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Review

The Relationship between IGF Pathway and Acquired Resistance to Tyrosine Kinase Inhibitors in Cancer Therapy

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Abstract

The tyrosine kinase signaling pathway is an important pathway for cell signal transduction, and is involved in regulating cell proliferation, cell cycle, apoptosis and other essential biological functions. Gene mutations involved in the tyrosine kinase signaling pathway often lead to the development of cancers. Epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor-2 (HER2) are well known receptor tyrosine kinases (RTKs), which belong to the ERBB family and have high mutation frequency in cancers. Tyrosine kinase inhibitors (TKI) targeting EGFR and HER2 have been widely used in the clinical treatment of lung and breast cancers. However, after a period of treatment, patients will inevitably develop resistance to TKI. The insulin-like growth factor (IGF) receptor family, like the ERBB receptor family, belongs to the receptor tyrosine kinase superfamily, which also conducts an important cell signal transduction function. There is an overlap between IGF signaling and EGFR signaling in biological functions and downstream signals. In this review, we summarize the current state of knowledge of how IGF signaling interacts with EGFR signaling can influence cell resistance to EGFR/HER2-TKI. We also summarize the current drugs designed for targeting IGF signaling pathways and their research progress, including clinical trials and preclinical studies. Altogether, we aimed to discuss the future therapeutic strategies and application prospects of IGF signaling pathway targeted therapy.

Keywords: insulin-like growth factor; tyrosine kinase inhibitors; drug resistance; cancer; EGFR; HER2

1. Introduction

Cancer is one of the major challenges to human health. Female breast cancer has the highest incidence (accounting for 11.7% of de novo tumors), followed by lung cancer (11.4%), which is the leading cause of cancer death (accounting for 18.0% of total cancer deaths) [1]. Thanks to the progress of life science research, we now have had a deep understanding of the mechanism of cancer, such as intracellular signal transduction, cell cycle regulation and apoptosis induction. It has been found that tyrosine kinases play a significant role in tumorigenesis and development [2]. Mutations in some genes can lead to sustained activation of tyrosine kinases, which results in uncontrolled cell growth. These genes, which can cause cells to become immortalized or cancerous, are called tumor driven genes [3]. Tyrosine kinase has become an important therapeutic target in the treatment of cancer. The increased use of tyrosine kinase inhibitors (TKIs), which are often small molecule inhibitors targeting tyrosine kinases, are a prelude to targeted therapy for cancer treatment, and have the potential to effectively prolong the survival of cancer patients [4]. A retrospective study analyzed the median survival (95% CI) of patients with lung adenocarcinoma, and found that the median survival of patients with tumor driven genes mutation who received targeted drug therapy was 3.49 months (3.02–4.33), which was significantly higher than that of patients with tumor driven genes mutation but receiving conventional treatment (surgery, radiotherapy or chemotherapy) (2.38 months (1.81–2.93)) and patients without tumor driven genes mutation and receiving conventional treatment (2.08 (1.84–2.46)) [5]. Another study suggested that 60%–80% of patients with chronic myeloid leukemia treated with imatinib achieved clinical benefits lasting more than a decade [6]. Although the use of targeted kinase inhibitors has brought significant benefits to many cancer patients, it is disappointing to note that these drugs are not curative and most only delay tumor progression, because acquired resistance ultimately develops in most patients with advanced metastatic disease [7]. Solving the problem of drug resistance and enhancing drug sensitivity are the key to improving the therapeutic effect and the prognosis of cancer patients.

In this review, we introduce two representative TKIs, epidermal growth factor receptor (EGFR)-TKIs and human epidermal growth factor receptor-2 (HER2)-TKIs, for the treatment of lung and breast cancer. We describe the clinical application of EGFR-TKI and HER2-TKI in these cancers, the current results of these therapies, and the status of the development of drug resistance for these TKIs. The mechanism of TKI resistance is complicated, and several studies have found that the insulin-like growth factor (IGF) signaling pathway plays a crucial role in TKI resistance [8–10]. In this review, we describe the relationship between the IGF pathway and acquired resistance to TKIs.

2. Application of TKIs in Tumor Therapy

Protein kinase/phosphatase-regulated signaling pathways are involved in the occurrence and development of almost all types of cancer and have become one of the most important drug targets in the 21st century [4]. The tyrosine residues of the receptor protein are phosphorylated and interact with downstream signaling molecules to activate the Ras/Raf/MAPK or PI3K/Akt signaling pathways and regulate the survival, proliferation and metastasis of tumor cells. Receptor tyrosine kinases (RTKs), which have become the key targets for cancer treatment, are composed of multiple receptor families, including the ERBB receptor family (such as EGFR, HER2), the IGF receptor family (such as IGF-1R, InsR), the VEGF receptor family, the FGF receptor family, the c-MET receptor, and the ALK receptor. Since the end of 2022, 78 small molecule protein kinases-targeted inhibitors have been approved by the Food and Drug Administration (FDA), of which 18 inhibitors target non-receptor tyrosine kinases and 38 inhibitors target receptor tyrosine kinases (Table 1, Ref. [11,12]). The main targets of TKIs include EGFR/HER, VEGFR, ALK, MET, JAK, FGFR, ABL, KIT [12], among which the most widely and successfully used are EGFR and HER2. EGFR and HER2 are members of the transmembrane RTKs ERBB family.

The ERBB family, also known as the EGF receptor family or Type I receptor family, is a transmembrane RTKs family, whose members include ERBB1 (EGFR/HER-1), ERBB2 (Neu/HER-2), ERBB3 (HER-3) and ERBB4 (HER-4) [13]. ERBB receptors are activated after homodimerization or heterodimerization, which sequentially activates intracellular signaling cascades. There are two main downstream pathways, the RAS-RAF-MEK-MAPK pathway and the PI3K-AKT-mTOR pathway [14]. The former controls gene transcription, cell cycle progression and cell proliferation, while the latter activates anti-apoptotic and pro-survival signaling cascades [15]. About 20% of non-small cell lung cancer (NSCLC) patients have *EGFR* activating mutations. The main subtype includes exon 19 deletion (Ex19del) and exon 21 L858R mutation [16]. *HER2* mutations are found in approximately 25–30% of tumors in invasive breast cancer [17]. Mutations in the *EGFR* and *HER2* genes lead to persistent activation of the ERBB signaling pathway, resulting in uncontrolled cell growth, immortalization of cells and transformation into cancer cells. Using targeted drugs to specifically inhibit abnormally expressed genes can effectively inhibit the process of tumor growth, metastasis and invasion, and have the potential to treat several malignancies. To accomplish this, scientists have designed a variety of small molecule inhibitors targeting EGFR and HER2. In this review, we will introduce the clinical application of EGFR-TKI and HER2-TKI in the treatment of lung and breast cancers.

