer stem cells (CSCs) while preserving the function of normal stem cells, potentially reducing toxicity and improving treatment precision.

Limitations and controversies

Despite its promise, several limitations and unresolved questions affect the application of α6ITG in research and therapy.

Specificity challenges

α6 integrin (α6ITG) is not exclusive to stem cells; it is also expressed on differentiated epithelial cells and actively proliferating non-stem cells. This overlap in expression may reduce α6ITG's discriminatory power in complex tissues and limit its therapeutic specificity. This widespread expression may reflect evolutionary reuse of this integrin across different cell types for niche-specific survival, rather than confounding its utility as a stemness marker per se.

Environmental sensitivity

α6 integrin (α6ITG) expression is highly context-dependent, being modulated by factors such as hypoxia, inflammatory signals, culture substrates, and passage history. This variability introduces reproducibility issues across both in vitro and in vivo studies, highlighting the need for standardized protocols to ensure more consistent and comparable results[73].

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Isoform complexity

The α6 integrin exists in two isoforms – α6A and α6B – which differ in their tissue distributions and intracellular signaling roles. However, inconsistent reporting of these isoforms in the literature creates confusion and hampers accurate interpretation[6].

Therapeutic safety

While targeting α6ITG in cancer stem cells (CSCs) is promising, it also poses significant risks. α6ITG is expressed in several healthy regenerative tissues, including the skin, intestinal crypts[74], and bone marrow, which raises concerns about potential off-target toxicity. Damage to these tissues could impair normal tissue homeostasis and compromise the body's ability to regenerate and maintain essential functions.

Network complexity

Integrins function within complex signaling webs, interacting with other integrins such as α3, β1, and β4, as well as with extracellular matrix (ECM) components and growth factor receptors. Because of these extensive interactions, isolating α6ITG's unique functional contributions requires multi-omics and systems biology approaches[75].

To unlock α6ITG's full clinical potential, it is essential to address these technical, biological, and therapeutic limitations. Further research using standardized models, isoform-specific tools, and high-resolution single-cell analyses is necessary.

CONCLUSION

This paper reviewed the diverse roles of α6 integrin (α6ITG), highlighting the dual identity of α6 integrin (CD49f): a surface biomarker widely used to identify stem cells, yet also a functional regulator of adhesion, signaling, and survival. Key findings indicate that α6ITG interacts with laminin to facilitate adhesion and signal transduction, and plays a critical role in maintaining stemness through the regulation of self-renewal, differentiation, and migration. It is also involved in several oncogenic pathways, contributing to therapy resistance and metastasis. Furthermore, α6ITG demonstrates potential as a common stemness marker across different tissues and species, and its expression appears environmentally responsive, suggesting additional applications in culture quality control and cryopreservation.

Based on integrative findings, we propose that CD49f may function primarily as a survival integrin facilitating cell anchorage in supportive niches, rather than acting as a direct inducer of stem cell pluripotency. Its elevated expression across malignancies appears to be a consequence of adaptive selection rather than a driver of oncogenic transformation.

The central open question remains: can α6ITG truly serve as a pan-stemness marker, or should it be redefined as a niche-access factor and therapeutic vulnerability? Future research must disentangle isoform-specific functions, integrate multi-omics approaches, and translate these insights into precise clinical strategies.

ABBREVIATIONS

α6ITG, Alpha 6 Integrin; ECM, Extracellular Matrix; CD49f, Cluster of Differentiation 49f; ITGA6, Integrin Subunit Alpha 6; β1, Integrin Beta 1; β4, Integrin Beta 4; RTK, Receptor Tyrosine Kinase; FACS, Fluorescence-Activated Cell Sorting; MACS, Magnetic-Activated Cell Sorting; CSC, Cancer Stem Cell; HSC, Hematopoietic Stem Cell; BMSC, Bone Marrow Mesenchymal Stem Cell; MSC, Mesenchymal Stem Cell; ESC, Embryonic Stem Cell; SSC, Spermatogonial Stem Cell; HNSCC, Head and Neck Squamous Cell Carcinoma; TNBC, Triple-Negative Breast Cancer; EGFR, Epidermal Growth Factor Receptor; HER2, Human Epidermal Growth Factor Receptor 2; ColXVIII, Collagen Type XVIII; VEGF, Vascular Endothelial Growth Factor; PI3K, Phosphoinositide 3-Kinase; IRS-1/2, Insulin Receptor Substrates 1 and 2; Akt, Protein Kinase B; mTOR, Mechanistic Target of Rapamycin; 4E-BP1, Eukaryotic Translation Initiation Factor 4E-Binding Protein 1; eIF4E, Eukaryotic Translation Initiation Factor 4E; MAPK, Mitogen-Activated Protein Kinase; ERK, Extracellular Signal-Regulated Kinase; RhoA/Rac1, Ras Homolog Family GTPases; GTPase, Guanosine Triphosphatase; TAZ, Transcriptional Co-Activator with PDZ-Binding Motif; Hippo pathway, Regulatory pathway controlling organ size and stem cell fate; FGFR1, Fibroblast Growth Factor Receptor 1; ZEB1, Zinc Finger E-Box Binding Homeobox 1; YAP1, Yes-Associated Protein 1; HIFs, Hypoxia-Inducible Factors; YB-1, Y-Box Binding Protein 1; ALDH1, Aldehyde Dehydrogenase 1; EpCAM, Epithelial Cell Adhesion Molecule; OCT4, Octamer-Binding Transcription Factor 4; SOX2, SRY-Box Transcription Factor 2; MYF5, Myogenic Factor 5; FAK, Focal Adhesion Kinase; BMP, Bone Morphogenetic Protein; siRNA, Small Interfering RNA; GFP, Green Fluorescent Protein.

Search strategy and selection criteria

Our research strategy was aimed to evaluate studies on the role of α6ITG (CD49f) and usage. Scientific articles were searched using the PubMed databases from 1989.

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