

Beyond the membrane: Internalization and compartmentalization of insulin-like growth factor 1 receptor signaling in cancer pathogenesis and treatment (Review)

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Abstract. The insulin-like growth factor 1 receptor (IGF-1R) plays a central role in tumor initiation, progression and response to treatment. IGF-1R internalization and compartmentalization have profound effects on tumor biology, extending beyond classical signaling associated with receptors at the cell membrane. Following internalization, IGF-1R alters its intracellular localization and induces new signaling functions. These changes affect the duration and spatial dynamics of signal activation, thereby influencing tumor cell proliferation, migration and the development of drug resistance. However, the exact molecular mechanisms that mediate these processes remain elusive, and the inherent complexity of the downstream signaling network continues to limit the clinical translation of IGF-1R-targeted therapies. The present review systematically summarizes the current knowledge on the molecular mechanisms of IGF-1R internalization and compartmentalization, highlighting their roles in tumor progression and treatment response. The recent advancements and persistent challenges in this field are also critically discussed, aiming to provide a theoretical foundation and new insights for the development of more efficient and effective therapeutic plans that specifically target IGF-1R.

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1. Introduction

The insulin-like growth factor 1 receptor (IGF-1R) is a tyrosine kinase (TK) receptor that plays a crucial role in regulating various biological processes, such as cell growth, differentiation and apoptosis (1-3). Upon binding its ligand, IGF-1, IGF-1R activates downstream signaling pathways that modulate cellular functions and contribute to physiological processes, such as embryonic development, organ formation and tissue regeneration (4-6). Aberrant activation of the IGF-1R is closely associated with the initiation and progression of various malignancies. For instance, elevated IGF-1R expression has been strongly correlated with tumor cell proliferation, invasion, metastasis and therapy resistance in multiple solid tumors, including hepatocellular carcinoma (7), prostate cancer (8), ovarian cancer (9), laryngeal carcinoma (10) and breast cancer (11). Furthermore, IGF-1R promotes malignant progression by modulating the tumor microenvironment, specifically by positively correlating with the infiltration of immune cells, including CD4⁺ T cells, dendritic cells and macrophages (12) and sustaining cancer stem cell properties (13).

Traditionally, IGF-1R has been viewed as a mediator of signal transduction at the plasma membrane. However, studies have suggested that after being internalized, IGF-1R can either be recycled back to the cell surface, directed for degradation or moved to specific intracellular compartments (14-18). The internalization and subsequent localization of IGF-1R to various subcellular regions, such as the Golgi apparatus, nucleus and mitochondria, exert distinct and critical regulatory effects on tumor behavior (15,16). Notably, IGF-1R accumulation in the Golgi apparatus is associated with enhanced tumor cell migration, whereas its nuclear expression is strongly correlated with increased invasiveness and poor clinical

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prognosis (17,18). Furthermore, compartmentalized signaling of IGF-1R plays a role in regulating various cellular processes, such as gene expression and mitochondrial function, revealing new mechanisms that contribute to tumor progression and resistance to therapy (19,20).

Emerging evidence underscores the subcellular localization of IGF-1R as a novel predictive biomarker of therapeutic response, providing a compelling rationale for its integration into precision oncology frameworks to optimize targeted therapy (16). Although initial clinical trials of IGF-1R monotherapy have yielded limited efficacy, recent insights into its compartmentalized signaling have revitalized the therapeutic landscape, prompting the investigation of synergistic combination strategies (17-19). Co-targeting IGF-1R with immunotherapy, chemotherapy or other targeted agents has demonstrated improved outcomes in preclinical and clinical settings (1,21). In conclusion, IGF-1R contributes crucially to tumor pathogenesis via canonical plasma membrane signaling and through internalization and compartment-specific signaling, which critically influences malignant progression and treatment resistance. The present study provides a comprehensive review of the molecular mechanisms that govern IGF-1R internalization and compartmental signaling, explores their implications in tumor progression and therapeutic resistance, and integrates recent advancements in the field, thereby providing a theoretical foundation and a novel perspective for precision cancer therapy.

2. IGF-1R-related signaling pathway

Literature search strategy. A comprehensive and systematic literature search was conducted to identify relevant studies on the internalization, compartmentalization and signaling of IGF-1R in cancer cells. The search was performed across multiple electronic databases, including PubMed (<https://pubmed.ncbi.nlm.nih.gov/>), Web of Science (<https://www.webofscience.com/>) and ScienceDirect (<https://www.sciencedirect.com/>), from their inception in September 2025. To ensure the inclusion of the most recent and comprehensive evidence, Google Scholar (<https://scholar.google.com/>) was also used for supplementary searches, minimizing the risk of publication bias. The search strategy employed a combination of key words and Medical Subject Headings related to the core themes. The primary search terms included: ('Insulin-like growth factor 1 receptor' OR 'IGF-1R' OR 'IGF1R') AND ('Internalization' OR 'Subcellular Localization' OR 'Compartmentalization') AND ('Cancer' OR 'Tumor') AND ('Signaling' OR 'Pathway'). Boolean operators (AND and OR) were used to combine these terms effectively. The following inclusion criteria were applied: i) Studies focused on IGF-1R internalization, subcellular localization, compartmentalized signaling or related trafficking mechanisms in cancer contexts; ii) articles providing mechanistic insights, functional data or clinical correlations; and iii) publications in peer-reviewed journals. Exclusion criteria included: i) Non-English articles; ii) conference abstracts, editorials, case reports or studies without full-text availability; and iii) studies not directly addressing IGF-1R biology in malignancy. The initial search results were screened based on titles and abstracts to select studies that focused on the molecular mechanisms and biological functions

of IGF-1R internalization and compartmentalization in cancer. The full texts of potentially eligible articles were retrieved and assessed for inclusion. Reference lists of key reviews and eligible studies were manually searched to identify additional relevant publications. Only articles published in English were included. Original research articles, authoritative reviews and significant clinical trial reports were selected.

Molecular structure and functional domains of IGF-1R. IGF-1R is a classic receptor TK (RTK), structurally comprising two α subunits and two β subunits linked by disulfide bonds to form a heterotetramer. Studies in structural biology have shown that IGF-1R presents a symmetrical 'A' or 'U' conformation in its unactivated state (22,23). The α subunit is entirely located extracellularly and is primarily responsible for the recognition and binding of ligands (such as IGF-1); its structure contains multiple functional domains, including leucine-rich repeats (L1 and L2), a cysteine-rich region (CR) and three fibronectin type III (FnIII-1, FnIII-2 and FnIII-3) domains, which together constitute a high-affinity binding site for IGF-1 (23). The ligand-binding sites of IGF-1R are mainly distributed in the L1 and α -carboxyl terminal (CT) helix regions of the α subunit, where these regions form multiple points of contact with the IGF-1 ligand, ensuring high specificity of binding (23,24). The CR domain and the FnIII-1 domain do not directly interact strongly with the ligand; they assist in maintaining the spatial conformation of the binding pocket and in transmitting conformational signals, thereby enhancing the stability and specificity of ligand binding (14,23,24).

The β subunit spans the cell membrane and possesses TK activity, capable of triggering downstream signaling pathways. The extracellular portion is connected to the α subunit, while the intracellular portion contains the juxtamembrane region, TK domain and CT region (25). The TK domain is the core of signal transduction, located in the intracellular region of the β subunit, and contains a highly conserved ATP-binding site and catalytic residues. Upon receptor-ligand binding, conformational changes in the kinase region lead to the phosphorylation of key tyrosine residues (such as Y1131, Y1135 and Y1136), forming anchor sites for downstream effector proteins (25,26). For instance, insulin receptor substrate (IRS) proteins in the cytoplasm are recruited and bind to the activated IGF-1R via their specific domains (such as the pleckstrin homology and phosphotyrosine binding domains), which in turn leads to the phosphorylation of multiple tyrosine residues on IRS (26). Each phosphorylated tyrosine site on phosphorylated IRS-1 can recruit downstream signaling proteins with Src homology 2 (SH2) domains [such as PI3K and growth factor receptor-bound protein 2/son of sevenless]. Once these proteins are recruited and bound, they initiate multiple signaling cascades, including two major signaling pathways: The PI3K-Akt and Shc-Ras-MAPK pathways. These signaling pathways play critical roles in cell metabolism, proliferation and survival (27,28) (Fig. 1). In summary, the structure and function of IGF-1R highlight its important role in cell proliferation and survival, and the activation of multiple signaling pathways indicates a critical role of IGF-1R in tumor progression.

