

Review Article

Therapeutic Significance of IGF1R Cell Signaling

Mobin Saliha and Xian-Jun Qu*

Department of Pharmacology, School of Basic Medical Sciences, Capital Medical University, Beijing, China

Abstract

Insulin-like growth factor-1 receptor (IGF-1R) plays a key role in several types of tumors and cancers. Unsurprisingly, it is found that IGF1R take hostage by astray oncogenic processes. Comprehensive research data thoroughly demonstrate the link between IGF-1R and malignancy across most of the cancer types in human cells. Overexpression of IGF1R leads to the proliferation and inhibit apoptosis. Signaling of IGF1R impacts the protease secretion, motility of the tumor cells, adhesion and hypoxia signaling which distresses the tendency for invasion as well as metastasis. The standard model discloses the IGF-1R attaching to IGF-1/IGF-2 that leads to the activation of signaling cascades, driving non-stop cell division and defective cell cycle check points. Therefore, IGF1R is now considered as one of the most important therapeutic target for the treatment of cancer. This review outline the therapeutic significance of cell signaling component of IGF1R.

Keywords: IGF-1R; IGF1; Beta-arrestins; Cancer; Ubiquitination; GPCR; RTK; Akt

Introduction

The insulin-like growth factor receptor (IGF-1R) has pathophysiological significance in signaling pathways. IGF-1R has potent antiapoptotic and transformative functions, according to clinical evidence, increased expression of IGF-1R is related to oncogenesis, cancer growth, metastasis, drug resistance, and poor prognosis [1]. Biomarker studies have shown that activated IGF-1R can promote tumor growth by activating 2 significant downstream signaling pathways: PI3K-Akt and Ras-mitogen-activated protein kinase (RasMAPK) [2]. Functional mechanism of IGF-1R, which can be traced back to an ancient insulin-like signaling system near the beginning of bacteria and archaea existence [3]. The IR/IGF-1R network evolved to allow a multicellular organism to organize a sustainable reactions to supply nutrient [4]. While similar structure are able to act in biologically

*Corresponding author: Xian-Jun Qu, Department of Pharmacology, School of Basic Medical Sciences, Capital Medical University, Beijing, China, E-mail: qxj@sdu.edu.cn

Citation: Saliha M, Qu XJ (2021) Therapeutic Significance of IGF1R Cell Signaling. J Clin Immunol Immunother 7: 065.

Received: June 15, 2021; **Accepted:** June 22, 2021; **Published:** June 29, 2021

Copyright: © 2021 Saliha M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

analogous ways at supraphysiological ligand levels or in Knock out (KO) animal models. The IR plays mitochondrial role, while the IGF-1R plays an anti-apoptotic function [5].

Signal Transduction of IGF1R

IGF-1R signaling starts when the receptor is connected in the extracellular domain by one of its ligands. Ligand binding is a trans-autophosphorylation event where sequentially phosphorylated three tyrosine residues, Tyr1135, Tyr1131 and Tyr1136, in a kinase loop. This causes the . The kinase can therefore efficiently phosphorylate additional residues that act as docking sites of SH2 proteins in order to translate the IGF signal via a cascade of cytoplasmic signal pathways.

A lot of residues were identified in the subunits β as crucial to the function of IGF-1R. For binding of adaptor proteins insulin receptor substrata (IRS) 1-4 and Shc, Tyr950 in the juxtamembrane region is important. Together with Tyr950 Lys1003 is the ATP binding site and the mitogenic or transformational properties of IGF-1R are important sites. For both anti-Apoptotic and transformation properties, Tyr1250, Tyr1251, His1293 and Lys1294 are critical. More recently, residues of Ser1248 have demonstrated their ability to activate the Akt signaling pathway, regulating IGF-1R auto phosphorylation [6].

Signaling mechanisms involving the IGF-1R kinase bind IGF-1 (or IGF2) to the IGF-1R which helps to promote dephosphorylation and inherent tyrosine kinase activity. Substrates including IRS and Shc can be recruited and phosphorylated by an activated receptor. Signaling agents such as Grb2 and PI 3-kinase bind to IRS and Shc proteins after they are phosphorylated on tyrosine. These interactions activate downstream signaling, predominantly through the MAPK and PI3K pathways, which coordinate downstream IGF anticancer effects. The IRSs is the first enzyme to achieve complete binding in 1-2 minutes after methylation of the tyrosine sequences of the beta-subunits of the IGF-1R. IRS1 to IRS4 are the 4 proteins that make up the IRS kinase domain. IRS1 and IRS2 are well-known for their functions in facilitating the physiological effects of IGFs as well as their cell development factor behaviors. At the N-terminal region of each IRS, there are two high homologous areas: a pleckstrin homo domain (PH) and a PTB domain. The association with target cells is found to be essential in these areas.

However, C-terminal regions of IRS proteins are poorly preserved, which means that this region facilitates the various biochemical processes of each IRS. And it has a C-terminal motif with several phosphorylation sites that associate with SH2 domain-containing proteins with strong possibility depending on the phosphatase motif concerned [7]. IRS1 has been implicated in interactions with a variety of metabolites as a result of IGF1R stimulation, and 1 receptor appears to play a key role in cell attachment to laminin after IGF-1 activation [8]. Furthermore, a recent study shows that IRSs form high-molecular-mass compounds with a range of enzymes in a phospho-tyrosine-independent fashion and attenuate their accessibility to the IGF-1R [9].