2.1 The Clinical Application of EGFR-TKI in Lung Cancer

Lung cancer is the leading cause of cancer-related deaths worldwide, with more than half (57%) of lung cancer patients having metastases at the time of diagnosis, with only a 5% 5-year survival rate [18]. NSCLC is the most dominant subtype of lung cancer, accounting for 85% of all lung cancer cases [19]. *EGFR* is one of the most common driven gene in NSCLC. The proportion of *EGFR* activation mutation in NSCLC patients is about 20% [16]. Females (69.7%), non-smokers (66.6%), and patients with adenocarcinoma (80.9%), have a higher frequency of *EGFR* mutations ($p < 0.001$ for all comparisons) [20]. EGFR-TKIs, which target *EGFR* activating mutations, are recommended by current treatment guidelines for the first-line treatment of advanced NSCLC patients with activating mutations of *EGFR* [21,22]. Representative drugs of the first generation of EGFR-TKIs include gefitinib, erlotinib, icotinib. These are reversible inhibitors that compete with adenosine triphosphate (ATP) to bind to the tyrosine kinase domain of EGFR and reversibly inhibit the kinase activity of EGFR [23]. Gefitinib was approved by the FDA in 2015 as a first-line treatment for advanced NSCLC patients with *EGFR* activating mutations [24]. The second generation of EGFR-TKIs, including afatinib and dacomitinib, were originally designed to overcome resistance of the first generation of EGFR-TKIs and are irreversible inhibitors of EGFR. Afatinib is also a dual specific inhibitor against EGFR/HER2, which can covalently combine with EGFR and HER2. Dacomitinib is an irreversible pan-HER inhibitor. Compared with the first-generation EGFR-TKIs, the broad-spectrum activity of the second-generation drugs enhances their ability to inhibit EGFR-dependent tumor growth. However, the second generation EGFR-TKIs have a higher incidence of adverse events compared with gefitinib, such as enhancive skin and gastrointestinal toxicity and decreased tolerance to maximum therapeutic doses, limiting their use in patients resistant to first-generation drugs [25]. After 9~13 months of treatment with the first- or second-generation EGFR-TKIs, most patients inevitably develop acquired resistance, among which 50%–60% have the *EGFR* exon 20 T790M mutation [26–28]. Therefore, the T790M mutation is known as the "gatekeeper" mutation, which increases the steric hindrance of the EGFR tyrosine kinase domain. Sequentially, it increases the affinity of ATP to the mutant EGFR receptor and increases the competition between ATP and reversible EGFR-TKIs, ultimately decreasing the effectiveness of the first- and second-generation EGFR-TKIs [26]. The representative drug of the third generation of EGFR-TKIs is osimertinib, which can effectively overcome EGFR-TKIs resistance caused by the T790M mutation and achieves increased clinical activity and tolerance. Compared with chemotherapy, osimertinib improved progression-free survival (PFS) and overall survival (OS) for patients with disease progression during treatment with first-generation EGFR-TKIs and concurrently with T790M

Table 1. FDA-approved small molecule inhibitors or monoclonal antibodies (mAb) targeting protein kinase[4].

Drug	Primary targets[1]	The type of target/drugs[2]	Year approved	Therapeutic indications[3]
Abemaciclib	CDK4/6	CMGC	2017	Combination therapy with an aromatase inhibitor or with fulvestrant or as a monotherapy for breast cancers
Abrocitinib	JAK	TK	2022	Atopic dermatitis
Acalabrutinib	BTK	TK	2017	Mantle cell lymphomas, CLL, SLL
Afatinib	EGFR/HER	TK	2013	NSCLC
Alectinib	ALK	TK	2015	ALK-positive metastatic NSCLC that progressed on or is intolerant to crizotinib
Alpelisib	PI3K	LK	2019	Combination therapy with fulvestrant for advanced or metastatic breast cancer with hormone receptor-positive, HER2-negative (HR+/HER2-) and *PIK3CA*-mutation, in postmenopausal women or men
Amivantamab-vmjw	EGFR/MET	ADCs	2021	NSCLC with *EGFR* exon 20 insertion mutation
Asciminib	ABL	TK	2021	Ph+ CML in chronic phase (CP), previously treated with 2 or more tyrosine kinase inhibitors (TKIs)
Avapritinib	KIT	TK	2020	GIST with *PDGFR*α exon 18 mutation
Axitinib	VEGFR	TK	2012	RCC
Baricitinib	JAK	TK	2017	Extensive alopecia
Binimetinib	MEK1/2	STE	2018	Combination therapy with encorafenib for *BRAF* V600E/K melanomas
Bosutinib	ABL	TK	2012	Newly diagnosed chronic phase Ph+ CML
Brigatinib	ALK	TK	2017	ALK-positive metastatic NSCLC that have progressed or are intolerant to crizotinib
Cabozantinib	RET	TK	2012	Medullary thyroid cancers, RCC, HCC
Capmatinib	MET	TK	2020	NSCLC with *MET* exon 14 skipping
Ceritinib	ALK	TK	2014	ALK-positive metastatic NSCLC that progressed on or is intolerant to crizotinib
Cetuximab	EGFR/HER	mAb	2004	EGFR-expressing metastatic colorectal carcinoma intolerant to irinotecan-based chemotherapy
Cobimetinib	MEK1/2	STE	2015	*BRAF* V600E/K melanomas in combination with vemurafenib
Copanlisib	PI3K	LK	2017	Adult patients with recurrent marginal zone lymphoma who have received at least two-line treatment
Crizotinib	ALK	TK	2011	Locally advanced or metastatic NSCLC with ALK-positive
Dabrafenib	BRAF	TKL	2013	*BRAF* V600E/K melanomas, *BRAF* V600E NSCLC, *BRAF* V600E anaplastic thyroid cancers
Dacomitinib	EGFR/HER	TK	2018	*EGFR*-mutant NSCLC
Dasatinib	ABL	TK	2006	CML
Deucravacitinib	TYK2	TK	2022	Adult patients with moderate to severe plaque psoriasis suitable for systemic therapy or phototherapy
Duvelisib	PI3K	LK	2018	SLL, CLL, FL
Encorafenib	BRAF	TKL	2018	Combination therapy with binimetinib for *BRAF* V600E/K melanomas
Entrectinib	TRK	TK	2019	Solid tumors with NTRK fusion proteins, ROS1-positive NSCLC
Erdafitinib	FGFR	TK	2019	Urothelial bladder cancers
Erlotinib	EGFR/HER	TK	2004	NSCLC, pancreatic cancers
Everolimus	mTOR	AK	2009	HER2-negative breast cancers, pancreatic neuroendocrine tumors, RCC, angiomyolipomas, subependymal giant cell astrocytomas
Fam-trastuzumab deruxtecan-nxki	HER2	ADCs	2022	Unresectable or metastatic non-small cell lung cancer with *HER2* mutation
Fedratinib	JAK	TK	2019	Myelofibrosis

Table 1. Continued.

