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IGF System in Cancer

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IGF System and Cancer Risk

Insulin-like growth factor (IGF) plays an important role in tissue growth and development. As such, several studies have demonstrated the association between circulating levels of IGF-1 and -II and cancer risk. In patients with acromegaly, an endocrine disorder which is characterized by a hypersecretion of growth hormone (GH) and consequently higher endogenous IGF, several studies have shown a 2-fold increased risk of gastrointestinal cancers [1–4]. Other studies have shown a modest association between higher circulating IGF-1 and -2 levels and an increased risk for prostate, breast, colorectal, and ovarian cancer [5–11]. However, several other studies do not show a similar increase in cancer risk [12–19]. Exogenous recombinant GH has been proposed as a potential cancer-promoting agent but no convincing link between cancer risk and its use in children or adults have been identified [20, 21]. The role of IGF in cancer risk is multifactorial and taken together, the preponderance of data suggests a slight increased risk of some cancers due to higher activity of the IGF system. Conversely, patients with congenital deficiencies in IGF-1 have a protective effect against developing cancer [22].

The IGF System in Cellular Proliferation and Survival

The lifecycle of a normal human cell is tightly regulated by intra- and extracellular signals, working in concert to appropriately control cellular proliferation, senescence, and apoptosis. When the sum of growth stimulatory and inhibitory signals favors proliferation, the cell enters mitosis. For example, circulating IGF-1 and IGF-2 bind to the IGF-1 receptor (IGF-1R) and trigger a signal transduction cascade that leads to increased proliferation and enhanced survival of IGF-responsive cells (Figure 1). Such signaling is central to the processes of oncogenesis. The mitogenic activity of the IGF-1R is mediated through the Ras and AKT pathways and results in the upregulation of cyclin D1 and its binding partner CDK4, leading to the phosphorylation of retinoblastoma protein, release of E2F transcription factor, and expression of downstream target genes like cyclin E [23, 24]. Moreover, IGF-1R activation downregulates cell cycle suppressors $p27^{kip1}$, $p57^{kip2}$, and PTEN [25, 26], indicating multiple pathways are involved.

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In addition to promoting cellular proliferation, the IGF system is a potent pro-survival stimulus. Apoptosis is the essential process of programed cell death by which normal embryonic tissue architecture is formed and adult tissues are maintained following cellular senescence, injury, and hyperplasia. In adults, apoptosis is responsible for the elimination of senescent mammary epithelial cells during postmenopausal breast tissue involution [27], cardiac remodeling seen in ischemic cardiomyopathy [28], and the removal of excess lobular epithelial cells following periodic breast hyperplasia associated with menstruation [27]. However, cancer cells can often evade the normal apoptosis mechanisms and thus evade programmed cell death. The AKT pathway plays a critical role in apoptosis by inhibiting pro-apoptotic proteins like BAD [29] and FKHR [30] and activating anti-apoptotic factors such as NF-kappa B [31] and MDM2 [32]. The importance of AKT in cancer-related IGF signaling is further exemplified by its role in invasion and metastasis [33]. Taken together, the IGF-1R provides a growth advantage to IGF responsive cells by the promotion of cellular proliferation and enhanced survival.

The Insulin Receptor and Hybrid Receptors

The insulin receptor (IR) is a tetrameric receptor consisting of two extracellular alpha and two intracellular beta subunits with significant over-all homology to the IGF-1R and 84% homology at tyrosine kinase domains [34]. The identification of two isoforms generated from the alternative splicing (IR-A) of the full-length transcript (IR-B) results in a 12-amino difference between the two isoforms [35] and differential expression during mammalian development. IR-B is the classic form of the IR which is primarily expressed in liver, muscle, and adipose tissues. It only binds insulin at physiologic concentrations with predominantly metabolic effects [36, 37]. On the other hand, IR-A is expressed during fetal development and in cancer cells with the ability to bind insulin as well as IGF-2, resulting in metabolic and mitogenic effects, respectively [36]. Breast and ovarian tumor cells have higher IR expression relative to normal epithelial cells [38, 39] and patients with very high IR expression have worse disease free survival [40].