The second huge route involves Shc, which phosphorylates maximally within 5-10 minutes of IGF-1R stimulation. Shc is made up of

four distinct members, ShcA, B, C, and D, as well as several sequencing isoforms [10]. Shc proteins, in general, have a PTB domain at the N-terminus and an SH2 domain at the C-terminus. Three tyrosine sequences, probably proteins encoded by IGF-1R, are involved in Grb2 recruiting between the PTB and SH2 domains. IRS association with a p85 response regulator of PI3K class I activates the catalytic subunit p110 of PI3K, resulting in phosphatidylcholine products that trigger the downstream signaling pathway [11]. It's also been discovered that tyrosine phosphorylation of the IGF-1R can cause PI3K to attach directly to the receptor's intracellular area.

At the inner side, of a membrane, PI3K synthesizes the second messenger phosphatidylinositol [12] triphosphate (PIP3), which is one of its essential components. These phospholipids act as ligands, attracting PH domain-containing residues to the cell membrane's inner surface [13]. The 3-phosphoinositide-dependent target genes (PDKs) found around the membrane communicate with these fatty acids, allowing the Akt/PKB serine-threonine kinase to translocate to the inner mitochondrial membrane and be enabled.

IGFs stimulate the PI3K pathway by phosphorylating the Thr308 and Ser473 residues on Akt, which then activates the kinase [14]. In particular, active Akt phosphorylates and inhibits many pro-apoptotic proteins, including Bad and caspase 9, as well as at least 3 other Akt effectors: the preservation transcription factor cyclic AMP main components binding protein (CREB), the pro-apoptotic receptor protein glycogen synthase kinase-3 (GSK-3), and the winged-helix family of forkhead transcriptional regulatory FKHL1, FK [15].

Akt activation can also stimulate mTOR, which allows the p70S6 kinase to phosphorylate the 40S ribosomal S6 protein, allowing efficient translation of the 5' terminal oligopyrimidine tract (5'TOP) mRNA [16]. This form of mRNA is essential for controlling the protein transcription process and controlling the cell cycle's transformation from G0 to G1. Activated mTOR may also cause eukaryotic initiation factor 4E (eIF-4E) binding-protein (4E-BP) to be phosphorylated, controlling cell cycle proteins like cyclin D1 [17].

The stimulation of matrix metalloproteinase (MMP) by mTOR has implications for signal transduction and fibrosis potential [18]. Methylation of Mdm2 on serine 166 and serine 186 is another consequence of Akt activation. Proteolysis of these sites is needed for Mdm2 to translocate from the cytoplasm to the nucleus, where it reduces p53 gene transcription and thus neuronal levels of p53 [19].

IGF-1R is also drive the RTK pathway because it contains an intracellular tyrosine kinase domain, and phosphorylation was thought to be the central mechanism regulating IGF-1R signaling. Several labs have been researching the pathways that regulate ensuing receptor down regulation and signaling desensitization over the last century. Other post-translational alterations, such as autophosphorylation, serine phosphorylation, ion channels, and sumoylation, are progressively being recognized as modulators of receptor concentrations and activity in this background.

Many cell surface receptors are integrated into clathrin- or caveolin-coated vesicles during pinocytosis. Internalization and recycling of certain receptors are automatic (e.g., the transferrin receptor); however, internalization of most RTKs and G-protein-coupled receptors (GPCRs) is caused by ligand binding [20]. Internalization usually down-regulates ligand-activated receptors, enabling cells to revert to an unaroused, primitive state. Internalization is observed to arise only in phosphorylated receptors, making it ligand-dependent [21].

Ubiquitin is involved in the internalization and oxidation of plasma protein complexes, in contrast to cytoplasmic protein synthesis. A range of ubiquitinated protein complexes, such as the IGF-1R [22]. In certain cases, (e.g., the RTK Met), the proteasome cleaves intracellular particles from the receptor and degrades them in addition to proteolytic cleavage [23].

Some proteins are filtered for reuse to the cell membrane after internalization. Inclusion of the IGF-1R from the plasma membrane was followed by a decrease in its mRNA in stimulated T lymphocytes. Following this, IGF-1R was re-expressed on the cell membrane, and IGF-1R mRNA levels in the cytoplasm increased to points greater than those previously observed. The older restoration of IGF-1R was due to receptor reuse, accompanied by de novo synthesis, according to a slower rise in mRNA levels [24].

Internal routes for recycling IGF-1R back to the cell surface do exist, and this balance between regeneration and depletion can be exploited. IGF-1R is degraded by both the proteasome and endosomal processes or recycled to the plasma membrane after internalization although the relative functions are unclear [25].

A particular internalization signal located within the cytoplasmic domain of the receptor which directs ligand-activated receptors to clathrin-coated membrane invaginations [26]. Internalized oppression signals are thought to have a tyrosine-based modulation that is normally found in the receptor's juxtamembrane region [27]. The juxtamembrane region of the human IGF-1R requires three transcription factors that may be implicated in internalization. However, there have been conflicting reports on the function of tyrosine-based motifs as internalization signals. The NPXY motif in IGF-1R is essential for receptor internalization, and tyrosine 1250 inside the IGF-1R tail is the operational tyrosine-based internalization signal [28].