Drug	Primary targets[1]	The type of target/drugs[2]	Year approved	Therapeutic indications[3]
Fostamatinib	SYK	TK	2018	Immunothrombocytopenia
Futibatinib	FGFR	TK	2022	Locally advanced or metastatic cholangiocarcinoma with *FGFR2* gene rearrangement/fusion
Gefitinib	EGFR/HER	TK	2003	NSCLC
Gilteritinib	FLT3	TK	2018	AML
Ibrutinib	BTK	TK	2013	CLL, mantle cell lymphomas, marginal zone lymphomas, graft vs. host disease, Waldenstrom macroglobulinemia
Idelalisib	PI3K	LK	2014	SLL, CLL, FL
Imatinib	ABL	TK	2001	Ph+ CML or ALL, aggressive systemic mastocytosis, chronic eosinophilic leukemias, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, GIST, myelodysplastic/ myeloproliferative disease
Infigratinib	FGFR	TK	2021	Cholangiocarcinomas with FGFR2 fusion proteins
Lapatinib	EGFR/HER	TK	2007	In combination with letrozole for post-menopausal women with HR-positive metastatic breast cancer that overexpresses the HER2 receptor
Larotrectinib	TRK	TK	2018	Solid tumors with NTRK fusion proteins
Lenvatinib	VEGFR	TK	2015	Differentiated thyroid cancers
Lorlatinib	ALK	TK	2018	ALK-positive metastatic NSCLC that has progressed on crizotinib and at least one other ALK inhibitor or alectinib/ceritinib as the first ALK inhibitor therapy
Margetuximab	HER2	mAb	2020	Metastatic HER2-positive breast cancer
Midostaurin	FLT3	TK	2017	AML, mastocytosis, mast cell leukemias
Mobocertinib	EGFR/HER	TK	2021	NSCLC for *EGFR*-positive exon 21 insertions
Necitumumab	EGFR/HER	mAb	2015	Combined with gemcitabine and cisplatin for the first-line treatment of metastatic squamous NSCLC
Neratinib	EGFR/HER	TK	2017	HER2-positive breast cancers
Netarsudil	ROCK1/2	AGC	2017	Glaucoma
Nilotinib	ABL	TK	2007	Ph+ CML
Nintedanib	VEGFR	TK	2014	Idiopathic pulmonary fibrosis
Olaratumab	PDGFR-α	mAb	2016	Combined with doxorubicin for adult soft tissue sarcomas
Osimertinib	EGFR/HER	TK	2015	Metastatic *EGFR* T790M mutation-positive NSCLC that progressed on or after EGFR TKI therapy
Pacritinib	JAK	TK	2022	Myelofibrosis
Palbociclib	CDK4/6	CMGC	2015	In combination with letrozole for postmenopausal women with ER-positive, HER2-negative advanced breast cancer for metastatic disease
Panitumumab	EGFR/HER	mAb	2006	EGFR-expressing metastatic colorectal carcinoma
Pazopanib	VEGFR	TK	2009	RCC, soft tissue sarcomas
Pemigatinib	FGFR	TK	2020	Advanced cholangiocarcinoma with a *FGFR2* fusion or rearrangement
Pertuzumab	HER2	mAb	2012	In combination with trastuzumab and docetaxel for neoadjuvant treatment of HER2-positive locally advanced inflammatory or early-stage breast cancer
Pexidartinib	CSF1R	TK	2019	Tenosynovial giant cell tumors
Ponatinib	ABL	TK	2012	Ph+ CML or ALL
Pralsetinib	RET	TK	2020	*RET*-fusion NSCLC, medullary thyroid cancer, thyroid cancer
Ramucirumab	VEGFR	mAb	2014	Gastric or gastroesophageal junction adenocarcinoma, metastatic non-small cell lung cancer, colorectal cancer

Table 1. Continued.

Drug	Primary targets[1]	The type of target/drugs[2]	Year approved	Therapeutic indications[3]
Regorafenib	BRAF	TKL	2012	Colorectal cancers
Ribociclib	CDK4/6	CMGC	2017	Combination therapy with an aromatase inhibitor for breast cancers
Ripretinib	KIT	TK	2020	Fourth-line treatment for GIST
Ruxolitinib	JAK	TK	2011	Myelofibrosis, polycythemia vera, atopic dermatitis
Selpercatinib	RET	TK	2020	Metastatic *RET* fusion-positive NSCLC, thyroid cancers, *RET* mutant medullary thyroid cancers
Selumetinib	MEK1/2	STE	2020	Neurofibromatosis type I
Sirolimus	mTOR	AK	1999	Kidney transplants, lymphangioleiomyomatosis
Sorafenib	BRAF	TKL	2005	HCC, RCC, thyroid cancer (differentiated)
Sunitinib	VEGFR	TK	2006	GIST, pancreatic neuroendocrine tumors, RCC
Temsirolimus	mTOR	AK	2007	RCC
Tepotinib	MET	TK	2021	NSCLC with *MET* mutations
Tirbanibulin	SRC	TK	2020	Actinic keratosis
Tivozanib	VEGFR	TK	2021	Third-line treatment of RCC
Tofacitinib	JAK	TK	2012	Rheumatoid arthritis, psoriatic arthritis, ulcerative colitis
Trametinib	MEK1/2	STE	2013	In combination with dabrafenib for unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations
Trastuzumab	HER2	mAb	1998	HER2-positive breast cancer
Trastuzumab–deruxtecan	HER2	ADCs	2019	HER2 low expression metastatic breast cancer
Trastuzumab–emtansine	HER2	ADCs	2013	HER2 positive breast cancer
Trilaciclib	CDK4/6	CMGC	2021	Chemotherapy-induced myelosuppression
Tucatinib	EGFR/HER	TK	2020	Combination second-line treatment for HER2-positive breast cancers
Umbralisib	PI3K/CK1	LK/CK	2021	Marginal zone lymphoma, FL
Upadacitinib	JAK	TK	2019	Second-line treatment for rheumatoid arthritis
Vandetanib	VEGFR	TK	2011	Medullary thyroid cancers
Vemurafenib	BRAF	TKL	2011	*BRAF* V600E melanomas
Zanubrutinib	BTK	TK	2019	Mantle cell lymphomas

[1] Although many of these drugs are multikinase inhibitors, only the primary therapeutic targets are given here. ALK, anaplastic lymphoma kinase; BTK, Bruton tyrosine kinase; CDK4/6, cyclin-dependent kinase 4/6; CK1, casein kinases; CSF1R, colony-stimulating factor 1 receptor; FGFR, fibroblast growth factor receptors; FLT3, Fms-like TyrosineKinase-3; JAK, Janus kinase; MET, mesenchymal-epithelial transition factor; mTOR, mammalian target of rapamycin; PDGFR-α, platelet-derived growth factor receptor-α; PI3K, phosphatidylinositol 4,5-bisphosphate 3-kinase; ROCK1/2, Rho-associated coiled-coil-containing protein kinases 1/2;SYK, spleen tyrosine kinase; TRK, tropomyosin receptor kinase; TYK2, tyrosine kinase 2; VEGFR, vascular endothelial growth factor receptor.

[2] ADCs, antibody-drug conjugates; AGC, protein kinase A/G/C; AK, atypical kinases; CMGC, cyclin-dependent kinases, MAP kinases, glycogen synthase kinases, CDC-like kinases; LK, lipid kinases; mAb, monoclonal antibody; STE, homologues of sterile 7; TK, tyrosine kinases; TKL, tyrosine kinase like.