The significant sequence homology has important implications for IGF-1R function in general, and oncogenesis in particular. The discovery that some cancers, such as thyroid, breast, and colon cancer, exhibit a higher relative abundance of IR-A compared to normal cells provided insight into the intimate association between the insulin and IGF systems [36, 41, 42]. Indeed, the homology between IR and IGF-1R permit the formation hybrid receptors (Hybrid-Rs), comprised of one alpha/beta monomer of IR and one of IGF-1R, with the hybrid receptor ligand specificity determined by the IR isoform [43]. For example, heterodimerization of IGF-1R with IR-A or IR-B gives rise to Hybrid-RA or Hybrid-RB, respectively. Both receptor hybrids have affinity for IGF-1 and IGF-2, (and to a lesser extent, insulin for Hybrid-RA) to activate downstream targets leading to cellular proliferation [44, 45].

The precise role of Hybrid-Rs in oncogenesis is under active investigation. Hybrid-Rs may increase the functional pool of receptors capable of activating the IGF system and provide further growth advantages to a subset of cells over-expressing IGF-1R, IR-A, or both. Hybrid-Rs also have therapeutic implications since novel therapies targeted against the IGF-1R may have lower efficacy in cancers signaling through IR-A or Hybrid-RA receptors, especially those with a high Hybrid-R:IGF-1R ratio [46]. Furthermore, hyperinsulinemic states may directly stimulate IR-A or Hybrid-RA expression and increase the bioavailability of IGF-1[14, 47]. The role of Hybrid-Rs and IR isoforms in breast and other cancers is an active area of investigation.

Signal Transduction Crosstalk

Signaling crosstalk is characterized by the influence of one receptor/signaling system on a separate receptor/signaling system. There is growing evidence that such crosstalk in cancer cells has important implications in the efficacy of novel therapeutics. One such crosstalk pathway occurs between IGF-1R and the erbB family of receptors, which include erbB1 (EGFR) and erbB2 (HER2/neu) (Figure 2). Treatment of breast and ovarian cancer cells with the duel IGF-1R/IR tyrosine kinase inhibitor (TKI) BMS-536924 caused a reciprocal upregulation of the erbB family of receptors which conferred resistance to IGF-1R inhibition [48]. Conversely, treatment of EGFR-dependent, tamoxifen-resistant breast cancer cells with the EGFR-selective TKI gefitinib led to activated IGF-1R signaling and subsequent resistance to EGFR inhibition [49]. Similarly, trastuzumab, a monoclonal antibody that binds HER2, is used to treat HER2-positive breast cancer but resistance is problematic [50] and *in vitro* studies with SKBR3 breast cancer cells implicate activated IGF-1R in this process [51], which is reversed by inhibition of IGF-1R [52]. One mechanism of resistance to IGF-1R or erbB targeted therapy occurs by the heterodimerization of IGF-1R with erbB receptors [52, 53], which provides an alternative signaling pathway to activate downstream mediators of cell proliferation and survival (Figure 2). Another example of crosstalk involves the estrogen receptor (ER), which is an important therapeutic target in adjuvant breast cancer treatment. The IGF-1R may contribute to tamoxifen resistance by two possible mechanisms: 1) IGF-mediated activation of AKT and subsequent estrogen-independent activation of ER [54] or 2) a direct interaction between ER and IGF-1R [55]. An emerging body of evidence supports an additional layer of crosstalk involving mammalian target of rapamycin (mTOR), a downstream effector of AKT with effects on cell proliferation, survival, and angiogenesis. The interaction of mTOR with either Raptor or Rictor results in the formation of functionally-distinct mTOR complex 1 (mTORC1) or 2 (mTORC2), respectively. Activation of mTORC1 leads to S6K1-mediated destabilization of insulin receptor substrate 1 (IRS1) and subsequent inhibition of IR and IGF-1R signaling [56], providing a negative feedback loop to downregulate AKT (Figure 1). Conversely, activation of mTORC2, leads to the upregulation of AKT by the specific phosphorylation of serine 473 [57]. This IGF-1R/AKT/mTOR signaling crosstalk has important therapeutic implications since rapalogs such as sirolimus, temsirolimus, everolimus, and ridaforolimus preferentially inhibit mTORC1 and can promote AKT activation by increased mTORC2 activation in addition to a loss of feedback inhibition [58].