It has been reported that certain mutations in the kinase domain of IGF-1R (such as K1055R) can significantly reduce

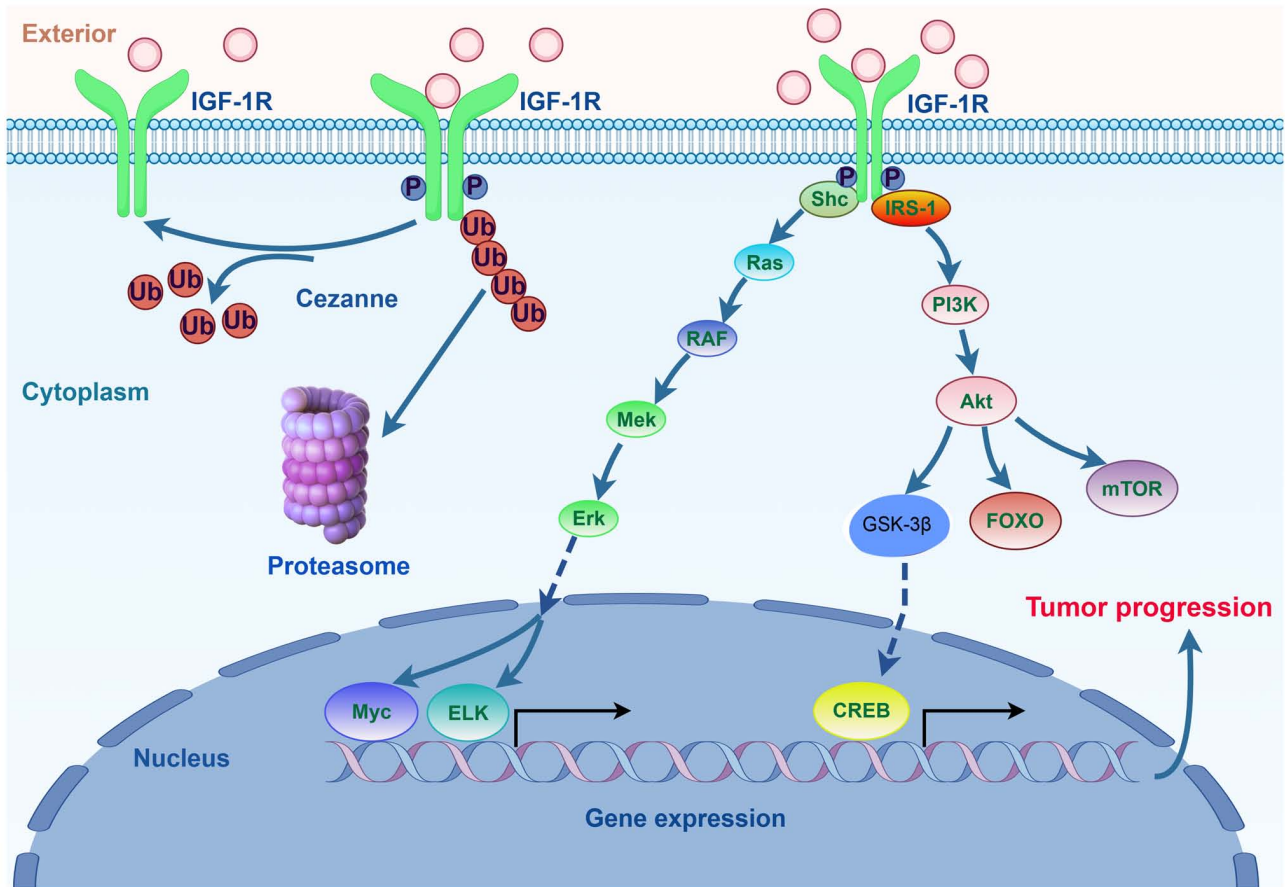


Figure 1. Schematic of the canonical IGF-1R signaling pathway. Upon binding to its ligand, IGF-1, IGF-1R activates major downstream signaling cascades, primarily the PI3K-Akt and Shc-Ras-MAPK pathways. These pathways collectively promote cell proliferation, survival and metabolic reprogramming, while inhibiting apoptosis, thereby driving oncogenic processes (created with Figdraw). IGF-1R, insulin-like growth factor 1 receptor; P, Phosphorylated; Ub, Ubiquitin; IRS-1, Insulin receptor substrate 1; ELK, E twenty-six-like kinase 1.

kinase activity but have limited effects on the subcellular localization of the receptor and some non-classical signaling functions, suggesting that the structural microenvironment of the kinase activity center finely regulates receptor function (26). Additionally, the kinase region of IGF-1R interacts with various regulatory proteins (such as Ras GTPase-activating-like protein IQGAP1) and is associated with glycosylation modifications that affect receptor stability and signal output (29). These structural characteristics determine the signaling capability of IGF-1R and provide a theoretical basis for targeted drug design. In conclusion, as a heterotetrameric RTK, the clearly defined structure and functional domain division of its α and β subunits, along with the precise regulation of ligand-binding sites and kinase domains, collectively determine the activation and signaling output characteristics of the receptor. A deeper understanding of the structure and functional domains of IGF-1R provides a solid molecular foundation for elucidating its signal transduction mechanism and targeted interventions.

Expression of IGF-1R in various tumor tissues. A comprehensive analysis of the IGF-1R expression patterns across 33 tumor types using the University of California Santa Cruz XENA tool (<https://xenabrowser.net/datapages/>) (30) was performed. Among the 33 tumor types, the expression

of IGF-1R was compared between pan-cancer cohorts from The Cancer Genome Atlas (<https://portal.gdc.cancer.gov>) and matched normal tissues from patients in the Genotype-Tissue Expression project (<https://gtexportal.org/home/>) using the Mann-Whitney U test. The R software and the R packages ggplot2[3.4.4], stats[4.2.1] and car[3.1-0] (R Core Team; R Foundation for Statistical Computing) were employed, with $P < 0.05$ considered to indicate a statistically significant difference. The results revealed that IGF-1R expression was significantly downregulated in adrenocortical carcinoma, bladder urothelial carcinoma, colon adenocarcinoma, lymphoid neoplasm diffuse large B-cell lymphoma, glioblastoma multiforme, liver hepatocellular carcinoma, lung adenocarcinoma, ovarian serous cystadenocarcinoma, rectum adenocarcinoma, testicular germ cell tumor, thyroid carcinoma, uterine corpus endometrial carcinoma and uterine carcinosarcoma compared with that in normal tissues. Conversely, significant upregulation was observed in breast invasive carcinoma, cholangiocarcinoma, esophageal carcinoma, head and neck squamous cell carcinoma, acute myeloid leukemia, brain lower grade glioma, lung squamous cell carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, skin cutaneous melanoma and thymoma tissues compared with that in corresponding normal controls (Fig. 2). These findings highlight the cancer type-specific nature of IGF-1R expression and suggest that its

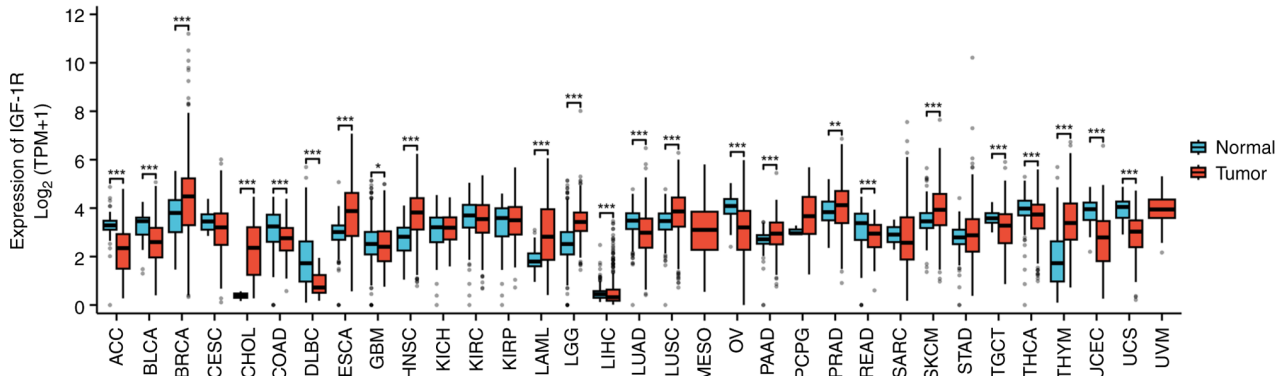


Figure 2. Pan-cancer analysis of IGF-1R expression across tumor and normal tissues. The expression levels of IGF-1R (in TPM) were compared between tumor samples from The Cancer Genome Atlas pan-cancer cohorts and matched normal tissue samples from the Genotype-Tissue Expression project. Data for 33 cancer types were uniformly processed and obtained from the University of California Santa Cruz XENA database. Statistical significances between tumor and adjacent normal groups for each cancer type were assessed using the non-parametric Mann-Whitney U test (Wilcoxon rank-sum test); * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$. CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; IGF-1R, insulin-like growth factor 1 receptor; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; MESO, mesothelioma; PCPG, pheochromocytoma and paraganglioma; SARC, sarcoma; STAD, stomach adenocarcinoma; TPM, transcripts per million; UVM, uveal melanoma.