[3] CLL, chronic lymphocytic leukemias; CML, chronic myelogenous leukemias; SLL, small lymphocytic lymphomas; PH, Philadelphia chromosome; RCC, renal cell carcinomas; ALL, acute lymphoblastic leukemias; GIST, gastrointestinal stromal tumors; FL, follicular lymphoma; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma; AML, acute myelogenous leukemias.

[4] Adapted from Ref. [11,12], and some information is obtained from https://www.fda.gov/.

mutation [28]. Osimertinib has dominated the treatment of EGFR-positive NSCLC worldwide, and is currently the first-line treatment for T790M-positive NSCLC patients and the first choice of patients who have become resistance to first or second-generation EGFR-TKIs [28,29]. But there are always new *EGFR* mutations that make the tumor resistant to current generation of EGFR-TKIs, such as the recently discovered *EGFR* C797S mutation [30]. In response to this problem, the fourth generation EGFR-TKIs are currently being developed, such as EAI045, BLU-945, TQB3804, grigatinib, but their clinical efficacy is still uncertain. Additional clinical trials may be needed in the future to verify the efficacy of the novel EGFR-TKIs in patients with advanced lung cancer.

From the history of multigenerational EGFR-TKIs development, it can be learnt that simply optimizing TKIs to improve the efficacy of targeted drugs may not be the best way to manage drug resistance, as the newly occurred mutations may be endless. Alternative approaches to managing patient resistance should be considered, such as combining immunotherapy or chemotherapy, using downstream signaling pathway inhibitors or targeting non-target-dependent resistance mechanisms.

2.2 The Clinical Application of HER2-TKI in Breast Cancer

According to the latest statistics, the morbidity of breast cancer is now the highest of all cancers and exceeds that of lung cancer [1]. Breast cancer can be divided into separate tumor subtypes according to the expression of prognostic factors such as estrogen receptor (ER), progesterone receptor (PR), and HER2, which are closely relevant to treatment strategies [31]. ER-positive tumor patients mainly receive endocrine therapy; HER2-positive tumors can be treated with antibodies or small molecule inhibitors targeting HER2; while patients with triple-negative tumors generally receive chemotherapy [32]. *HER2* (*ERBB2/Neu*) is one of the most typical oncogenes involved in the occurrence of breast cancer. HER2-positive breast cancer, characterized by HER2 protein overexpression or gene amplification, has been found in approximately 25% to 30% of invasive breast cancers, and is especially associated with a poor prognosis [17]. Unlike other members of the ERBB family, HER2 lacks natural ligands *in vivo*, and HER2 exerts its biological effects primarily by forming dimers with itself or other growth factor receptors [14]. The main dimerizing chaperones include EGFR/HER1, HER3, IGF-1R, IGF-2R, and c-MET [33]. Similar to EGFR, HER2 has ATP-dependent tyrosine kinase domains and extracellular domains, enabling it to be targeted with small molecule inhibitors or monoclonal antibodies (mAb).

There are several HER2-targeting drugs now used in clinical practice. Trastuzumab (Herceptin), a humanized mAb targeting the extracellular subdomain IV of HER2 [34], which induces antibody-dependent cell-mediated cytotoxicity (ADCC), is widely used as a targeted therapy in patients with HER2 overexpression. Lapatinib, a small molecule inhibitor that targets both EGFR and HER2, has been approved for HER2-positive breast cancer patients treated with trastuzumab with disease progression [35]. Pertuzumab is a second-generation recombinant humanized mAb, which can bind to the extracellular dimerization domain II of HER2, thereby preventing HER2 from forming heterodimer with HER1, HER3, HER4, and IGF-1R, consequently inhibiting cell proliferation [36]. In addition, trastuzumab emtansine (T-DM1) is an antibody-drug conjugates (ADCs) that combines the anti-HER2 effect of trastuzumab with the cytotoxicity of the anti-microtubule agent DM1 in order to selectively introduce potent cytotoxic agents into HER2-overexpressing cells by binding to HER2 [37].

3. The IGF Signaling Pathway is Involved in Acquired Resistance to TKIs

The application of TKIs has brought great hope to a large number of patients suffering from lung, breast, and colorectal cancers, leukemia and other tumors; however, most patients will inevitably develop drug resistance after the use of targeted drugs. NSCLC patients treated with EGFR-TKIs develop drug resistance in an average of 6 to 13 months [38]. The majority of patients who achieve an initial response to trastuzumab-based regimens develop resistance within 1 year [39]. A comprehensive understanding of the resistance mechanisms of TKIs will contribute to the development of a new generation of targeted drugs and follow-up therapy, which has the potential to effectively prolong patient survival. The resistance mechanisms of TKIs are complicated and varied, and are divided into target-dependent resistance mechanisms and non-target-dependent resistance mechanisms. The former is usually induced by a secondary mutation in the ATP-binding pocket of the receptor kinase, which alters its molecular conformation and declines its combination with TKI [40]. Similar to the development of the third generation EGFR-TKI, this type of drug resistance can be effectively improved by changing the chemical conformation of pharmaceutical molecules. Non-target-dependent drug resistance mechanisms are more complex and diverse, including compensation of other signaling pathways, sustained activation of downstream pathways, and phenotypic transformation [40,41]. For example, in spite of the capacity of EGFR-TKIs that can still inhibit the phosphorylation of mutant EGFR, drug-resistant cells maintain activation of survival and proliferation signals through other pathways.

Several studies have shown that the activation of the IGF signaling pathway can impact the sensitivity of cells to TKIs. Choi *et al.* [42] found that inhibition of IGF-1R enhanced the growth inhibition and pro-apoptotic effects of gefitinib on H1650 cells. Increased phosphorylation of IGF-1R and AKT was found in hepatocellular carci-