A two-hybrid yeast screen defined Grb10 as a binding site of the Nedd4 E3 ligase after it was identified as an IGF-1R exchanging partner and negative controller of IGF-1 signaling [29]. Grb10 gene expression enhanced on IGF-1R activation, internalization, and deterioration in a ligand-dependent manner. This activation did not happen in the presence of a catalytic domain Nedd4 or a mutant Grb10 that was impossible to bind Nedd4. Nedd4 was discovered to be an ubiquitin E3 ligase, and Grb10 was discovered to be the main adaptor protein that allowed Nedd4 to be recruited to the IGF-1R.

According to further research from the Morrione lab, Nedd4 ubiquitination of the IGF-1R is primarily of the multi-monoubiquitination form [30]. Furthermore, co-localization experiments revealed that Nedd4-mediated internalization was clathrin and caveolin based. Following the discovery of feedback in which wild-type p53 inhibits IGF-1R transcription, it was discovered that abundantly expressed mutant or wild-type p53 mitigates ligand-induced IGF-1R downregulation. The presence of IGF-1R mRNA rules out a gene expression mechanism, implying a post-translational p53-IGF-1R monitoring system. Further studies showed that inhibiting p53 induced the IGF-1R to be ubiquitinated and degraded, meaning that p53 and IGF-1R could be vying for much the same ubiquitin ligase [31].

Whereas, E3 ligases are now considered as most important in IGF1R depletion. Several experimental studies verified the direct IGF1R/Mdm2 relationship, defined Mdm2 as an IGF-1R ubiquitin ligase that promotes proteasome inhibitor mediated IGF-1R depletion, and revealed a positive post-translational monitoring system involving p53 and IGF-1R. Following that, researchers discovered that

beta-arrestins, also known as master regulators of GPCR biology, act as adaptors to carry the E3 ligase Mdm2 to the IGF-1R revealing the process of Mdm2 binding to the IGF-1R [32].

One experimental data shows, mouse models with homozygous disturbance of the IGF-1R gene have extreme growth impairment and generalized organ dysplasia, and they die due to septic shock at birth. Implied KO models that produced essentially 40% fewer IGF-1 binding sites were developed on receptor's post-natal function site. IGF-1R-deficient mice evolved at a slower pace than wild-type littermates [33]. The IGF system is made up of plasma membrane-anchored receptors that transform an outer membrane ligand into one of two intracellular pathways: the mitogen-activated protein kinase (MAPK) or the phosphatidylinositol 3-kinase (PI3K). The transcriptional activation of different pro-apoptotic, and cell proliferation, occurs as a result of these pathways. In the extracellular environment, there are three main ligands: insulin, IGF-1, IGF-2, and unlike insulin, which travels freely, the supply of growth factors is tightly regulated, with IGF-binding proteins (IGFBPs) keeping them in circulation. Proteases dismantle the IGF-IGFBP complex when it's needed, generating IGFs for oxidative metabolism [34].

The MAPK cascade starts when the docking proteins IRS and Shc attach to the receptors' membrane-spanning domains through their phosphotyrosine binding (PTB) domains and are phosphorylated on tyrosine. Grb2, the next in line part, recognizes their phosphorylated tyrosine residues through its src homology 2 (SH2) domain [35]. Grb2 binds to the Ras exchange factor son of sevenless (SOS), which allows GDP to be exchanged for GTP on Ras. Ras combines with the serine/threonine kinase Rafs to enable mitogen-activated protein kinase (MEK), which then phosphorylate tyrosine and threonine to trigger extracellular signal-regulated kinases (ERK1 and 2). Activated ERK1 and 2 moves to the nucleus, where they attach and activate transcription factors including Ets, Elk, and c-Fos, allowing the transcription of genomes implicated in cell cycle development, replication, and motility to begin ERK1/2 can also control gene expression/inhibition and chromatin renovation, as well as monitor tubulin interactions in the cytoplasm [36].

As phosphatidylinositol 3-kinase (PI3K) interfaces with IRS and the active receptor, it causes it to phosphorylate phosphatidylinositol 4, 5-bisphosphate, which starts the second major chain (PIP2). The messenger phosphatidylinositol 3, 4, 5-trisphosphate (PIP3) is generated at the membrane as a result of this activity. Then, at the inner layer of the membrane, 3-phosphoinositide-dependent kinase-1 (PDK1) and Akt attach to PIP3, and PDK1 phosphorylates Akt [37].

Downstream cell signaling of IGF-1R will go beyond these two well-known pathways. The ligand-activated receptor can also stimulate the protein kinase (SAPK) mechanisms, which control cell reaction to Oxidative stress and include Jun N terminal kinase (JNK) and p38. Grb10 has also been found to attach to the IGF-1R's ligand-activated auto-phosphorylated tyrosine residues, which tends to drive cell proliferation [38]. Many other substrates are used in different cellular contexts, such as the adapter proteins CrkII and CrkL, RACK1, focal adhesion kinase (FAK) [39], Syp [40], GTPase-activating-protein [41], and suppressor of cytokine signaling 2 (SOCS2) [42].