The aforementioned examples of reciprocal crosstalk underscore the complexity of the IGF system in cancer and the need for multi-pathway targeting. Indeed, concomitant treatment of ovarian cancer cells with BMS-536924 and BMS-599626, a pan-HER inhibitor, demonstrated synergistic anti-proliferative activity [48]. Duel therapy is currently being investigated in clinical trials with IMC-A12 (anti-IGF-IR antibody) and cetuximab(anti-EGFR antibody) in patients with head and neck cancer and IMC-A12 and lapatinib (tyrosine kinase inhibitor against HER2) in breast cancer[59]. Although a recent clinical trial investigating IMC-A12 and cetuximab in colorectal cancer patients did not show a benefit with IGF-1R inhibition [60], study patients were resistant to prior anti-EGFR therapy and staining for activated AKT, a marker of EGFR and IGF-1R signaling, did not correlate with outcome. With respect to mTOR/IGF-1R duel targeted therapy, early results from a phase I clinical trial evaluating ridaforolimus (small molecule inhibitor of MTOR) and the IGF-1R antibody dalotozumab demonstrates clinical benefit in 16.1% of patients with advanced cancer and 21.7% of breast cancer patient [61]. These data suggest multiple pathways are interconnected and support the argument for customized cancer therapy based on pathway activation rather than histologic diagnosis alone.

IGF Binding Proteins

There are six IGF binding proteins (IGFBPs) with high affinity for IGF-1 and IGF-2. Serum concentrations of IGF are affected primarily by IGFBP3, which is the most abundant binding protein with the highest affinity for IGF-1 and IGF-2 [62]. Although IGFBPs are synthesized primarily in the liver, many normal and malignant tissues such as lung, breast, and ovarian cancers express IGFBPs [63–65]. These molecules are thought to influence malignancy by several mechanisms. They regulate bioavailability and half-life of IGF-1/2 in the circulation, and provide a mechanism for transport to target organs. IGFBPs also modulate the activity of IGF through important interactions with extracellular proteases that degrade IGFBPs, resulting in the release of ligand and subsequent activation of IGF-1R. These proteolytic fragments, particularly of IGFBP-5 and -3, may also have ligand-independent biological activity [66, 67].

The involvement of IGFBPs in cancer varies by the type of malignancy. For example, IGFBP-2, -3, and -5 are associated with glioblastoma more commonly than other brain tumors and IGFBP-3 in particular is associated with shorter overall survival [68]. In breast cancer cells, IGFBP-5 is associated with metastasis [69] and poor prognosis [70]. However, the specific mechanisms by which IGFBPs affect tumor progression are complex and published data are sometimes discrepant. For instance, despite the aforementioned association between IGFBP-5 and metastasis, forced-overexpression of IGFBP-5 in breast cancer cell lines actually inhibits cell growth [71]. Further studies have determined that the subcellular localization of IGFBP-5 influences its biological effect. Indeed, cytoplasmic IGFBP-5 promotes cell proliferation and motility [72] while nuclear IGFBP-5 does not [71]. Interestingly, ligand-independent activity for IGFBP-5 [73] is thought to involve the AKT pathway with effects on ovarian cancer angiogenesis [74]. IGFBP-2 has also demonstrated ligand-independent activity, mediated by interactions with cell surface integrins [75, 76]. Another binding protein with ligand-independent activity is IGFBP-4, which physically interacts with Frz8, a Wnt receptor, in cardiomyocytes and inhibits activation by Wnt3A ligand [77]. This discovery adds to the complexity of the IGF system and previously-mentioned pathway crosstalk. However, the impact of IGFBP-4 on Wnt signaling in cancer biology remains to be characterized.

Specific Cancers

Breast

Breast cancer is the most common malignancy in American women and is the second most common cause of death due to cancer [78]. The IGF system has a presence in most solid and hematologic malignancies, including breast cancer. The extent of IGF-1R expression in breast cancer varies by methodology but may approach 90% of tumours [79]. This presents a potentially greater opportunity for targeted therapy than HER2, which is present in 20–25% of all breast cancers. Although the prognostic value of IGF-1R expression is debatable [80, 81], *in vitro* studies have demonstrated that IGF-1 contributes to breast cancer growth by promoting cell proliferation and chemotherapy resistance [82, 83]. The role of IGF-1, IGF-1R, IGFBPs, Hybrid-Rs, and IGF signaling crosstalk in breast cancer are discussed above. Targeting these crosstalk pathways in breast cancer remains an active area of clinical investigation.

