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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 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].

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

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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 inhibitors 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 FKHRL1, 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 IGF1R 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 unnoticedMany 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 it's 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 ß-arrestin binding sites. However, IGF-1R can be seen

as a functional RTK/GPCR hybrid and that trategy 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 anticancer 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.

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