IGF-1R: Signal Cessation

The RTK system has various levels of feedback that function properly across various spatial-temporal requirements in terms of signal cessation. Phosphorylation cascades are counteracted and can be

practically removed within moments of agonist binding. Desensitization is also helped by receptor down-regulation via the endolysosomal network after many hours. Finally, via transcriptional regulation, receptor or signaling component increased expression may be reduced at different time points. Many of these molecular antagonizing pathways are impaired or absent in cancer, indicating their oncogenesis capacity.

However, many elements specifically inhibits MAPK and PI3K signaling cascades for short time. A molecular switch, for instance, is embedded in the operation of the MAPK cascade to restore it to an inactive state: Ras is a small GTPase that alternates between active (GTP-bound) and inactive (non-GTPbound) states (GDP-bound). Guanine nucleotide exchange factors (GEFs) catalyze the displacement of GDP, enabling GTP to substitute it, in reaction to extracellular signals through RTKs. Ras-GTP binds to target proteins and stimulates downstream signaling. Ras then recovers to its GDP-bound inactive state, completing the loop. Ras was first identified as an oncogene in the mid-1980 [43], and is now recognized as among the most significant oncogenes in cancer [44].

IGF-1R System Updates

Although, for many years IGF1R pathways went unnoticed Many of the realizations that followed the return-to-bench years revolved through layers of uncertainty that had previously gone unnoticed. The vast crosstalk among numerous signal schemes, for example, provided plasticity and resistance to aiming. Though signal cascades are frequently represented using box-to-box diagrams, it has increasingly been known that there is a great deal of crosstalk among toll-like receptor systems. The first example of crosstalk between RTK and GPCR processes was when the EGFR became tyrosine proteins encoded after treatment with different GPCR agonists [45]. A Comprehensive research data supports RTK activation through GPCR, including PDGF [46], EGFR [47], and Trk A [48] had shown indications of GPCR-mediated RTK activation. Close-proximity frameworks GPCR-dependent activation of an RTK ligand [49], and GPCR-dependent activation of CTK such as Src and Pyk that cause RTK tyrosine phosphorylation [50] are just a few of the pathways.

IGF-1R: New Functional Classification

The IGF-1R domain always represented as a prototype RTK, and thus all the strategy targeting up to now was to inhibit its intrinsically kinase activity. The IGF-1R is a prototypical RTK. In relation to current alerts, nevertheless, it is clear that the IGF-1R can signal its classical kinase activity separately and that assumed blocking antibodies can start acting as biased agonists by circumventing the receptor's proposition. While receptor crosstalk examples have been known for quite a while, this example is somewhat different. Crosstalk is characterized by a rise in RTK activity based on GPCR, or vice versa, and many examples span the borders of the GPCR/RTK. For instance, lysophosphatidic acid (LPA) acts as the agonist for GPCR, but also triggers the activation of EGFR-the mechanism supposedly released by GPCR from an EGFR ligand.

Essentially, the kinase ability of the EGFR is still important [51].

However, IGF-1R has been shown by all functional definitions to be capable of being classified in terms of functional GPCR, for example, Ligand-binding activates signaling by means of heterotrimeric G proteins, GRK phosphorylate serine residues by active receptor and the creation of β -arrestin binding sites. However, IGF-1R can be seen

as a functional RTK/GPCR hybrid and that strategy for the kinase-mediated model can be inadequate to target. Therefore drug developers may need to focus on some other pathways to target it.

Redesigning IGF-1R Targeting Strategies

The IGF-1R is brought back into the banking system, which has slowly revealed a far more complex, multi-layered system since the first round of testing with several targeted strategies and almost complete pharmaceutical discontinuation. In addition to the traditional phosphorylation system control, numerous other post translation changes such as ubiquitination and SUMO-ylation (small ubiquitin-like modifiers) orchestrate the signal. In addition, new signaling players, G proteins, GRK and β -arrestin were added to regulatory layers. The theory of partial signaling with multiple activation opportunities, which originates in the field of GPCR studies, unlocks the IGF-1R system for better clinical use. In the years after unsuccessful clinical trials, the lessons learned must combine an actual, more accurate representation of the IGF-1R system [52].

It might be difficult to target the IGF-1R as compared to IGF-1. Initially, researchers designed kinase inhibitors or antibody blockers, but these couldn't pass the therapeutic aims to target cancer. However, many other strategies have been recognized but by using these ample mechanisms might produce a potent and efficient anticancer drug that can overthrow the key pillars of cancer [53].

The GPCR study field signifies the most effectively aimed drugs consequently features of this system could hold a possibility to control the functional hybrid IGF-1R. The biased signaling model of IGF1R is a ray of hope in the therapy design to an unprecedentedly detailed result despite the well-known exponential signal complexity.

Therapeutic Targeting

Owing the fact that IGF1R is significant in many cancers, many academic researchers investigated the likelihood of targeting the IGF-1R in oncology approaches with promising results [54]. Anti-IGF-1R approaches stopped or regressed tumor development in animal studies with reduced toxicity [55]. This sparked a lot of interest from pharmaceutical companies, and the IGF-1R quickly became the most researched oncological target. Several targets approaches emerged rapidly, most of them are the kinase inhibitors downstream signaling of the receptor: IGF-1 peptide equivalents, IGF-1R blocking antibody, and monoclonal antibody tyrosine kinase inhibitors [56]. As cell signaling study advances a more dynamic, network-like nature regulates step-by-step processes, providing plasticity and thus resistance to mono target strategies. Although the desired research path is bench-to bedside, this story takes a detour and returns IGF-1R aiming to the bench to further our understanding of operational complexities before seeking to develop smarter second-generation taking supplements.