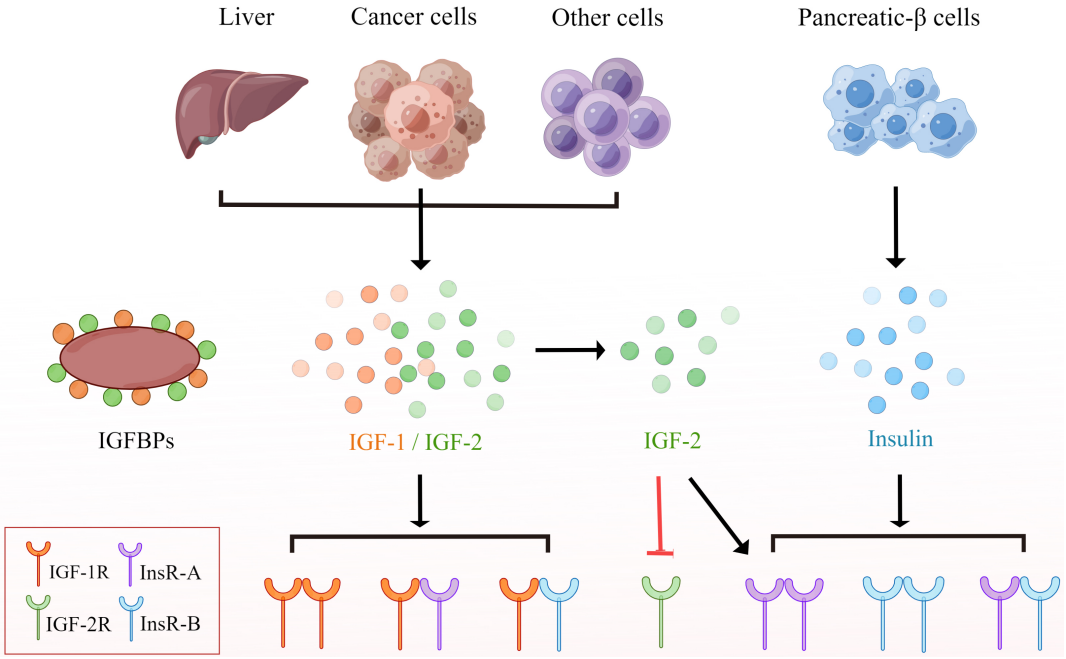

Fig. 1. IGF, insulin and their receptors. IGF is secreted by liver cells, tumor cells or other cells, while insulin is secreted by islet-β cells. IGF-1R can heterodimerize with InsR-A or InsR-B to form hybrid receptors, which is activated by binding to IGF-1 or IGF-2. IGF-2R can be used to isolate IGF-2 (red line), considering its lack of kinase activity. IGF-2 is also able to bind and activate InsR-A. IGFBPs usually serve as a serum bank for IGFs. This illustration was created by Figdraw.

noma cells after gefitinib treatment [43]. The expression of IGF-1 was also significantly increased in erlotinib-resistant glioblastoma cell lines, but not in sensitive cell lines [44]. Seropositivity of IGF-1 was found to be an independent adverse prognostic factor in NSCLC patients treated with gefitinib [45]. The specificity of predicting gefitinib resistance with high levels of total IGF-1R was 76%, and the positive predictive value was 81%. The specificity of predicting gefitinib resistance with high levels of phosphorylated IGF-1R was 100%, the sensitivity was 41%, the positive predictive value was 100%, and the negative predictive value was 23%, implying that the expression of IGF-1R can be used as a biomarker to predict the emerging resistance of NSCLC to gefitinib [46]. These findings suggest that the use of TKIs may promote the activation of the IGF pathway, and the activation of the IGF pathway is involved in the resistance of cells to TKIs.

The IGF pathway is an intricate network, mainly consisting of the following three components: three ligands, insulin, IGF-1, IGF-2; three cell surface receptors, IGF-1R, IGF-2R, insulin receptor (InsR); and six high-affinity insulin-like growth factor binding proteins (IGFBPs) [47]. IGFs are synthesized in the liver prevailingly, and the level of IGFs is regulated by IGFBPs principally [8,48]. There are 6 types of IGFBPs with high affinity *in vivo*, which bind to 98% of circulating IGF-1 and act as carrier proteins to regulate the transport of IGF-1 and prolong its relatively short half-life [49,50]. InsR, IGF-1R and IGR-2R are all transmembrane dimer receptors. IGF-1R and InsR belong to RTKs family. Since they are of the same domain, IGF-1R and InsR usually exist on the cell surface in the form of a homodimer or heterodimer [51]. Similarly, the extracellular domain structure of EGFR, which belongs to RTKs as well, is similar to that of IGF-1R [52], suggesting the possibility of IGF-1R/EGFR heterodimer formation [53]. The prime activating ligands of IGF-1R are IGF-1 and IGF-2. After combining with the ligands, IGF-1R activates its tyrosine kinase activity, phosphorylates some insulin receptor substrate (IRS) proteins, and then triggers multiple downstream signaling pathways, including the RAS-RAF-MEK-MAPK pathway, the PI3K-AK-mTOR pathway, TAK/STAT and Src pathways, which are closely associated with the proliferation, invasion, metastasis, epithelial mesenchymal transition (EMT) and drug resistance of tumor cells [8,54]. There are two subtypes of InsR, InsR-A and InsR-B, which differ in their ligand binding and signal transduction properties. InsR-A is associated with the mitotic pathway and binds to IGF-2 and insulin, mainly expressed in cancer and fetal cells; while InsR-B only combines with insulin at physiological concentrations, and mainly regulates glucose homeostasis, leading to major metabolic effects, that are prevailingly expressed in metabolic tissues [55,56]. Unlike IGF-1R and InsR, due to the loss of intracellular domain, IGF-2R lacks kinase activity, which removes IGF-2 mainly through receptor-mediated endocytosis and lysosomal degradation, preventing it from activating InsR and IGF-1R, thereby disrupting IGF-2 signal transduction [57,58] (Fig. 1).

IGFBPs, a type of circulating protein with sophisticated functions, are considered to be a carrier protein regulating the activity of IGFs and can be used as a serum bank for IGFs [9]. In addition to binding IGF through common IGF binding domains, several IGFBPs can also combine with specific membrane receptors and attach to the cell surface or extracellular matrix, ultimately performing a variety of intricate functions through IGF-dependent or IGF-independent mechanisms, including cell proliferation, movement, and tissue remodeling [49,59,60]. IGFBP2 is the second most abundant IGFBP in the circulation. Several studies have shown that IGFBP2 is overexpressed in various tumors [60–64]. However, another study demonstrated that the expression of IGFBP2 and IGFBP4 in PC-9DR2 cell lines with dual resistance to MET-TKI and gefitinib is deceased [65], indicating that the role of IGFBP2 is complicated. IGFBP3 is the staple IGF carrier protein in serum [66], with both stimulating and inhibiting effects on the biological activity of IGF, but little is known about these biological switches. IGFBP3 has long been considered a strong negative regulator of IGF-1R activity [67]. Studies have shown that deficiency of IGFBP3 expression results in resistance to osimertinib in NSCLC [68]. In contrast, other studies have demonstrated that enhancive expression of IGFBP3 results in resistance to afatinib in lung adenocarcinoma [66]. The increase of IGFBP3 and IGFBP5 was also found to contribute to the resistance of neuroblastomas to TKI [69]. Therefore, the effect of IGFBP3 on TKIs resistance is complicated. The function of IGFBP7, similar to that of IGFBP2 or IGFBP3, is complex. Studies have found that IGFBP7 can compete with IGFs to combine with IGF-1R, thereby inhibiting the activation of IGF-1R [70]. Another study found that the content of IGFBP7 is reduced in half of metastatic breast cancers, and the abnormal activation of IGFBP7 can inhibit the activation of the MAPK pathway [35], implying that IGFBP7 may negatively regulate the IGF pathway. On the contrary, overexpression of IGFBP7 has been shown to prevent tumor cell apoptosis, resulting in EGFR-TKIs resistance in lung cancer cells [71]. These findings demonstrate that IGFBPs have dual effects on tumor development, drug resistance of TKIs, and activation of the IGF pathway. The relevant biological switch is still unclear, and future studies need to further explore the mechanism. A variety of IGFBPs with similar structure and function have been shown in separate studies to be involved in regulating cell sensitivity to EGFR-TKI along. It is not clear whether their relationship is independent, synergistic, or antagonistic in this context. Therefore, we need more systematic and comprehensive research.