Sarcomas

Genetic and cytogenetic aberrations are predominate oncogenic forces in sarcoma development and this may have downstream consequences for the IGF system. For example, Ewing's sarcoma (ES) is characterized by a t(11;22) translocation producing the EWSR1-FLI1 fusion protein, which acts as an aberrant transcription factor leading to the

upregulation of downstream targets like c-myc [84], cyclin D1 [85], and PDGF-C [86]. IGF-1R expression is a pre-requisite to EWSR1-FLI1 mediated transformation [87], required for ES cell survival [88], and attenuates the efficacy of cytotoxic chemotherapy [89]. Inhibition of the IGF-1R with NVP-AEW541, a small molecule inhibitor, induces cell cycle arrest and apoptosis *in vitro* and reduces *in vivo* growth of ES cells [90]. A phase I single-agent clinical trial with a fully human IGF-1R monoclonal antibody inhibitor figitumumab (CP-751,871) demonstrated clinical benefit (objective response or stable disease) in 50% (n=16) of ES patients [91]. In a follow-up phase II trial with 125 ES patients with recurrent or refractory disease, objective responses where observed in 14.4% [92]. A smaller phase II trial with 35 ES or desmoplastic small round cell tumor patients demonstrated an objective response rate of 6% with single-agent AMG 479 [93]. The modest clinical responses despite strong pre-clinical data support the contention that patients should be selected based on a tumor phenotype rather than histologic classification. Moreover, the activation of parallel but interconnected signal transduction pathways in ES suggested a potential role for multi-pathway targeting of IGF-1R and mTOR [94–96].

Less is known about the IGF system in other sarcomas but interesting observations have been made that have not yet been described for carcinomas. For instance, alveolar rhabdomyosarcoma is a pediatric sarcoma characterized by a t(2;13) translocation that results in a Pax3–FKHR fusion gene. The Pax3-FKHR fusion protein can transactivate the *IGFR1* gene [97], leading to an overexpression of IGF-1R with growth and survival advantages that are abrogated by IGF-1R knockdown [98]. In gastrointestinal stromal cell tumors (GIST), *KIT*/platelet derived growth factor receptor (*PDGFR)-α* wildtype tumors are less responsive to imatinib therapy and pose a therapeutic challenge [99]. This subset of GIST exhibits *IGF1R* gene amplified and overexpression that drives cell growth and survival, suggesting a possible role for IGF targeting [100].

Gliomas

Gliomas are malignant central nervous tumors that include ependymomas, astrocytomas, oligodendrogliomas, and mixed gliomas. Glioblastoma multiforme (GBM) is the most common and aggressive subtype of astrocytomas. The primary treatment is surgical resection followed by chemotherapy and radiation therapy. However, prognosis remains poor and recurrence is common. Cumulative data indicates an important role for the IGF system in glioblastoma progression. For example, C6 glioblastoma cells exhibit growth inhibition when IGF-1R is down regulated *in vivo* and *in vitro* [101] and inhibition of IGF-1R by picropodophyllin(small molecule tyrosine kinase inhibitor) inhibits cell growth by reduced AKT activation [102]. The pro-survival influence of IGF-1R has been linked to increased expression of Bcl-2 [103]. GBM is known for its ability to invade the surrounding brain parenchyma as well as stimulate angiogenesis. The IGF system is implicated in this process as perivascular tumor cells express higher levels of IGF-1R [104], which is known to modulate production of VEGF [105]. In addition, treatment of glioblastoma cells with IGF-1 increases cellular migration [106]. Taken together with the observation that tumor cells within the margins of infiltration express higher levels of IGF-1R [104], the IGF system is intimately linked to glioblastoma tumor invasion. Although radiation therapy is effective in prolonging patient survival, local recurrences may actually be promoted by radiation therapy through activation of EGFR, IGF-1R, and PDGFR [107, 108], while inhibition of these pathways increases radiosensitivity [108]. An additional example of signal transduction crosstalk has been reported in GBM as IGF-1R up-regulation can induce resistance to EGFR inhibition [109]. Thus, targeting IGF signaling in gliomas may be a promising anti-cancer strategy.