Following the discovery of the IGF-1R axis' role in cancer, several different targeting techniques have been devised. Even though their mechanisms of action and exact targets varied, they all had the same goal of inhibiting the receptor kinase potential. Additionally, several inhibitors of downstream signal elements have been established, that could be utilized alone or in conjunction with IGF-1R targeting. Targeting IGF-1R may be a promising strategy in the future. Over ten IGF-1R-targeted drugs have been approved as anti-cancer therapeutics to date [56] Small-molecule medicines and anti-IGF-1R antibodies, for example, have other methods targeting

IGF1R with small nucleotides complementary to IGF-1R have also been accepted for clinical trials [57]. However, despite some positive preclinical findings, clinical disclosures that were later withheld haven't been particularly positive [58]. Furthermore, recent research has revealed that IGF-1R is a part of a dynamic and complex signaling network that interacts with other targets and frameworks through various intermodulation and corrective signaling mechanisms [59]. Further research into the mechanisms surrounding IGF-1R, especially its associations with other signaling pathways, may shed light on why selective IGF-1R-targeted therapies are less successful. We believe that blocking these IGF-1R bypass signaling pathways would result in a more successful treatment intervention in cancers.

Conclusion

Theoretically, if cells can literally re-route elemental activation, such crosstalk mitigates several inhibition techniques. Experimental data indicates that the RTK members of IGF-1R specifically utilized elements of the GPCR toolbox prompted a differentiation from mere crosstalk, calling into question the traditional boundaries of receptor groups. If we want to design effective targeting agents, we'll have to change our existing reporting models to accommodate non-canonical elements, which will have far-reaching to therapeutic consequences.

Grant Support

This work was supported by Natural Science Foundation of China (81673449/81872884/81973350).

References

- King H, Aleksic T, Haluska P, Macaulay VM (2014) Can we unlock the potential of IGF-1R inhibition in cancer therapy? *Cancer Treatment Reviews* 40: 1096-1105.
- Kasprzak A, Kwasniewski W, Adamek A, Gozdzicka-Jozefiak A (2017) Insulin-like growth factor (IGF) axis in cancerogenesis. *Mutation Research/Reviews in Mutation Research* 772: 78-104.
- Skorokhod A, Gamulin V, Gundacker D, Kavsan V, Müller IM, et al. (1999) Origin of insulin receptor-like tyrosine kinases in marine sponges. *Biol Bull* 197: 198-206.
- Giovannucci E (2003) Nutrition, insulin, insulin-like growth factors and cancer. *Horm Metab Res* 35: 694-704.
- Werner H, Weinstein D, Bentov I (2008) Similarities and differences between insulin and IGF-I: Structures, receptors, and signalling pathways. *Arch Physiol Biochem* 114: 17-22.
- Girmita A, Girmita L, del Prete F, Bartolazzi A, Larsson O, et al. (2004) Cyclolignans as inhibitors of the insulin-like growth factor-1 receptor and malignant cell growth. *Cancer Res* 64: 236-242.
- Wang J, Dai H, Yousaf N, Moussaif M, Deng Y, et al. (1999) Grb10, a positive, stimulatory signaling adapter in platelet-derived growth factor BB-, insulin-like growth factor I-, and insulin-mediated mitogenesis. *Mol Cell Biol* 19: 6217-6228.
- Goel HL, Fornaro M, Moro L, Teider N, Rhim JS, et al. (2004) Selective modulation of type 1 insulin-like growth factor receptor signaling and functions by β 1 integrins. *The Journal of Cell Biology* 166: 407-418.
- Yoshihara H, Fukushima T, Hakuno F, Saeki Y, Tanaka K, et al. (2012) Insulin/insulin-like growth factor (IGF) stimulation abrogates an association between a deubiquitinating enzyme USP7 and insulin receptor substrates (IRSs) followed by proteasomal degradation of IRSs. *Biochemical and Biophysical Research Communications* 423: 122-127.
- Wills MK, Jones N (2012) Teaching an old dogma new tricks: Twenty years of Shc adaptor signalling. *Biochemical Journal* 447: 1-16.