4. The Mechanism of the IGF Pathway Involved in Acquired Resistance to TKIs

The IGF pathway is involved in various processes of tumor growth, such as tumor proliferation, invasion, metastasis, and EMT [8]. Nuclear IGF-IR can also regulate gene expression [9], which is related to the involvement of the IGF pathway in resistance to chemotherapy, radiotherapy and targeted therapy. In this section, we discuss the mechanism of the IGF pathway to acquired resistance to TKIs from three aspects: (1) The IGF pathway is involved in the activation of the EGFR compensatory signaling pathway. Although EGFR-TKIs can still inhibit the phosphorylation of mutant EGFR, drug-resistant cells maintain activation of downstream signaling pathways through other pathways. (2) The IGF pathway promotes the activation of EMT and integrin pathways, which in turn promotes tumor growth, metastasis and drug resistance, leading to tumor progression. (3) Activation of the IGF pathway can inhibit apoptosis or cell cycle arrest caused by targeted drugs, leading to sustained growth of tumor cells and resistance to TKIs.

4.1 Activation of Compensatory Signaling Pathway

When the dominant pathway is blocked, cancer cells are able to activate alternative signaling pathways to maintain cell survival and proliferation [72]. Key downstream signaling pathways shared by many receptor and non-receptor tyrosine kinases such as ERK or AKT, can be activated by a variety of RTKs. As a result, when the EGFR pathway is blocked by TKIs, other RTKs, including the IGF signaling pathway, are alternatively upregulated, which directly activate downstream ERK or AKT signaling pathways to compensate for the lack of EGFR signal transduction function. The resistance to TKIs mediated by this process is independent of EGFR [73]. For example, a study has shown that the IGF pathway can activate AKT and phosphorylate PRAS40 (an AKT substrate, 40 kD and rich in proline) to stop its inhibition of mTOR, and then enhance mTOR signaling [27], resulting in continued cell proliferation and resistance to EGFR-TKIs [74]. Another study also found that the increased expression of IGFBP3 can enhance the expression of MET and phosphorylation of ERK by activating the IGF-1R pathway, which causes afatinib resistance in lung adenocarcinoma [66].

In addition, some tyrosine kinases can also be activated by a portion of overexpressed RTKs. It has been shown that overexpression of IGF-1R, EGFR, HER2 and HER3 can activate Src, a non-receptor tyrosine kinase, which has been verified to be a key mediator of trastuzumab resistance in HER2-positive breast cancer [75,76]. In conclusion, IGF-1R can induce trastuzumab resistance in HER2+ breast cancer by enhancing Src kinase activity [17].

In addition to its IGF-dependent mechanisms, IGFBPs can perform diversified functions through non-IGF-dependent mechanisms [49,59]. IGFBP3 has been shown to activate the TGF-β-Smad2/3 signaling pathway independently of the IGF pathway [77]. The *Met* promoter region contains a putative Smad2/3 binding site [78], suggesting that overexpression of IGFBP3 may enhance the expression of *Met* through the TGFb-Smad2/3 signaling pathway, which may result in part, to the acquired resistance of Met-TKI and EGFR-TKI [65].

IGF-1R can interact with the receptors of the ERBB family, and EGFR and IGF-1R can form heterodimers due to their similar extracellular domain structure [52]. Studies have shown that gefitinib [79] and erlotinib [80] can induce a direct interaction between IGF-1R and EGFR, which promotes the formation of the IGF-1R/EGFR heterodimer, thereby activating the IGF-1R pathway, causing an increase in the expression of survivin, and ultimately, resulting in acquired resistance to EGFR-TKIs. Closer binding of heterodimers results in stronger recovery of downstream signaling pathways, which negatively affects the efficacy of inhibitors [53]. The basal level of IGF-1R expression is important for initiating the formation of this heterodimer [79]. A study also found that IGF-2 is overexpressed in Herceptin-resistant breast cancer cells [81]. As a result, a large number of IGF-2 binds to IGF-1R to facilitate IGF-1R phosphorylation and activation, resulting in changes in its configuration, which promotes the interaction between activated IGF-1R and HER2 to form a heterodimer on the surface of the cell and accelerate its phosphorylation, activate its tyrosine kinase activity and downstream signaling pathways, and ultimately affect the sensitivity of cells to trastuzumab. Similarly, the heterodimerization also leads to gefitinib resistance in colon cancer cells [82]. Other than heterodimer, HER2/HER3/IGF-1R can also form heterotrimer [83], resulting in enhanced activity of downstream PI3K/Akt, Src kinase and other signaling pathways.

4.2 Promote the Activation of EMT and Integrin Pathways

It has been demonstrated that EMT is closely related to tumor metastasis and drug resistance [84]. The IGF system can regulate the EMT process [85]. Several studies have verified that activation of the IGF pathway may facilitate drug resistance by promoting EMT. For example, a study found that in PC-9/GR (gefitinib resistance) cells and H460/ER (erlotinib resistance) cells, IGF-1R can upregulate the expression of Snail by activating the ERK/AKT pathway (Snail is the main regulator of EMT [85]), which promotes the transport of β-catenin from the cell membrane to the nucleus, thereby resulting in direct inhibition of the expression of E-cadherin (a cell junction-related protein) and enhanced EMT in NSCLC cells [86]. Another study has shown that carcinoma-associated fibroblasts (CAFs) can overexpress IGF-1 and hepatocyte growth factor (HGF) through paracrine mechanisms, and activate the corresponding receptors IGF-1R and C-MET respectively, which increase the expression and phosphorylation of annexin A2 (ANXA2), and ultimately improve EMT and EGFR-TKIs resistance *in vitro* and *in vivo* [87]. This mechanism was also found in cholangiocarcinoma and gastric cancers, and mediated EGFR-TKIs resistance in these tumors [88–90].

IGFBP2 has been found to be involved in integrin pathways [91,92]. Integrins mediate cell adhesion and transmit mechanical and chemical signals to the interior of the cell to drive multiple stem cell functions, including tumor initiation, epithelial plasticity, metastatic reactivation, and resistance to therapies targeting oncogene and immune checkpoint. In tumor tissues, various mechanisms can deregulate integrin signaling, allowing tumor cells to proliferate unchecked, invade across tissue boundaries, and survive in heterogeneous microenvironments [93]. IGFBP2 contains Gly-Arg-Asp (RGD) and heparin-binding sequences, which directly bind integrins and extracellular matrix to trigger biological behaviors independent of IGFs, that promote tumor progression through activation of integrin pathways [94,95]. Focal adhesion kinase (FAK) is an important member of integrin-mediated signal transduction [96]. A study has shown that overexpression of IGFBP2 promotes FAK phosphorylation, leading to dasatinib resistance in NSCLC cells [60].