Lung Cancer

Lung cancer is the second most common malignancy afflicting American patients. While platinum-based chemotherapy may provide modest benefit for advanced disease, lung cancer remains the most common cause of cancer deaths in 2010 [78]. The IGF system has been implicated in essentially all phases of lung cancer oncogenesis. For instance, high grade bronchial dysplasia produces greater paracrine and autocrine IGF than benign bronchial epithelial cells [110], suggesting the IGF system has an early role in lung cancer development. In addition, non-small cell lung cancer (NSCLC) cells, particularly the squamous cell subtype, is associated with increased *IGF1R* gene copy number and mRNA/protein expression [111], providing a growth and survival advantage to malignant cells and resistance to chemotherapy [112]. Inhibition of IGF-1R with figitumumab (anti-IGF-IR antibody) leads to downregulated receptor expression, inhibition of tumor growth [113], and radiosensitization of cancer cells [114]. Promising preclinical data and a phase I clinical trial results with figitumumab in advanced cancers [115] led to a phase II trial with combination therapy in NSCLC [116]. The objective response rate was 54% for all NSCLC subtypes but reached an impressive 78% in patients with the squamous cell subtype. Although the subsequent phase III trial with figitumumab as first-line treatment in NSCLC cancer was greatly anticipated, it was stopped early when interim analysis failed to show a benefit in the figitumumab arm [117].

Ovarian

Ovarian cancer is the fifth most common cause of death due to cancer in women [78]. Epidemiologic data has linked IGF-1R to high tumor grade and stage, and is associated with poor survival [118]. Although localized disease is associated with a 93% 5-year survival rate, 79% of patients are stage III or IV at the time of initial diagnosis [78]. After debulking surgery and six cycles of platinum-based chemotherapy, 75% of patients will achieve complete remission but three-quarters of them will relapse within 20 months, on average [119]. While retreatment with a platinum-based regimen is reasonable after a six month platinum-free period, resistance is common and may be attributed to increased IGF-1R expression in ovarian tumor cells [120]. Although primary ovarian tumor cell cultures do not overexpress IGF, dysregulation of IGF homeostasis by the overexpression of IGFBP-2 in ovarian cancer cells may sequester and maintain an elevated localized pool of IGF for activation of IGF-1R [63, 121]. A phase II clinical trial is currently evaluating the efficacy and tolerability of front-line AMG-479, a fully-human monoclonal antibody against the IGF-1R, in combination with carboplatin and paclitaxel in advanced stage, optimally-debulked epithelial ovarian, primary peritoneal, and fallopian tube cancer (TRIO-014).

Conclusions

The IGF system has been implicated in the oncogenesis of essentially all solid and hematologic malignancies. The central involvement of IGF signaling in tumor cell proliferation, survival, invasion, and metastasis makes it an attractive therapeutic target. Importantly, the IGF signaling pathway has also been directly implicated in resistance to clinically important therapies, including hormonal agents, HER receptor targeting agents, radiation and cytotoxic chemotherapy. Indeed, several clinical trials are currently evaluating the efficacy of IGF-1R inhibition to either overcome these resistance mechanisms or directly induce anti-proliferative effects on tumors dependent on IGF signaling. Current strategies include monoclonal antibodies directed at IGF-1R, tyrosine kinase inhibitors with activity against IGF-1R +/− IR and anti-ligand antibodies. The optimal strategy for targeting IGF signaling in patients with cancer is not clear. The modest benefits reported thus far underscore the need for a better understanding of IGF signaling, which would enable

clinicians to identify the subset of patients with the greatest likelihood of attaining benefit from this targeted approach.