11. Werner H, Karnieli E, Rauscher FJ, LeRoith D (1996) Wild-type and mutant p53 differentially regulate transcription of the insulin-like growth factor I receptor gene. *Proceedings of the National Academy of Sciences* 93: 8318-8323.
12. Ullrich A, Gray A, Tam AW, Yang-Feng T, Tsubokawa M, et al. (1986) Insulin-like growth factor I receptor primary structure: Comparison with insulin receptor suggests structural determinants that define functional specificity. *The EMBO Journal* 5: 2503-2512.
13. Sepp-Lorenzino L (1998) Structure and function of the insulin-like growth factor I receptor. *Breast Cancer Research and Treatment* 47: 235-253.
14. Alessi DR, Andjelkovic M, Caudwell B, Cron P, Morrice N, et al. (1996) Mechanism of activation of protein kinase B by insulin and IGF-1. *The EMBO Journal* 15: 6541-6551.
15. del Peso L, González-García M, Page C, Herrera R, Nunez G (1997) Interleukin-3-induced phosphorylation of BAD through the protein kinase Akt. *Science* 278: 687-689.
16. Cardone MH, Roy N, Stennicke HR, Salvesen GS, Franke TF, et al. (1998) Regulation of cell death protease caspase-9 by phosphorylation. *Science* 282: 1318-1321.
17. Dupont J, Pierre A, Froment P, Moreau C (2003) The insulin-like growth factor axis in cell cycle progression. *Hormone and Metabolic Research* 35: 740-750.
18. Zhang D, Bar-Eli M, Meloche S, Brodt P (2004) Dual regulation of MMP-2 expression by the type I insulin-like growth factor receptor: the phosphatidylinositol 3-kinase/Akt and Raf/ERK pathways transmit opposing signals. *Journal of Biological Chemistry* 279: 19683-19690.
19. Mayo LD, Donner DB (2001) A phosphatidylinositol 3-kinase/Akt pathway promotes translocation of Mdm2 from the cytoplasm to the nucleus. *Proceedings of the National Academy of Sciences* 98: 11598-11603.
20. Robinson MS (1989) Cloning of cDNAs encoding two related 100-kD coated vesicle proteins (alpha-adaptins). *The Journal of Cell Biology* 108: 833-842.
21. Hicke L (2001) Protein regulation by monoubiquitin. *Nature reviews Molecular Cell Biology* 2: 195-201.
22. Sehat B, Andersson S, Girnita L, Larsson O (2008) Identification of c-Cbl as a new ligase for insulin-like growth factor-I receptor with distinct roles from Mdm2 in receptor ubiquitination and endocytosis. *Cancer Research* 68: 5669-5677.
23. Ancot F, Leroy C, Muharram G, Lefebvre J, Vicogne J, et al. (2012) Shedding-generated Met receptor fragments can be routed to either the proteasomal or the lysosomal degradation pathway. *Traffic* 13: 1261-1272.
24. Segretin ME, Galeano A, Roldán A, Schillaci R (2003) Insulin-like growth factor-1 receptor regulation in activated human T lymphocytes. *Hormone Research in Paediatrics* 59: 276-280.
25. Vecchione A, Marchese A, Henry P, Rotin D, Morrión A (2003) The Grb10/Nedd4 complex regulates ligand-induced ubiquitination and stability of the insulin-like growth factor I receptor. *Molecular and Cellular Biology* 23: 3363-3372.
26. Ceresa BP, Schmid SL (2000) Regulation of signal transduction by endocytosis. *Current Opinion in Cell Biology* 12: 204-210.
27. Johnson KF, Kornfeld S (1992) The cytoplasmic tail of the mannose 6-phosphate/insulin-like growth factor-II receptor has two signals for lysosomal enzyme sorting in the Golgi. *The Journal of Cell Biology* 119: 249-257.
28. Miura M, Baserga R (1997) The tyrosine residue at 1250 of the insulin-like growth factor I receptor is required for ligand-mediated internalization. *Biochemical and Biophysical Research Communications*, 239: 182-185.
29. Morrión A, Valentini B, Li S, Ooi JYT, Margolis B, et al. (1996) Grb10: A new substrate of the insulin-like growth factor I receptor. *Cancer Res* 56: 3165-3167.
30. Monami G, Emiliozzi V, Morrión A (2008) Grb10/Nedd4-mediated multiubiquitination of the insulin-like growth factor receptor regulates receptor internalization. *Journal of Cellular Physiology* 216: 426-437.
31. Werner H, Le Roith D (2000) New concepts in regulation and function of the insulin-like growth factors: implications for understanding normal growth and neoplasia. *Cellular and Molecular Life Sciences CMLS* 57: 932-942.
32. Girnita A, All-Ericsson C, Economou MA, Aström K, Axelson M, et al. (2006) The insulin-like growth factor-I receptor inhibitor picropodophyllin causes tumor regression and attenuates mechanisms involved in invasion of uveal melanoma cells. *Clin Cancer Res* 12: 1383-1391.
33. Holzenberger M, Leneuve P, Hamard G, Ducos B, Perin L, et al. (2000) A targeted partial invalidation of the insulin-like growth factor I receptor gene in mice causes a postnatal growth deficit. *Endocrinology* 141: 2557-2566.
34. Bach LA, Headey SJ, Norton RS (2005) IGF-binding proteins-the pieces are failing into place. *Trends in Endocrinology and Metabolism* 16: 228-234.
35. Skolnik EY, Lee CH, Batzer A, Vicentini LM, Zhou M, et al. (1993) The SH2/SH3 domain-containing protein GRB2 interacts with tyrosine-phosphorylated IRS1 and Shc: Implications for insulin control of ras signalling. *EMBO J* 12: 1929-1936.
36. Roskoski R (2012) ERK1/2 MAP kinases: Structure, function, and regulation. *Pharmacol Res* 66: 105-143.
37. Shepherd PR, Withers DJ, Siddle K (1998) Phosphoinositide 3-kinase: The key switch mechanism in insulin signalling. *Biochem J* 333: 471-490.
38. Wang J, Dai H, Yousaf N, Moussaif M, Deng Y, et al. (1999) Grb10, a positive, stimulatory signaling adapter in platelet-derived growth factor BB-, insulin-like growth factor I-, and insulin-mediated mitogenesis. *Mol Cell Biol* 19: 6217-6228.
39. Baron V, Calléja V, Ferrari P, Alengrin F, Obberghen EV (1998) p125Fak focal adhesion kinase is a substrate for the insulin and insulin-like growth factor-I tyrosine kinase receptors. *J Biol Chem* 273: 7162-7168.
40. Sepp-Lorenzino L (1998) Structure and function of the insulin-like growth factor I receptor. *Breast Cancer Res Treat* 47: 235-253.
41. Seely BL, Reichart DR, Staubs PA, Jhun BH, Hsu D, et al. (1995) Localization of the insulin-like growth factor I receptor binding sites for the SH2 domain proteins p85, Syp, and GTPase activating protein. *J Biol Chem* 270: 19151-19157.
42. Dey BR, Spence SL, Nissley P, Furlanetto RW (1998) Interaction of human suppressor of cytokine signaling (SOCS)-2 with the insulin-like growth factor-I receptor. *J Biol Chem* 273: 24095-25101.
43. Der CJ, Krontiris TG, Cooper GM (1982) Transforming genes of human bladder and lung carcinoma cell lines are homologous to the ras genes of Harvey and Kirsten sarcoma viruses. *Proc Natl Acad Sci U S A* 79: 3637-3640.
44. Ledford H (2015) Cancer: The Ras renaissance. *Nature* 520: 278-280.
45. Daub H, Weiss FU, Wallasch C, Ullrich A (1996) Role of transactivation of the EGF receptor in signalling by G protein-coupled receptors. *Nature* 379: 557-560.
46. Kruk JS, Vasefi MS, Liu H, Heikkilä JJ, Beazely MA (2013) 5-HT(1A) receptors transactivate the platelet-derived growth factor receptor type beta in neuronal cells. *Cell Signal* 25: 133-143.
47. Shah BH, Catt KJ (2004) GPCR-mediated transactivation of RTKs in the CNS: Mechanisms and consequences. *Trends Neurosci* 27: 48-53.
48. Rajagopal R, Chao MV (2006) A role for Fyn in Trk receptor transactivation by Gprotein-coupled receptor signaling. *Mol Cell Neurosci* 33: 36-46.
49. Pyne NJ, Pyne S (2011) Receptor tyrosine kinase-G-protein-coupled receptor signalling platforms: Out of the shadow? *Trends in Pharmacological Sciences* 32: 443-450.