levels and activity are dynamically regulated across different tissues and pathological contexts, thereby influencing diverse biological functions. This variability was further supported by evidence from specific malignancies, such as myxoid liposarcoma, where elevated IGF-1R expression was associated with poor metastasis-free survival, underscoring its role in tumor pathogenesis (31).

Multilayered regulatory network of IGF-1R as a central oncogenic driver. Emerging evidence indicates that the functional role of IGF-1R extends beyond classical cell membrane signaling, with its nuclear localization garnering increasing attention. For instance, IGF-1R can undergo nuclear translocation and participate in the regulation of gene transcription, suggesting a potential mechanism for tumor progression (27). Furthermore, the internalization, intracellular trafficking and sublocalization of IGF-1R have been shown to significantly influence signaling dynamics. These processes may lead to distinct biological outcomes, thereby impacting cellular behavior and oncogenesis (26,28). Therefore, elucidating the detailed mechanisms of IGF-1R localization and trafficking is essential for deepening our understanding of its biological functions and for identifying novel therapeutic targets for cancer treatment.

IGF-1R signaling serves as a central oncogenic driver in multiple malignancies, including colorectal, breast, lung, ovarian and endometrial cancer; its aberrant activation, often induced by ligand overexpression (e.g., IGF2), environmental factors (e.g., nicotine) or cues from the tumor microenvironment [e.g., tumor-associated macrophage (TAM)-derived C-X-C motif chemokine ligand 1 (CXCL1) or collagen], orchestrates an extensive downstream signaling network (32-44). Key pathways regulated by IGF-1R include PI3K/AKT/mTOR (32-35), Elk1/AP1/Myc (36), STAT3/HMGB1 (37-39), NuMA/53BP1 (40) and forkhead box P3 (FOXP3)/ β -catenin (41). Collectively, these pathways facilitate critical oncogenic processes, such as tumor proliferation (42), metastasis (43), stemness maintenance (44), metabolic reprogramming via glycolysis (45), therapy resistance (46-49)

and immune evasion (50). For instance, TEA domain transcription factor 4 transcriptionally upregulates RNA-binding motif protein 8A (RBM8A), which partners with eukaryotic initiation factor-4A3 to stabilize the IGF-1R and IRS-2 mRNAs, thereby activating the PI3K/AKT signaling pathway and promoting breast cancer progression. This RBM8A-mediated post-transcriptional regulation represents a novel mechanism underlying IGF-1R-driven oncogenesis (32). G-protein coupled receptor-associated sorting protein 1 (GASP1) stabilizes IGF-1R by competitively inhibiting MDM2-mediated ubiquitination and activating the downstream NF- κ B, PI3K/AKT and MAPK/ERK pathways to drive breast cancer progression. This GASP1-IGF-1R signaling loop creates a vicious cycle that enhances malignant phenotypes and reduces paclitaxel sensitivity, suggesting the potential for dual therapeutic targeting (51). Metformin inhibits endometrial cancer cell viability *in vitro* by inducing cytotoxicity and cell cycle arrest, while, *in vivo*, it suppresses tumor growth and downregulates key components of the IGF-1R and PI3K/AKT/mTOR signaling pathways. The drug's antitumor effects involve the modulation of multiple targets, including mTOR and MAPK3, suggesting a complex mechanism of action beyond direct IGF-1 level reduction (52). Elevated FOXP3 expression promotes breast cancer progression by directly binding to the β -catenin promoter and enhancing its transcription. IGF-1R signaling activates this FOXP3- β -catenin axis, suggesting a novel therapeutic target that is effectively inhibited by the compound elesclomol (41). Monensin suppresses colorectal cancer proliferation and migration by elevating IGF1 to inhibit IGF-1R signaling and concurrently targeting multiple oncogenic pathways, including Elk1/AP1/Myc. This antibiotic demonstrates repurposing potential as an IGF-1R-axis-targeting agent in colorectal cancer therapy (36). Nicotine upregulates cholinergic receptor nicotinic α 9 subunit and IGF-1R expression to promote cancer stemness, migration and metastasis in triple-negative breast cancer (TNBC). Targeting IGF-1R signaling suppresses nicotine-induced malignancy and represents a therapeutic strategy for high-risk patients with TNBC (53). Lactate-induced lactylation stabilizes the IGF-1R protein and enhances its binding

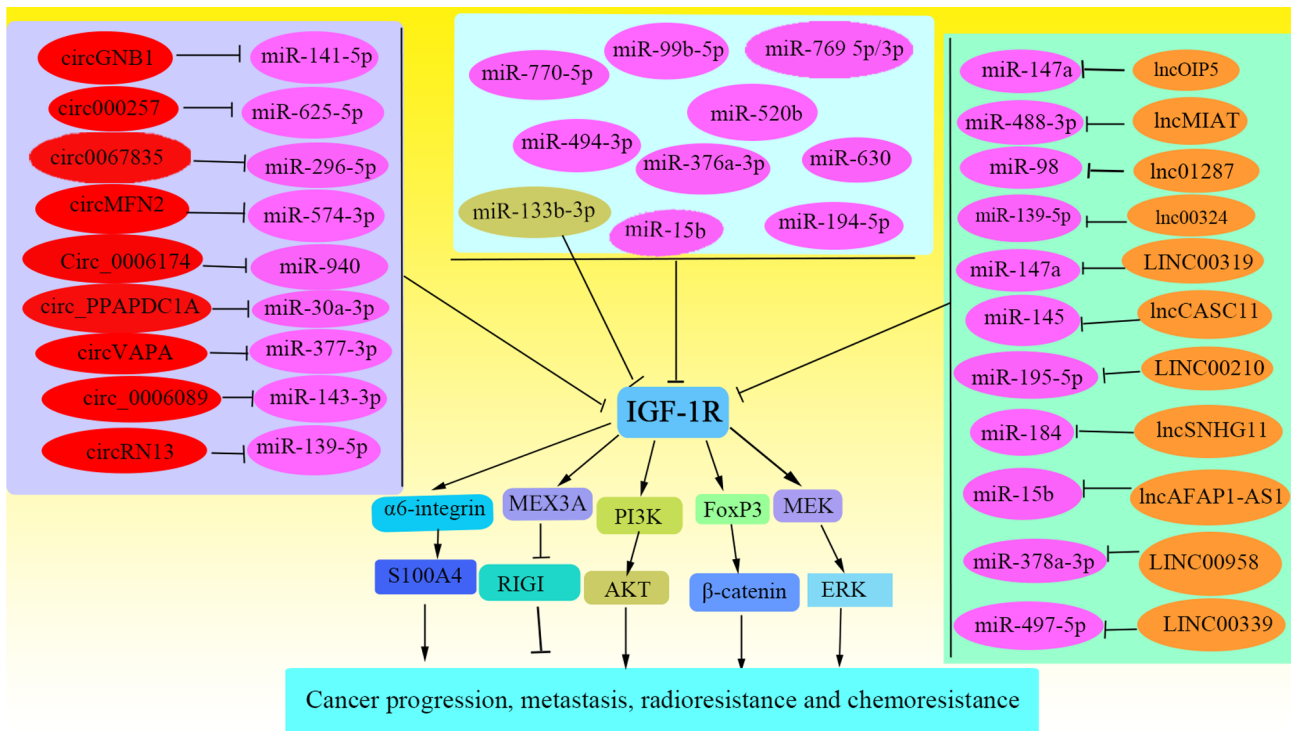


Figure 3. ceRNA network regulating IGF-1R-mediated cancer phenotypes. A conceptual model illustrating how ncRNAs, including lncRNAs and circRNAs, can function as molecular sponges to sequester miRNAs that target *IGF-1R* mRNA. Through this ceRNA mechanism, these ncRNAs indirectly upregulate IGF-1R expression and activity, thereby influencing key cancer hallmarks, such as tumor progression, metastasis and therapeutic resistance to radiotherapy and chemotherapy. ceRNA, competing endogenous RNA; IGF-1R, insulin-like growth factor 1 receptor; ncRNAs, non-coding RNAs; lncRNAs, long non-coding RNAs; circRNA, circular RNAs; miRs/miRNAs, microRNAs; MEX3A, Mex-3 RNA binding family member A; RIGI, antiviral innate immune response receptor RIG-I.