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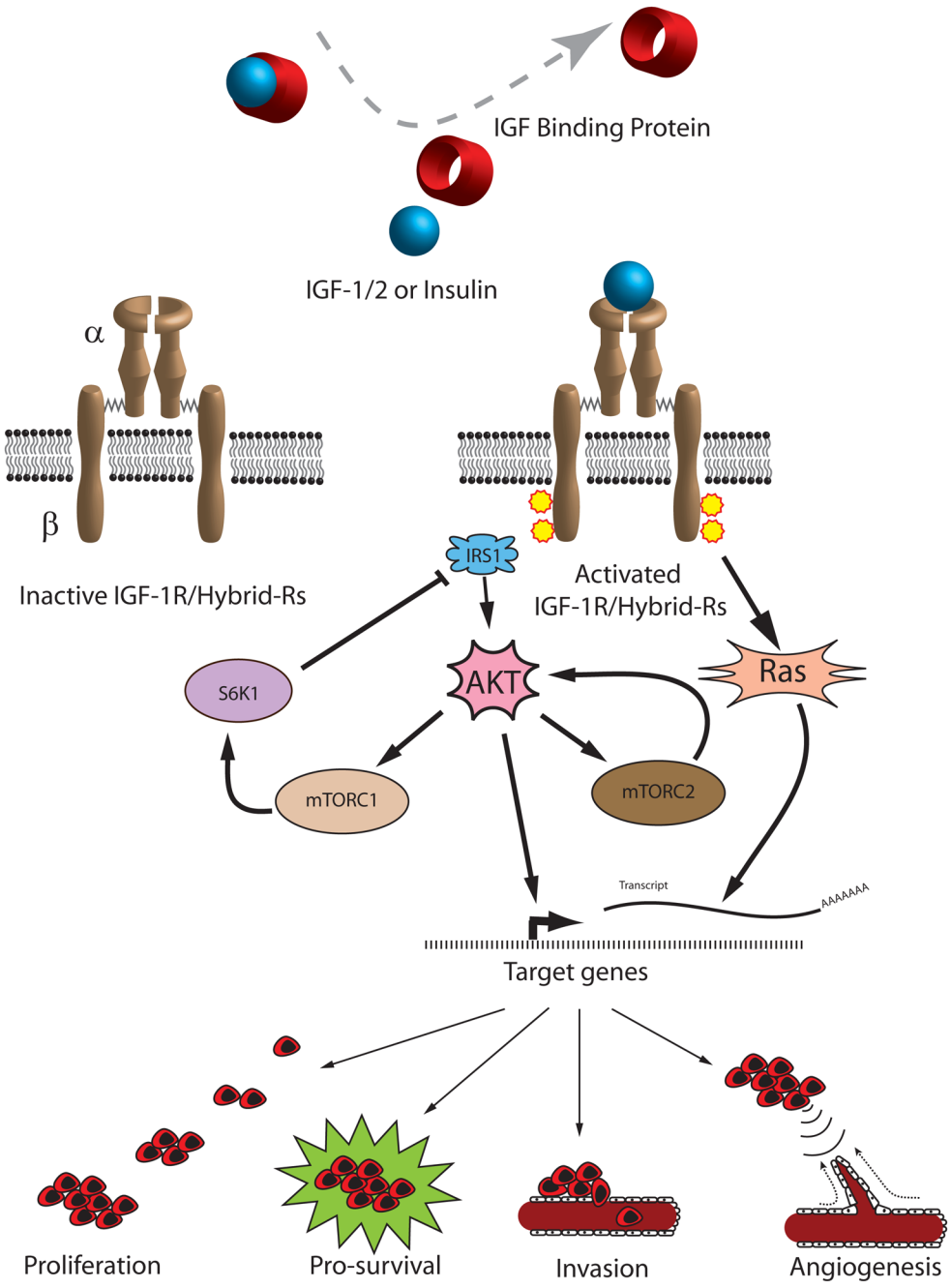

Figure 1.

Circulating IGF-1/2 is bound to IGF binding proteins and released at the IGF-1R, which is comprised of an alpha and beta tetrameric receptor. This leads to the activation of Ras and AKT with subsequent upregulation of genes involved in cell proliferation, survival, invasion, and angiogenesis. AKT is also an upstream regulator of mTORC1 and downstream effector of mTORC2. Both mTOR complexes play an important role in positive and negative feedback on the IGF/AKT signaling pathway.

Legend: Insulin like growth factor (IGF), IGF receptor 1 (IGF-1R), Hybrid receptors (Hybrid-Rs), insulin receptor substrate 1 (IRS1), mammalian target of rapamycin complex (mTORC), p70 S6 kinase (S6K1).