50. Keely SJ, Calandrella SO, Barrett KE (2000) Carbachol-stimulated trans-activation of epidermal growth factor receptor and mitogen-activated protein kinase in T(84) cells is mediated by intracellular Ca^{2+} , PYK-2, and p60(src). *J Biol Chem* 275: 12619-12625.
51. Deng H, Lin Y, Badin M, Vasilcanu D, Strömberg T, et al. (2011) Over-accumulation of nuclear IGF-1 receptor in tumor cells requires elevated expression of the receptor and the SUMO-conjugating enzyme Ubc9. *Biochem Biophys Res Commun* 404: 667-671.
52. Worrall C, Nedelcu D, Serly J, Suleymanova N, Oprea I, et al. (2013) Novel mechanisms of regulation of IGF-1R action: Functional and therapeutic implications. *Pediatr Endocrinol Rev* 10: 473-484.
53. Galandrin S, Oligny-Longpre G, Bouvier M (2007) The evasive nature of drug efficacy: Implications for drug discovery. *Trends Pharmacol Sci* 28: 423-430.
54. Yuen JSP, Macaulay VM (2008) Targeting the type 1 insulin-like growth factor receptor as a treatment for cancer. *Expert Opinion on Therapeutic Targets* 12: 589-603.
55. Resnicoff M, Coppola D, Sell C, Rubin R, Ferrone S, et al. (1994) Growth inhibition of human melanoma cells in nude mice by antisense strategies to the type 1 insulin-like growth factor receptor. *Cancer Res* 54: 4848-4850.
56. Buck E, Mulvihill M (2011) Small molecule inhibitors of the IGF-1R/IR axis for the treatment of cancer. *Expert Opin Investig Drugs* 20: 605-621.
57. Christopoulos PF, Corthay A, Koutsilieris M (2018) Aiming for the Insulin-like Growth Factor-1 system in breast cancer therapeutics. *Cancer Treatment Reviews* 63: 79-95.
58. Jin M, Buck E, Mulvihill MJ (2013) Modulation of insulin-like growth factor-1 receptor and its signaling network for the treatment of cancer: Current status and future perspectives. *Oncology Reviews* 7: e3.
59. Jones RA, Campbell CI, Wood GA, Petrik JJ, Moorehead RA (2009) Reversibility and recurrence of IGF-1R-induced mammary tumors. *Oncogene* 28: 2152-2162.