to IGF1, thereby promoting glycolysis and proliferation in lung cancer cells. This metabolic reprogramming establishes a feed-forward loop in which IGF-1R-driven lactate production further amplifies its own oncogenic signaling (45). TAM-secreted CXCL1 promotes autophagic chemoresistance in breast cancer by stabilizing the IGF-1R through suppressed von Hippel-Lindau (VHL)-mediated ubiquitination, subsequently activating STAT3/HMGB1 signaling. Targeting the CXCL1/IGF-1R axis reverses paclitaxel resistance and correlates with improved clinical outcomes (37). Additionally, p52-zinc-finger estrogen receptor interaction clone 6 (ZER6) maintains cancer stem cell populations by transcriptionally upregulating IGF-1R to enhance pro-survival mitophagy, distinguishing its function from that of the p71-ZER6 isoform. Targeting this axis represents a promising therapeutic strategy to exhaust cancer stem cells (CSCs) and inhibit tumor progression (44).

Furthermore, IGF-1R activity is fine-tuned through multifaceted regulatory mechanisms, including transcriptional control (e.g., by SOX4), post-translational modifications (e.g., VHL-mediated ubiquitination) and non-coding RNA networks (e.g., circular (circ)RNA/microRNA (miR/miRNA)-mediated competing endogenous RNA mechanisms), underscoring its role as a dynamic signaling hub (Fig. 3) (54). Specifically, some miRNAs (Table SI), including miR-770-5p, miR-376a-3p, miR-133b, miR-99b-5p, miR-144, miR-98-5p, miR-520b, miR-99a, miR-15b and miR-194-5p, have also been reported to regulate corresponding downstream signaling pathways by interfering with IGF-1R expression, thereby

exhibiting anticancer effects or promoting chemotherapy sensitivity (35,46,47,55-61). In addition, long non-coding RNAs that regulate IGF-1R (Table SII) include MLETA1, LINC02381, HULC, OIP5-AS1, MIAT, LINC01287, SNHG11, AFAP1-AS1, CASC11, LINC00324, Linc00210, LINC00958, LINC00319 and LINC00339 (11,62-74), and circRNAs (Table SIII) including Circ_0006174, Circ_PPAPDC1A, Circ-IGF-1R, CircVAPA, Circ_0067835, CircRNF13, Circ_0002577, CircGNB1 and Circ_0006089 (75-83) promote the expression or stability of IGF-1R by inhibiting miRNAs.

Molecular mechanisms of IGF-1R internalization and compartmentalized signaling. Emerging research has fundamentally shifted the traditional paradigm, revealing that IGF-1R internalization is not an endpoint, but a critical regulatory node that diversifies signaling outputs through subsequent compartmentalization (15-18). This review section delineates the molecular journey from endocytosis to functional engagement within distinct subcellular locations, providing a mechanistic basis for context-dependent signaling.

Mechanism for the initiation of ligand-dependent endocytosis. The ligand-dependent endocytosis of IGF-1R begins with the binding of IGF-1 to the receptor, which induces a conformational change in the receptor's structure. This triggers a spatial rearrangement of the extracellular domain of IGF-1R and promotes receptor dimerization and exposure of its autophosphorylation active sites, thereby activating its TK function (14,84). This conformational change marks the

initiation of signal transduction and is a crucial prerequisite for endocytosis. Receptor endocytosis and subsequent subcellular localization are critical for determining specific signaling responses. For example, IGF-1R is regulated by cell adhesion receptors and endocytosis-related proteins in different cell types, indicating that endocytosis has a high degree of cell specificity (14).

Receptor phosphorylation is the second most important event in ligand-dependent endocytosis. After ligand binding, the intracellular tyrosine residues of IGF-1R are rapidly phosphorylated. This phosphorylation activates downstream signaling pathways and provides molecular recognition sites for the recruitment of endocytosis-related proteins. Specifically, phosphorylated IGF-1R can attract various endocytic adaptor proteins, among which the adaptor-related protein complex 2 subunit $\alpha 1/2$ (AP2A1/2) complex and flotillin-1 (Flot-1) are core adaptor molecules that mediate the classical clathrin-dependent and noncaveolar lipid raft-associated endocytic pathways, respectively (84). It has been reported that AP2A1/2 dominates receptor endocytosis at high IGF-1 concentrations, whereas Flot-1 is more sensitive at low IGF-1 concentrations. Dual knockdown of both proteins significantly inhibits endocytosis, indicating their functional synergy (84). Additionally, the palmitoylation modification of Flot-1 dynamically regulates its function, with acyl protein thioesterases-1 (APT-1) and palmitoyltransferase ZDHHC19 (ZDHHC19) responsible for its depalmitoylation and repalmitoylation, maintaining its cycling and function, thereby preventing IGF-1R desensitization and degradation while promoting sustained receptor signaling output (85). The cooperation of these proteins determines the efficiency of IGF-1R endocytosis and affects subsequent signal partitioning and downstream biological effects of the receptor. Thus, the dynamic regulation of endocytosis-related proteins provides a molecular basis for the adaptive response of cells to IGF-1 signaling, and the selectivity of different endocytic pathways may be closely linked to changes in the cell type and microenvironment.

Internalization: Pathways, trafficking and fate decisions. IGF-1R initiates signal transduction at the plasma membrane under ligand stimulation and undergoes endocytosis, entering different compartments within the cell. Studies have found that IGF-1R forms specific signaling complexes in endosomes, providing spatial specificity to signal transduction (14,86). Using methods such as confocal microscopy and immunoprecipitation, it has been confirmed that IGF-1R can enter Rab5-positive early endosomes via clathrin-mediated endocytosis, where IGF-1R can form active complexes with downstream signaling proteins (such as IRS and AKT), maintaining continuous signal transmission. Notably, the endocytosis and transport of IGF-1R in different cell types are regulated by cell adhesion receptors and related proteins, affecting the specificity of the signals (14). In intestinal epithelial cell models, IGF-1R, after clathrin-dependent endocytosis, enters Rab5-positive endosomes and is transported to the Golgi apparatus with the help of the dynein-microtubule system, laying the groundwork for subsequent signal compartmentalization and nuclear transport (86) (Fig. 4). This process reveals that endosomes are sites for signal termination and key nodes for the continuous regulation and compartmentalization of signals.

Furthermore, the signaling activity of IGF-1R in endosomes is closely related to its subsequent sorting. Some IGF-1Rs in early endosomes are recycled to the plasma membrane, maintaining the cell's sensitivity to IGF-1, while another portion is transported to the lysosomes for degradation, terminating the signal (14). Thus, once internalized, IGF-1R may undergo one of three main outcomes: Dephosphorylation, degradation through ubiquitination or recycling (87). The internalization and subsequent dephosphorylation of IGF-1R play critical roles in signal termination and prevention of aberrant activation (88). The precise regulation of these processes has emerged as an important area of research in cancer and metabolic diseases. These mechanisms suggest that receptor signaling activation in endosomes results from a balance between receptor degradation and recycling, and this balance underlies the cell's finely tuned response to external stimuli.

i) Clathrin-mediated endocytosis mechanism. The endocytosis of IGF-1R is mainly mediated by the clathrin-mediated endocytic pathway, a process that is far from a simple signal termination mechanism, but rather initiates a precisely regulated intracellular journey and becomes a critical hub determining receptor signal partitioning and downstream biological effects (86,87). It has been reported that, in various cell types, after IGF-1 binds to the receptor, the activated IGF-1R interacts with clathrin and its core adaptor protein complex (such as AP2A1/2) and is encapsulated into clathrin-coated vesicles, thus completing endocytosis. This pathway is particularly pronounced under stimulation at high concentrations of IGF-1 (84).