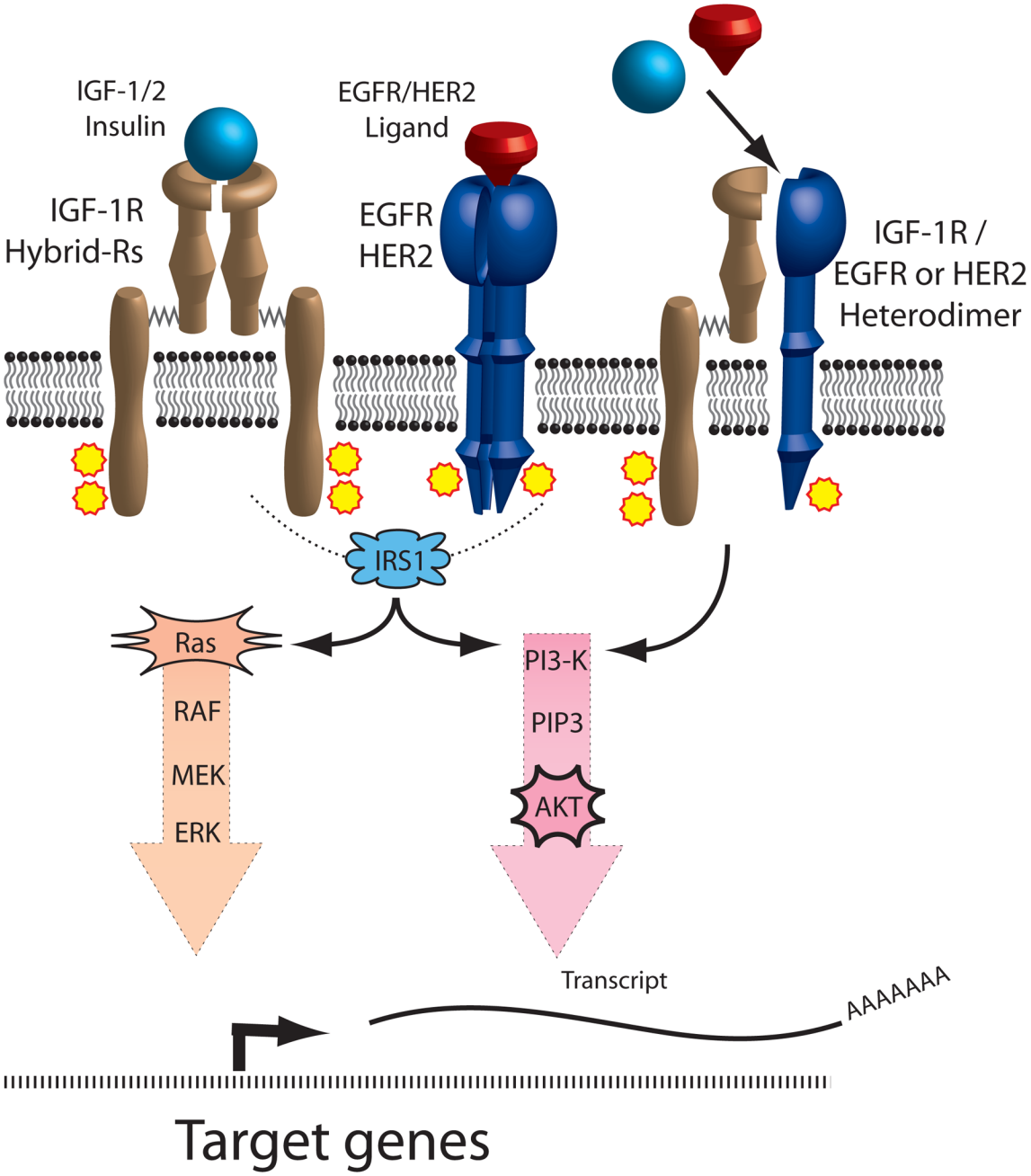

Figure 2.

IGF-1R and EGFR/HER2crosstalk occurs by two main mechanisms. Since both pathways share a common signal transduction mediator, IRS1, resistance to inhibition of one receptor pathway can result from activation of IRS1 by the alternate receptor pathway. In addition, the formation of IGF-1R and EGFR/HER2 heterodimers increases the functional pool of receptors capable of binding IGF or EGFR/HER2 ligands, thus conferring resistance to single-agent targeted therapy.

Legend: Insulin like growth factor (IGF), IGF receptor 1 (IGF-1R), Hybrid receptors (Hybrid-Rs), epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), insulin receptor substrate 1 (IRS1), phosphatidylinositol 3-kinase (PI3K)