4.3 Regulation of the Cell Cycle and Apoptosis

Evidence accumulated in recent years indicates that, in addition to typical cell-surface localization pattern and ligand-activated mechanism of action, IGF-1R is present in the cell nucleus of both normal and cancer cells [97–99]. Nuclear translocation of IGF-1R is attained via proteosomal, lysosomal and endocytic pathways, and importin-β is a key factor in nuclear mobilization [100,101]. Nuclear IGF-1R exhibits a number of biological activities similar to those of typical transcription factors, and regulates cellular metabolism, tumor growth, metastasis, and resistance to anti-cancer therapies [101]. Guerard *et al*. [102] demonstrated that gefitinib induces IGF-1R internalization and the intracellular redistribution of amphiregulin in mucinous lung adenocarcinoma. This promotes the formation of amphiregulin/IGF-1R/importin-β1 complexes, allowing the nuclear transport of IGF-1R. Nuclear IGF-1R subsequently leads to accumulation of $p21^{Waf1}$ (a cyclin-dependent kinase inhibitor) and G1 phase arrest, which in turn inhibits gefitinib-induced apoptosis and contributes to gefitinib resistance [102].

In addition to the nuclear IGF-1R pathway, IGF-1R on the cell surface can also activate the AKT-dependent survival pathway through the classic ligand-activated mechanism of action, and participate in the resistance of tumor cells to EGFR-TKIs [102]. It is known that p27 is a cell cycle regulator and it can induce cell cycle arrest by impairing the ability of cyclin E to promote G1-S phase transition, which is mainly regulated by the amount of nuclear p27. It has been shown that TKIs can induce cell cycle arrest by promoting the expression of nuclear p27, thus preventing the continuous proliferation of tumor cells [103]. The IGF pathway can activate AKT, which phosphorylates p27 at T157, resulting in cytoplasmic isolation of p27 and a significant decrease in the number of nuclear p27, ultimately contributing to continued cell proliferation and EGFR-TKIs resistance [104]. Furthermore, PRAS40,

Table 2. Strategies of targeting IGF pathway.

Drug type	Compound	Preclinical studies
Monoclonal antibodies	Cixutumumab (IMC-A12)	[107–109]
	Ganitumab (AMG-479)	[110–113]
	Figitumumab (CP-751871)	[114–117]
	Dalotuzumab (MK-0646)	[118]
	Teprotumumab (R1507)	[119,120]
Small molecule inhibitors	Linsitinib (OSI-906)	[121–124]
	BMS-754807	[122,125–127]
	Picropodophyllin (AXL1717)	[128–131]
	NT157	[132,133]
	AG-1024	[134]
	NVP-AEW541	[135–137]
	NVP-ADW742	[138–140]
	GSK1904529A	[141–143]
Ligand neutralization	Dusigitumab (MEDI-573)	[144]
	Xentuzumab (BI 836845)	[145,146]

a substrate of AKT, can be phosphorylated as a result of the activation of AKT by the activated IGF pathway, and that phosphorylated PRAS40 can interact with forkhead box O3 (FOXO3a) to decrease the transcription of apoptotic genes [28], ultimately leading to continued cell proliferation and EGFR-TKIs resistance [74].

It has also been demonstrated that the overexpressed IGFBP7 can inhibit the activity of pro-apoptotic protein caspase and the expression of B-cell lymphoma-2-like 11 (BIM), thus restraining the apoptosis of tumor cells, and finally, leading to the resistance of EGFR-TKIs in lung cancer [71].

The above reported drug resistance mechanisms are related to the role of the IGF pathway in promoting tumorigenesis and development, promoting EMT, and regulating gene expression with atypical functions of nuclear IGF-1R, which belong to the non-target-dependent resistance mechanism of TKIs. Whether the IGF pathway can regulate the expression of target genes through other mechanisms, and then lead to cell resistance to TKIs through a target-dependent mechanism is still unknown. In addition, the mechanism by which the expression levels of various molecules in the IGF pathway are altered in tumor tissues is another topic worthy of discussion. Since the IGF pathway molecules can regulate the resistance of cells to TKIs in different mechanisms, future studies can focus on whether the factors or diseases that affect the expression levels of IGFBPs and IGF-1/2 *in vivo* will affect the therapeutic effect of TKIs, so as to help better guide medication and predict efficacy.

5. Therapeutics Targeting the IGF Pathway

The activation of the IGF signaling pathway is related to the acquired resistance to TKIs in cells. As a result, the combination of IGF pathway inhibitors and TKIs has emerged as an effective strategy to prevent drug resistance. A number of studies have demonstrated that blocking the IGF pathway can reverse the resistance of TKIs. Jung-Min Choi *et al*. [105] demonstrated that in EI24-mediated PC9 resistance to gefitinib, the efficacy of EGFR-TKI could be improved by co-inhibiting the IGF-1R pathway by using the IGF-1R small molecule inhibitor PQ-401 or AG-1024. They also found that AG-1024 enhanced the growth inhibition and pro-apoptotic effect of gefitinib in drug-resistant H1650 cells [42]. In addition, Juan Zhou *et al*. [86] found that the IC50 of gefitinib and erlotinib in PC-9 derived gefitinib resistant cells and H460 derived erlotinib resistant cells were significantly reduced after silencing IGF-1R expression by siRNA, suggesting that IGF-1R plays an important role in restoring the sensitivity of cells to gefitinib or erlotinib. Browne *et al*. [106] observed that in trastuzumab-resistant or sensitive HER2+ breast cancer cells (BT474, BT474/Tr, SKBR3, SKBR3/Tr), the efficacy of trastuzumab was improved by using siRNA or IGF-1R TKI NVP-AEW541 to inhibit the expression of IGF-1R. These studies suggest that blocking the IGF pathway may improve the efficacy of TKIs in drug-resistant cells. However, *in vivo* evidence for this conclusion is lacking. Relevant animal experiments can be designed for future research, including using IGF inhibitors.

These studies have demonstrated that the IGF signaling pathway affects drug resistance of tumor cells. There are three major strategies to design drugs that block the IGF signaling pathway for clinical anti-tumor treatment: receptor blocking, kinase inhibition, and ligand isolation (Table 2, Ref. [107–146]) [147]. Among them, mAb is the most commonly used strategy for receptor blocking in clinical studies. The ideal IGF-1R antagonist mAb, with strong specificity in epitope recognition, does not bind to InsR, which avoids side effects such as insulin resistance and hyperglycemia caused by targeting InsR-B. Nevertheless, IGF-1R mAb does not block the activation of InsR-A

[148]. InsR-A is capable of binding to IGF-2 to activate downstream signaling pathways, which is a potential cause of drug resistance to IGF-1R mAb. Currently, commonly used IGF-1R mAbs are: cixutumumab (IMC-A12) and ganitumab (AMG-479). Inhibition of tyrosine kinases is another therapeutic strategy targeting the IGF pathway. Since the major sequences of kinase domains of the IGF system receptors are similar, and the sequences of their ATP-binding pocket are almost absolutely conformed [149], kinase inhibitors can theoretically inhibit virtually all IGF receptors. This suggests the possibility of synthesizing drugs that target both the IGF pathway and the EGFR pathway. Such drugs include linsitinib (OSI-906) and BMS-754807. OSI-906 is a dual IGF-1R/InsR inhibitor. Since kinase inhibitors may impair the action of InsR-B, they may cause adverse effects on normal metabolism. The third strategy is ligand isolation using anti-ligand mAb or recombinant IGF-BPs, such as dusigitumab (MEDI-573), and xentuzumab (BI 836845). Compared with the other two anti-IGF pathway strategies, ligand isolation does not result in severe metabolic disorders in preclinical animal models [150].