After entering the cell, the receptor is sorted into the Rab5-positive early endosome, which is the first decision point in the intracellular transport pathway. The key transport regulatory factors determine the subsequent destination. Specifically, the transport system relies on the microtubule network, particularly for retrograde transport, mediated by the dynein activator complex subunit p150Glued (89). This system transports receptors back to the perinuclear region. A critical step for the receptor's entry into the nucleus depends on the classical nuclear transport mechanism: The receptor interacts with the nuclear transport receptor importin β at the nuclear pore and ultimately crosses the pore under the regulation of the nuclear pore protein NUP358 (RanBP2) (86). Notably, small ubiquitin-related modifier 1 (SUMO1) modification of IGF-1R is a key driving factor in this process, which is catalyzed by SUMO E3 ligases, such as RanBP2, and is crucial for stabilizing the receptor and promoting its interaction with the nuclear pore complex (89). Specifically, IGF-1 stimulation can induce SUMO1 modification on three conserved lysine residues (Lys1025, Lys1100 and Lys1120) of the IGF-1R β subunit. This modification is a prerequisite for nuclear translocation, and mutations at these sites completely block nuclear entry without affecting the classical kinase signaling pathway (90). In a number of cancer types (such as breast and colorectal cancer), IGF-1R has been observed to accumulate in the nucleus. This is closely related to increased tumor malignancy and a poor prognosis, suggesting that inhibiting its nuclear translocation may be a potential therapeutic strategy (14).

By contrast, the pathway directing receptor degradation is controlled by the GTPase Rab7a. Rab7a guides the maturation of early endosomes to late endosomes/lysosomes, ultimately

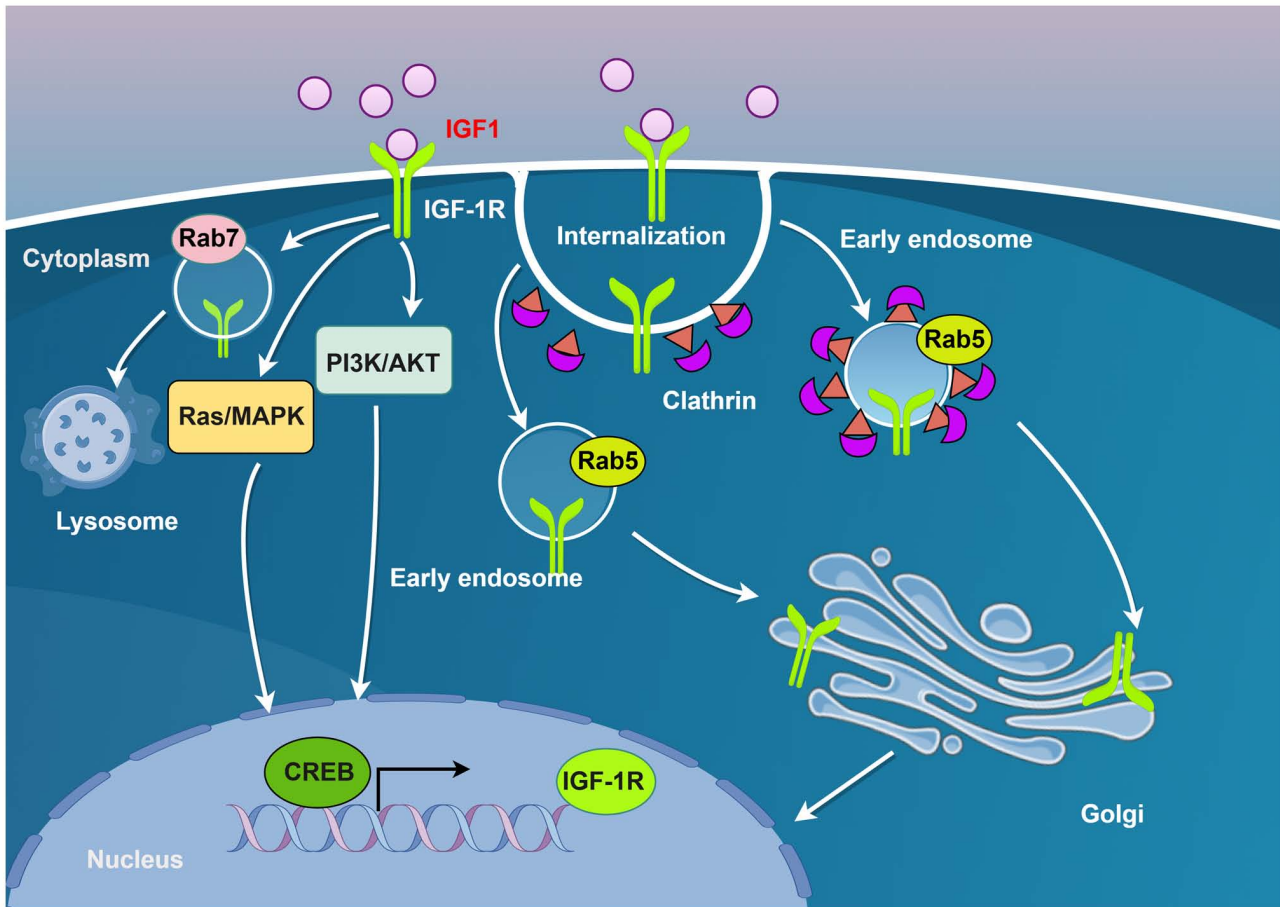


Figure 4. Compartmentalized signaling of IGF-1R regulates diverse tumor biological behaviors. Following ligand-induced activation and internalization, IGF-1R undergoes complex intracellular trafficking. It can be i) recycled back to the plasma membrane to sustain signaling; ii) targeted to lysosomes for degradation to attenuate signaling; iii) transported to the Golgi apparatus, where it can influence cell migration and invasion; or iv) translocated to the nucleus, where it may directly regulate gene expression. This spatial regulation critically determines the diverse biological outputs of IGF-1R signaling in cancer. (Created with Figdraw). IGF-1R, insulin-like growth factor 1 receptor.

leading to receptor degradation (91,92). Inhibiting the function of Rab7a significantly enhances IGF-1R stability and prolongs its downstream signaling, highlighting the core role of this molecule in the precise regulation of receptor turnover (93).

ii) Non-clathrin-mediated endocytic pathways and their molecular basis. In addition to the classical clathrin-mediated mechanism, IGF-1R can also mediate intracellular transport through non-clathrin-mediated endocytic pathways (such as caveolae- and macropinocytosis-mediated pathways), where Flot-1 plays a central role. It has been reported that the dynamic regulation of Flot-1 palmitoylation affects IGF-1R sensitivity and degradation, preventing receptor desensitization and lysosomal degradation (85). Specifically, the palmitoylation of Flot-1 is co-regulated by APT-1 depalmitoylating enzyme and ZDHHC19 palmitoyl transferase, modulating the membrane localization and functional activity of Flot-1. The dynamic changes in this modification can prevent excessive degradation of IGF-1R after endocytosis, maintain the receptor's continuous activation state, and particularly promote malignant phenotypes such as epithelial-mesenchymal transition, migration and invasion in tumor cells (85). Furthermore, the endocytosis of IGF-1R is also regulated by cell adhesion molecules, with $\beta 1$ integrin (ITGB1) enhancing receptor endocytosis and Golgi apparatus accumulation by promoting

the phosphorylation of the C-terminal Tyr1250/1251 sites of IGF-1R, thereby initiating specific intracellular signaling distinct from the insulin receptor (18,94). In migratory cancer cells, IGF-1R can localize to the Golgi apparatus and continuously activate signaling pathways, enhancing cell migration ability (15-18). Considering the high expression of Flot-1 and its associated enzymes, which are closely related to cancer progression (85), interventions targeting this pathway are expected to provide new strategies for antitumor therapy. In summary, the endocytic mechanisms of IGF-1R exhibit diversity and high plasticity, and the synergy and complementarity between different endocytic pathways assure the fine regulation of receptor signals.

iii) Post-endocytic trafficking and fate determination. The fate of the internalized IGF-1R represents a critical branch point in signal regulation, culminating in three primary outcomes: Recycling back to the membrane following dephosphorylation by protein tyrosine phosphatases (PTPs) (including PTP1B and SHP2), targeted destruction via ubiquitination-mediated degradation and compartmental sequestration of organelles, such as the Golgi apparatus or nucleus. Regulatory inputs, including ITGB1-mediated phosphorylation at Tyr1250/1251, significantly bias this fate decision by modulating receptor accumulation in specific subcellular compartments, a process

distinct from that involving the insulin receptor (18,94). Nuclear translocation requires interaction with nuclear pore complex components (e.g., NUP358) to facilitate receptor transport into the nucleus (95,96).