- Advances In Industrial Biotechnology | ISSN: 2639-5665
- Advances In Microbiology Research | ISSN: 2689-694X
- Archives Of Surgery And Surgical Education | ISSN: 2689-3126
- Archives Of Urology
- Archives Of Zoological Studies | ISSN: 2640-7779
- Current Trends Medical And Biological Engineering
- International Journal Of Case Reports And Therapeutic Studies | ISSN: 2689-310X
- Journal Of Addiction & Addictive Disorders | ISSN: 2578-7276
- Journal Of Agronomy & Agricultural Science | ISSN: 2689-8292
- Journal Of AIDS Clinical Research & STDs | ISSN: 2572-7370
- Journal Of Alcoholism Drug Abuse & Substance Dependence | ISSN: 2572-9594
- Journal Of Allergy Disorders & Therapy | ISSN: 2470-749X
- Journal Of Alternative Complementary & Integrative Medicine | ISSN: 2470-7562
- Journal Of Alzheimers & Neurodegenerative Diseases | ISSN: 2572-9608
- Journal Of Anesthesia & Clinical Care | ISSN: 2378-8879
- Journal Of Angiology & Vascular Surgery | ISSN: 2572-7397
- Journal Of Animal Research & Veterinary Science | ISSN: 2639-3751
- Journal Of Aquaculture & Fisheries | ISSN: 2576-5523
- Journal Of Atmospheric & Earth Sciences | ISSN: 2689-8780
- Journal Of Biotech Research & Biochemistry
- Journal Of Brain & Neuroscience Research
- Journal Of Cancer Biology & Treatment | ISSN: 2470-7546
- Journal Of Cardiology Study & Research | ISSN: 2640-768X
- Journal Of Cell Biology & Cell Metabolism | ISSN: 2381-1943
- Journal Of Clinical Dermatology & Therapy | ISSN: 2378-8771
- Journal Of Clinical Immunology & Immunotherapy | ISSN: 2378-8844
- Journal Of Clinical Studies & Medical Case Reports | ISSN: 2378-8801
- Journal Of Community Medicine & Public Health Care | ISSN: 2381-1978
- Journal Of Cytology & Tissue Biology | ISSN: 2378-9107
- Journal Of Dairy Research & Technology | ISSN: 2688-9315
- Journal Of Dentistry Oral Health & Cosmesis | ISSN: 2473-6783
- Journal Of Diabetes & Metabolic Disorders | ISSN: 2381-201X
- Journal Of Emergency Medicine Trauma & Surgical Care | ISSN: 2378-8798
- Journal Of Environmental Science Current Research | ISSN: 2643-5020
- Journal Of Food Science & Nutrition | ISSN: 2470-1076
- Journal Of Forensic Legal & Investigative Sciences | ISSN: 2473-733X
- Journal Of Gastroenterology & Hepatology Research | ISSN: 2574-2566
- Journal Of Genetics & Genomic Sciences | ISSN: 2574-2485
- Journal Of Gerontology & Geriatric Medicine | ISSN: 2381-8662
- Journal Of Hematology Blood Transfusion & Disorders | ISSN: 2572-2999
- Journal Of Hospice & Palliative Medical Care
- Journal Of Human Endocrinology | ISSN: 2572-9640
- Journal Of Infectious & Non Infectious Diseases | ISSN: 2381-8654
- Journal Of Internal Medicine & Primary Healthcare | ISSN: 2574-2493
- Journal Of Light & Laser Current Trends
- Journal Of Medicine Study & Research | ISSN: 2639-5657
- Journal Of Modern Chemical Sciences
- Journal Of Nanotechnology Nanomedicine & Nanobiotechnology | ISSN: 2381-2044
- Journal Of Neonatology & Clinical Pediatrics | ISSN: 2378-878X
- Journal Of Nephrology & Renal Therapy | ISSN: 2473-7313
- Journal Of Non Invasive Vascular Investigation | ISSN: 2572-7400
- Journal Of Nuclear Medicine Radiology & Radiation Therapy | ISSN: 2572-7419
- Journal Of Obesity & Weight Loss | ISSN: 2473-7372
- Journal Of Ophthalmology & Clinical Research | ISSN: 2378-8887
- Journal Of Orthopedic Research & Physiotherapy | ISSN: 2381-2052
- Journal Of Otolaryngology Head & Neck Surgery | ISSN: 2573-010X
- Journal Of Pathology Clinical & Medical Research
- Journal Of Pharmacology Pharmaceutics & Pharmacovigilance | ISSN: 2639-5649
- Journal Of Physical Medicine Rehabilitation & Disabilities | ISSN: 2381-8670
- Journal Of Plant Science Current Research | ISSN: 2639-3743
- Journal Of Practical & Professional Nursing | ISSN: 2639-5681
- Journal Of Protein Research & Bioinformatics
- Journal Of Psychiatry Depression & Anxiety | ISSN: 2573-0150
- Journal Of Pulmonary Medicine & Respiratory Research | ISSN: 2573-0177
- Journal Of Reproductive Medicine Gynaecology & Obstetrics | ISSN: 2574-2574
- Journal Of Stem Cells Research Development & Therapy | ISSN: 2381-2060
- Journal Of Surgery Current Trends & Innovations | ISSN: 2578-7284
- Journal Of Toxicology Current Research | ISSN: 2639-3735
- Journal Of Translational Science And Research
- Journal Of Vaccines Research & Vaccination | ISSN: 2573-0193
- Journal Of Virology & Antivirals
- Sports Medicine And Injury Care Journal | ISSN: 2689-8829
- Trends In Anatomy & Physiology | ISSN: 2640-7752

Submit Your Manuscript: <https://www.heraldopenaccess.us/submit-manuscript>