Dysregulation of these finely balanced fate decisions, a common hallmark of cancer, results in sustained IGF-1R signaling and ultimately promotes malignant progression. This can manifest as failed degradation and as aberrant receptor accumulation on the plasma membrane, as observed with IGF1R in acute lymphoblastic leukemia, which prolongs surface residency to enhance pro-survival signaling (97).

Compartmentalized signaling and its functional outputs. The spatial segregation of internalized IGF-1R confers distinct signaling capabilities, profoundly influencing tumor cell behavior and therapeutic response. This compartmentalized signaling is a key mechanism behind the functional pleiotropy of IGF-1R.

i) Golgi apparatus. IGF-1R localized to the Golgi complex is actively involved in promoting cell migration and invasion (3,98). This accumulation is a hallmark of migratory cancer cells and is regulated by phosphorylation at Tyr1250/1251, often downstream of integrin signaling (18,94). From this perinuclear location, IGF-1R activates signaling pathways that facilitate cytoskeletal reorganization and support invasive behavior (18). New cell adhesion events can dynamically shift Golgi complex-accumulated IGF-1R back to the plasma membrane, illustrating a sophisticated feedback loop between migration and adhesion (18,94).

ii) Nucleus. Emerging research solidifies the direct involvement of nuclear IGF-1R in orchestrating the DNA damage response (DDR), a key mechanism underlying therapy resistance (99). IGF-1R modulates DDR through both cytoplasmic signaling and direct nuclear actions. Cytoplasmically, IGF-1R-activated PI3K/AKT and MAPK/ERK pathways can upregulate the expression of DNA repair scaffold proteins, such as X-ray repair cross-complement group 1, which is crucial for base excision repair (100,101). Consequently, inhibition of these pathways can attenuate repair capacity and enhance chemosensitivity. More directly, IGF-1R translocates to the nucleus via mechanisms involving SUMOylation (102). Once inside, it influences DDR in two primary ways: First, by binding to enhancer regions and regulating the transcription of genes involved in repair and survival; and second, by physically facilitating the repair process itself. Functional studies in colorectal cancer models provide direct evidence, as depletion or inhibition of IGF-1R markedly sensitizes cells to radiation. This sensitization is mechanistically linked to a significant reduction in the formation of RAD51 and 53BP1 foci, key markers of homologous recombination and non-homologous end joining repair, respectively, following irradiation. This impairment in the repair complex assembly leads to an accumulation of unrepaired DNA damage and enhanced G₂/M-phase cell cycle arrest (99). Therefore, nuclear IGF-1R acts both as a transcriptional regulator and as a direct coordinator of DNA repair machinery, making it a central player in conferring resistance to radiotherapy and genotoxic chemotherapies.

iii) Endosomes/lysosomes. Signaling from endosomal compartments can prolong pathway activation, while lysosomal degradation represents a definitive signal termination

mechanism (103). The balance between these outcomes is critically regulated by Rab GTPases (e.g., Rab5 and Rab7a) and the ubiquitination status (104,105).

iv) Mitochondrial crosstalk. Through the PI3K-AKT axis, IGF-1R signaling indirectly promotes mitophagic clearance and reduces reactive oxygen species, supporting metabolic adaptation and cell survival (106-108).

This compartmentalized signaling network ensures that IGF-1R can elicit appropriate biological responses, such as proliferation, migration, DNA repair or metabolic adaptation, depending on its subcellular localization and the cellular context (109,110). In summary, the internalization and compartmentalization of IGF-1R constitute a sophisticated spatial regulatory system. By directing the receptor to specific organelles, tumor cells harness distinct signaling outputs to drive migration, enhance survival, repair DNA damage and adapt metabolically, thereby fueling progression and evading therapies. This refined understanding moves beyond the membrane-centric view and reveals novel vulnerabilities for therapeutic intervention, such as targeting specific endocytic adaptors (Flot-1 and Cezanne) or disrupting the nuclear translocation machinery.

Immune regulation by IGF-1R and the tumor microenvironment. The internalization and compartmentalized signaling of IGF-1R influence the biological behavior of tumor cells and profoundly shape the adaptability and immune-modulatory capacity of the tumor microenvironment (TME) (111,112). Following internalization, IGF-1R can sustain the activation of downstream signaling pathways, such as PI3K/AKT/mTOR and MAPK/ERK, from subcellular compartments, including endosomes and lysosomes (113). This enhances the adaptive responses of tumor cells to stressors and therapeutic pressures within the TME. Compartmentalized IGF-1R signaling modulates how tumor cells respond to classic TME features, such as metabolic stress, hypoxia and acidosis, while also influencing the recruitment and differentiation of immune cells. For example, aberrant activation of mTOR signaling promotes the metabolic reprogramming of tumor cells and regulates immune cell metabolism and function, thereby fostering an immunosuppressive microenvironment (111). For instance, IGF-1R activation promotes colorectal tumor growth through a non-canonical β -arrestin-2/Mex-3 RNA binding family member A pathway that degrades antiviral innate immune response receptor RIG-I and suppresses type I interferon responses in the tumor microenvironment. Targeting this immune evasion mechanism restores sensitivity to checkpoint inhibitors, revealing a novel therapeutic strategy for IGF-1R-driven cancers (50). Inhibition of IGF2-IGF-1R signaling with PQ401 delays the growth of IGF2-high colorectal cancer cells by modulating myeloid-derived suppressor cells (MDSCs), which enhance T cell-mediated antitumor immunity. PQ401 treatment reduces the suppressive function and recruitment of MDSCs, leading to increased infiltration and activity of CD4(+) and CD8(+) T cells, thereby inhibiting tumor growth in IGF2-high colorectal cancer (114). Collagen-rich tumor microenvironments in TNBC upregulate the IGF-1R via SOX4 and DDR1, promoting immunosuppression and T-cell exhaustion. Targeting IGF-1R reverses this cold phenotype and synergizes with anti-programmed cell death protein 1 (PD-1) therapy to enhance antitumor immunity (115).

Combined IGF-1R inhibition and PD-1 blockade synergistically enhance dendritic cell maturation and CD8(+) T cell-mediated antitumor immunity in epithelial ovarian cancer. This dual targeting strategy reduces the tumor burden more effectively than monotherapy by remodeling the immunosuppressive tumor microenvironment (116). Glucosidase 2 subunit β (PRKCSH) stabilizes IGF-1R and enhances its oncogenic signaling, thereby conferring resistance to tumor necrosis factor superfamily (TNFSF)-mediated apoptosis in lung cancer. Targeting PRKCSH sensitizes tumors to natural killer (NK) cell-mediated cytotoxicity, suggesting a combined therapeutic approach for TNFSF-resistant malignancies (49). Furthermore, tumor cells facilitate the recruitment and functional enhancement of immunosuppressive cells through exosome-mediated transfer of signaling molecules, while simultaneously inhibiting the antitumor response of effector immune cells. This process ultimately promotes tumor progression and immune escape (117). IGF-1R promotes lung metastatic implantation and progression by remodeling the tumor microenvironment through enhanced vascularization, inflammation and immunosuppression. Host IGF-1R deficiency significantly attenuates the metastatic burden and alters multiple stromal components, positioning IGF-1R as both a therapeutic target and potential biomarker in non-small cell lung cancer metastasis (118). In summary, the internalization and compartmentalized signaling of IGF-1R represent a key adaptive mechanism through which tumor cells respond to microenvironmental changes and serve as a crucial determinant of immune regulation and treatment response within the TME. These insights provide a strong theoretical foundation for the development of novel therapeutic strategies that target TME adaptation and immunomodulation.

For the present review, a correlation analysis was performed between IGF-1R expression and immune infiltration profiles across pan-cancer datasets from The Cancer Genome Atlas (TCGA) database. Immune cell infiltration levels were quantified via the single-sample Gene Set Enrichment Analysis algorithm implemented in the R package GSVA (v1.46.0) (119), based on a curated panel of 24 immune cell-specific gene sets described by Bindea *et al* (120). Spearman's rank correlation test was applied between IGF-1R expression (ENSG00000140443.15) and the infiltration scores of each immune subset. The analysis was conducted using R software (v4.2.1; R Foundation for Statistical Computing) with the ggplot2 package (v3.4.4) for visualization. Correlation coefficients and corresponding P-values were calculated for all immune cell types across TCGA cancer cohorts. Data are presented as Spearman's rho (ρ) in the heatmap (Fig. 5; Tables SIV and SV), with statistical significance defined as a two-sided P-value of <0.05 . The results, visualized by a heatmap (Fig. 5; Tables SIV and SV), revealed a positive correlation between the IGF-1R and T central memory (Tcm) cells and significant negative correlations with plasmacytoid dendritic cells (pDCs), T cells, NK CD56bright cells, NK CD56dim cells, and T helper 1 (Th1) cells. These findings indicate that the IGF-1R signaling pathway plays a key regulatory role in the TME. Although other immune subsets (e.g., general T helper cells) also show correlations in the heatmap, the selected populations exhibited the most robust and reproducible associations with IGF-1R expression, supporting their potential mechanistic

and translational relevance. The effect of IGF-1R signaling on immune cells is primarily reflected in the regulation of their differentiation, recruitment and functional states. For instance, IGF-1R activation can promote the accumulation of immunosuppressive cells, such as regulatory T cells and MDSCs, while inhibiting the antitumor activity of effector T cells and NK cells, thereby facilitating immune evasion by tumor cells. Furthermore, various signaling molecules within the TME, including growth factors, lipid metabolites and metal ions, interact with the IGF-1R pathway to modulate the functional state of tumor-associated immune cells. For example, the PI3K/AKT/mTOR signaling axis, a key downstream pathway of IGF-1R, regulates immune cell differentiation, metabolism and effector functions; its aberrant activation often creates an immunosuppressive microenvironment that can compromise the efficacy of immunotherapy (111). IGF-1 and IGF-1R demonstrate distinct pan-cancer expression patterns with significant prognostic implications, with elevated levels correlating with poor survival outcomes in specific malignancies and altered tumor immune microenvironments. Their association with immune checkpoint markers and genomic instability features positions IGF-1R signaling as both a prognostic biomarker and a potential immunotherapeutic target across multiple cancer types (12).

Role of IGF-1R internalization and compartmentalized signaling in cancer therapy

Mechanisms of resistance to IGF-1R-targeted therapy. Targeted therapy against IGF-1R has demonstrated considerable therapeutic potential in multiple cancer types; however, drug resistance remains a major limitation to its clinical efficacy. Receptor recycling and sustained signaling activation are among the key mechanisms that confer resistance to IGF-1R inhibitors (112). Tumor cells enhance IGF-1R recycling, enabling continuous signal transduction under therapeutic conditions, thereby diminishing drug inhibition. Furthermore, internalized IGF-1R can engage in crosstalk with other signaling pathways, such as by forming heterodimers with EGFR or HER2, leading to activation of downstream survival and proliferation pathways, including PI3K/AKT and Ras/RAF/ERK. This results in redundant signaling networks that further exacerbate resistance (121). Additionally, certain tumor cells upregulate IGF-1R ligands (e.g., IGF-1 and IGF-2) or downstream signaling molecules to enhance pathway activity and counteract monotherapeutic inhibition (122,123). IGF-1R signaling also interacts with DNA damage repair mechanisms and resistance-associated proteins such as polycomb complex protein BMI-1. Co-inhibition of these pathways can increase sensitivity to radiotherapy, chemotherapy and targeted agents, thereby delaying the emergence of resistance (99,124). Therefore, combination therapeutic strategies that simultaneously target IGF-1R internalization/compartmentalization and its synergistic pathways may enable multilevel, multitarget interventions in tumor biology, offering a rational approach to overcome mono-drug resistance and improve treatment outcomes.

Progress in drug development and preclinical research. Targeting of the IGF-1R signaling axis has led to the development of diverse therapeutic agents, including monoclonal antibodies, small-molecule TK inhibitors and soluble receptor

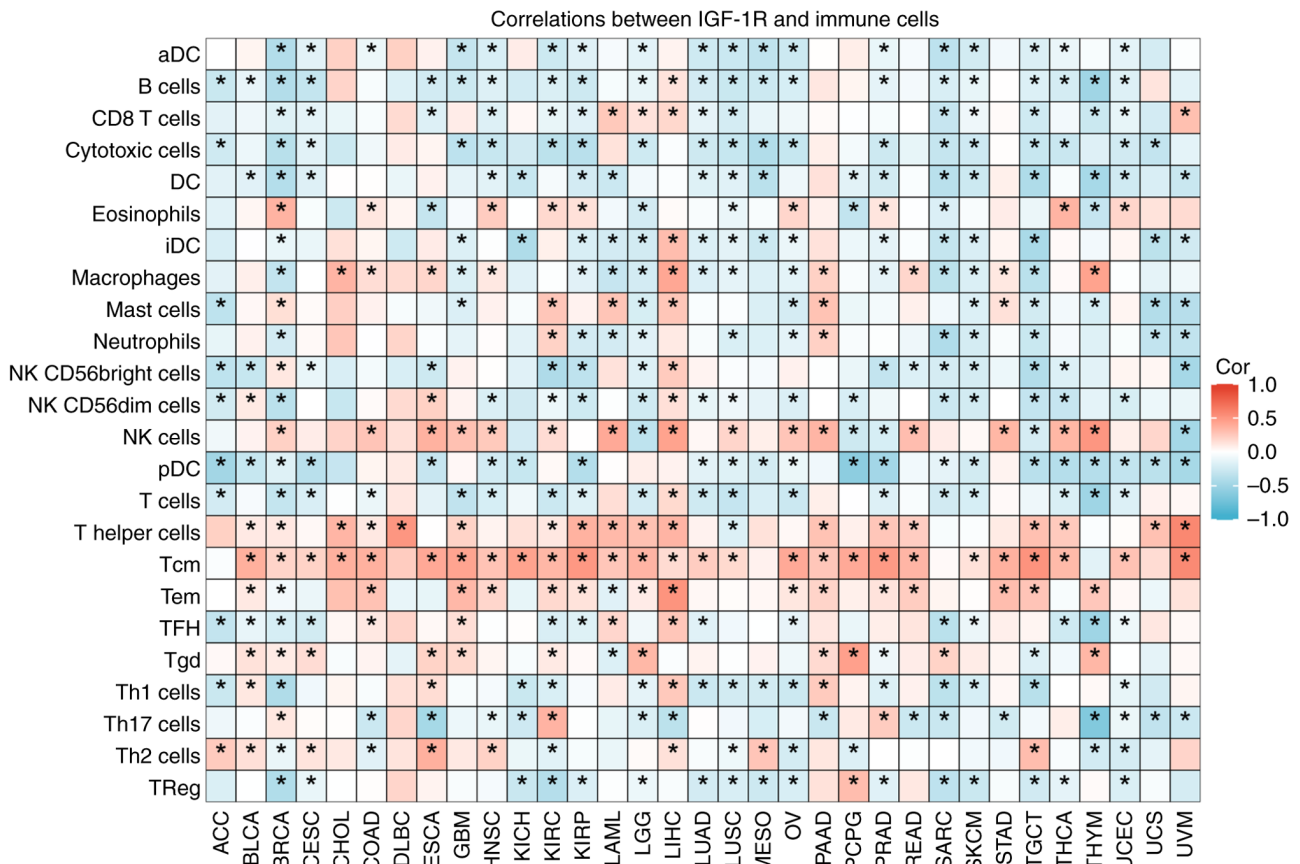


Figure 5. Correlation between IGF-1R expression and immune cell infiltration in the tumor microenvironment across cancers. A heatmap depicting Spearman's correlation coefficients between IGF-1R expression levels (transcripts per million) and the estimated abundance of various immune cell populations across 33 cancer types from The Cancer Genome Atlas ($P < 0.05$). Red indicates positive correlations and blue indicates negative correlations. This pan-cancer analysis suggests the potential role of IGF-1R in modulating the tumor-immune microenvironment. IGF-1R, insulin-like growth factor 1 receptor; cor, correlation. ACC, adrenocortical carcinoma; BLCA, bladder urothelial carcinoma; BRCA, breast invasive carcinoma; CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CHOL, cholangiocarcinoma; COAD, colon adenocarcinoma; DLBC, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GBM, glioblastoma multiforme; HNSC, head and neck squamous cell carcinoma; KICH, kidney chromophobe; KIRC, kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LAML, acute myeloid leukemia; LGG, brain lower grade glioma; LIHC, liver hepatocellular carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MESO, mesothelioma; OV, ovarian serous cystadenocarcinoma; PAAD, pancreatic adenocarcinoma; PCPG, pheochromocytoma and paraganglioma; PRAD, prostate adenocarcinoma; READ, rectum adenocarcinoma; SARC, sarcoma; SKCM, skin cutaneous melanoma; STAD, stomach adenocarcinoma; TGCT, testicular germ cell tumors; THCA, thyroid carcinoma; THYM, thymoma; UCEC, uterine corpus endometrial carcinoma; UCS, uterine carcinosarcoma; UVM, uveal melanoma; iDC, immature dendritic cells; NK, natural killer cells; Tem, T central memory cells; Tgd, $\gamma\delta$ T cells; TFH, T follicular helper cells; Th1, T helper 1 cells.

mutants (125-128). In preclinical studies, a recombinant adenovirus-expressing dominant-negative mutant of IGF-1R effectively suppressed tumor cell proliferation, migration and tumorigenesis, demonstrating broad inhibition of downstream pathways such as PI3K/AKT and Ras/RAF/MAPK (125). Moreover, IGF-1R-specific inhibitors (e.g., NVP-AEW541 and picropodophyllin) have shown promising antitumor activity in multiple tumor models. Combination therapies involving mTOR inhibitors (e.g., rapamycin), immune checkpoint inhibitors, CDK4/6 inhibitors, BRAF/MEK inhibitors or DNA damage repair inhibitors significantly enhance treatment efficacy and help overcome resistance and tumor heterogeneity (1,126). Preclinical evidence indicates that IGF-1R inhibitors can synergize with radiotherapy and chemotherapy by increasing tumor cell sensitivity to DNA damage and promoting cell cycle arrest and apoptosis (99). In the context of CSC-targeted therapies, IGF-1R signaling inhibitors effectively reduce stemness and suppress tumor recurrence and metastasis (7,13). Novel tools, such as molecular imaging probes and

fluorescently labeled antibodies against IGF-1R, are also under development, providing a technical foundation for precise diagnosis and treatment response monitoring (127,128).

Biomarkers and prediction of therapeutic response. Recent advances have highlighted the potential of IGF-1R internalization- and compartmentalization-associated molecules as predictive biomarkers of tumor therapeutic responses. The subcellular localization of internalized IGF-1R, such as within the Golgi apparatus or the nucleus, has been closely linked to specific biological behaviors and clinical outcomes (15-18). For instance, IGF-1R accumulation in the Golgi apparatus of migratory cancer cells promotes invasive behaviors, such as cell migration, while nuclear localization of IGF-1R is associated with poorer clinical outcomes (14), suggesting that the intracellular distribution of IGF-1R may serve as a potential biomarker for tumor progression and prognosis (14). In osteosarcoma and other malignancies, elevated levels of phosphorylated IGF-1R in the nucleus negatively correlate with patient survival, further supporting its prognostic utility (129).

Moreover, changes in IGF-1R expression in circulating tumor cells (CTCs) are closely related to treatment outcomes. These findings reveal that the loss of IGF-1R expression in CTCs is significantly associated with unfavorable outcomes in patients with metastatic breast cancer, suggesting that the abundance of IGF-1R-negative CTCs may serve as an independent prognostic indicator to guide patient stratification and personalized treatment strategies (130). Collectively, these findings underscore the clinical value of IGF-1R and its compartmentalization-related molecules for predicting therapeutic responses and evaluating prognosis in cancer treatment.

3. Limitations and future perspectives

Despite the efforts of the present review to provide a comprehensive overview of the non-canonical roles of IGF-1R, several limitations of both it and the current body of literature must be acknowledged. First, the review was constrained by the availability and quality of published literature. Despite the systematic search, relevant studies may have been missed, leading to a potential selection bias. Second, a significant portion of the evidence supporting the direct role of IGF-1R in DNA repair comes from observational studies (e.g., co-localization and knockdown/knockout experiments showing reduced repair focus formation). While these associations are highly suggestive, more direct biochemical evidence (e.g., detailed structural interactions) *in vivo* is needed to unequivocally establish causality. Finally, although preclinical data on targeting IGF-1R are promising, the transition to clinical success has been limited. This highlights the complexity of human biology and the challenges in overcoming compensatory pathways and on-target toxicity. However, our understanding of the crosstalk between IGF-1R and other resistance mechanisms remains incomplete.

Future research should therefore prioritize several avenues: i) Utilizing advanced techniques (e.g., cryo-electron microscopy, live-cell imaging and proximity labeling) to map the precise molecular interactions of nuclear IGF-1R; ii) developing more sophisticated *in vivo* models to validate these mechanisms and test novel therapeutic strategies, such as inhibiting IGF-1R nuclear translocation rather than its kinase activity; and iii) designing biomarker-driven clinical trials to identify patient subpopulations most likely to benefit from IGF-1R-targeted therapies, potentially in combination with other agents to overcome resistance.

4. Conclusion

In recent years, internalization and compartmentalization of IGF-1R have been demonstrated to play critical regulatory roles in tumor initiation, progression and therapeutic response. Advances in molecular and cellular biology techniques have significantly advanced our understanding of the dynamic membrane trafficking, subcellular localization and signaling networks of the IGF-1R. Studies have revealed that IGF-1R internalization influences ligand binding and signal transduction efficiency, and triggers compartment-specific downstream effects, thereby regulating key oncogenic processes, such as proliferation, apoptosis, migration and drug resistance.

Despite substantial progress in elucidating the mechanisms and functional consequences of IGF-1R internalization, several aspects remain controversial, including the detailed molecular networks, cross-compartmental signal integration and interactions with the TME. While some studies have emphasized the role of classical endocytic pathways in the spatiotemporal regulation of IGF-1R signaling, others have suggested that non-canonical internalization routes and interactions with the cytoskeleton and vesicular transport systems critically contribute to tumor heterogeneity and drug resistance. Therefore, further experimental validation is required to clarify how IGF-1R internalization and intercompartmental signaling regulate tumor progression and treatment resistance.

From a clinical perspective, a deeper understanding of IGF-1R internalization and compartmentalization provides a theoretical foundation for the development of novel therapeutic strategies. The limited efficacy of traditional IGF-1R inhibitors may be attributed, in part, to signal adaptation via internalization and spatial reorganization. Future targeting strategies should aim to precisely intercept compartment-specific IGF-1R signaling or combine it with agents that prevent adaptive resistance, thereby improving antitumor efficacy. Furthermore, emerging biomarkers that capture the dynamic subcellular behavior of IGF-1R hold promise for tumor classification, prognostic assessment and personalized therapy. Advances in liquid biopsy and single-cell multiomics will likely accelerate the application of IGF-1R dynamic signaling features in precision oncology.

In summary, research on IGF-1R internalization and compartmentalization represents a cutting-edge area in tumor biology that extends our understanding of oncogenesis and offers new avenues for targeted therapy. Future studies should focus on the molecular complexity of IGF-1R trafficking and signaling, strengthen interdisciplinary collaboration, and promote the development and clinical translation of novel biomarkers. These efforts will ultimately contribute to more precise and effective therapeutic strategies that improve the survival outcomes and quality of life for patients with cancer.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

TZ, LL and CD guarantee the integrity of the entire study. TZ designed the paper. TZ, LL and CD performed the literature research, data acquisition and data analysis. LL and CD prepared the manuscript, and TZ wrote the manuscript. TZ and LL confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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