Many clinical trials have begun to evaluate the efficacy of drugs targeting the IGF pathway (Table 3, Ref. [151–173]). Several clinical trials using combined therapy with cetuximab in the treatment of lung or breast cancer have shown no significant clinical benefit. Notably, combined treatment significantly increases the incidence of adverse hyperglycemic reactions (NCT01232452, NCT00870870, NCT00955305, NCT00684983). Another clinical trial demonstrated that the survival rate of patients with recurrent small cell lung cancer treated with linsitinib (OSI-906) alone was significantly lower than that treated with the chemotherapeutic drug topotecan (NCT01533181) [174]. Furthermore, other clinical studies on OSI-906 have not yet resulted in satisfactory outcomes [151,152,175, 176]. A clinical trial on the combination of xentuzumab, a dual anti-IGF-1/2 neutralizing antibody, in breast cancer patients showed that the combination of xentuzumab on the basis of everolimus or exemestane did not improve the PFS of the overall population, resulting in an early cessation of the trial (NCT03659136) [153]. Therefore, IGF-1R mAb treatment is largely ineffective in unselected cancer patients. A few clinical trials have suggested that IGF-1R targeted therapy may be beneficial only in specific cancer patients [154,177]. Several preclinical studies suggested potential predictive biomarkers, such as BRCA1, β-catenin/TCF activity, BACH1, *TMPRSS2-ERG* fusion gene, IRS2 copy number gain, InsR-A/IGF-IR overexpression, mutation of *BRAF* and *KRAS* [178–182]. There should be clinical trials to evaluate these biomarkers.

Though the anticancer efficacy of the drugs targeting the IGF pathway is promising in preclinical models, the results of clinical trials have been disappointing. Up to now, there has not been any anti-IGF-1R mAb approved as a cancer drug treatment by the FDA. The following three issues need to be addressed when considering targeting the IGF pathway as a therapeutic strategy. (1) The poor response of selective IGF-1R targeting drugs may be primarily due to the compensation of the activated InsR pathway or the reduction of cellular IGF-1R [51]. As a consequence, inhibition of InsR appears to be imperative, and future research will focus on developing InsR inhibitors that target cancer cells. (2) There is a lack of predictive biomarkers to select patients who will benefit from targeted therapy. Therefore, a large number of marker studies are needed to confirm the appropriate screening method for selecting patients suitable for IGF pathway-targeted therapy. (3) Drugs can cause adverse effects on normal metabolism by impairing the physiological action of InsR, leading to side effects such as metabolic disorders and hyperglycemia. Therefore, when targeting IGF-1R or InsR to treat cancers, alterations in InsR-B function should be avoided. When these issues are resolved, targeting InsR-A may become a promising strategy to exert antitumor effects without causing severe metabolic side effects.

6. Conclusions and Perspectives

TKIs can interfere with the signal transduction of tumor cells, and inhibit the proliferation of tumor cells and neovascularization, with little effect on normal cells [2], making it a promising clinical therapy for cancer patients. A growing number of TKI are being approved by the FDA to treat tumors. The most widely and successful used TKIs are EGFR-TKIs and HER2-TKIs, which are mainly used in the targeted therapy of lung and breast cancers. Although the application of TKIs has brought great hope to a large number of patients, most will inevitably develop drug resistance. The resistance mechanisms of TKIs are complicated, which can be divided into target-dependent resistance mechanisms and non-target-dependent resistance mechanisms. It has been shown that the activation of the IGF signaling pathway can impact the sensitivity of cells to TKIs. The IGF pathway contributes to acquired resistance to TKIs primarily by promoting the activation of compensatory signaling pathways, promoting the activation of EMT and integrin pathways, and regulating the cell cycle and apoptosis. A variety of drugs targeting the IGF pathway have been designed for cancer therapy. Although the anticancer efficacy of the drugs targeting the IGF pathway is promising in preclinical models, the results of clinical trials have been disappointing, limiting the current clinical application of IGF pathway inhibitors.

In order to address drug resistance to EGFR-TKIs caused by the IGF signaling pathway, simultaneously targeting the IGF pathway and EGFR may be an effective strategy. One option is to combine drugs to augment the response time of targeted agents, such as the combination of IGF pathway inhibitors and TKIs for cancer treatment. In addition, single-molecule drugs that inhibit multiple correlative kinases can be developed, such as small molecule

Table 3. Clinical trial of drugs targeting IGF pathway in cancer patients.

Drugs	Combination	Cancer type	Phase	Participants	Results[1]	Ref. or trial ID
Dalotuzumab	Irinotecan, cetuximab	Chemorefractory, *KRAS* exon 2 mutant colorectal cancer	II/III	69	ORR, 5.6%. Median PFS, OS were not statistically significantly different with dalotuzumab alone or placebo.	[155]
Dalotuzumab	Erlotinib	Refractory advanced non-small-cell lung cancer	I/II	I 20 II 75	II, ORR, 2.7%. No significant difference in PFS, OS, compared to erlotinib.	[156]
Dalotuzumab	Pemetrexed, cisplatin	Untreated non-squamous lung cancer stage IV	II	26	PR, 25%. SD, 33.33%. PD, 33.33%.	[157] NCT00799240
Dusigitumab	None	Advanced solid tumors	I	43	CR, 0. PR, 0. SD, 33.33%.	[158]
Figitumumab	Erlotinib	Stage IIIB/IV or recurrent disease with nonadenocarcinoma histology	II	583	OS, 5.7 months. Median PFS, 6.2 months. No improvement, compared to erlotinib.	[159] NCT00673049
Figitumumab	Paclitaxel, carboplatin	Stage IIIB/IV or recurrent NSCLC disease with nonadenocarcinoma histology	III	681	OS, 8.6 months. Median PFS, 4.7 months. ORR, 33%. No improvement, compared to paclitaxel, plus carboplatin.	[160]
Figitumumab	Docetaxel or prednisone	Progressing castration-resistant prostate cancer	II	204	Median PFS was 4.9 months, with HR = 1.44 (95% CI, 1.06–1.96), compared to docetaxel/prednisone alone.	[161]
Ganitumab	None	Metastatic progressive carcinoid or pancreatic neuroendocrine tumors	II	60	Median PFS, 6.3 months (95% CI, 4.2–12.6). OS at 12 months was 66% (95% CI, 52–77%).	[162]
Ganitumab	Gemcitabine	Previously untreated metastatic pancreatic adenocarcinoma	II	125	OS at 6 months was 57% (95% CI, 41–70%).	[163]
Teprotumumab	Erlotinib	Progressing advanced-stage non-small-cell lung cancer (NSCLC)	II	172	12-week PFS rates were 39%, 37%, and 44%, and median OS was 8.1, 8.1, and 12.1 months for the three groups (erlotinib plus placebo, or R1507 weekly, or R1507 every 3 weeks), respectively.	[154]
Teprotumumab	None	Recurrent or refractory soft tissue sarcomas	II	163	ORR, 2.5% (95% CI, 0.7–6.2%). Median PFS, 5.7 weeks. Median OS, 11 months.	[164]
Teprotumumab	None	Refractory or recurrent Ewing sarcomas	II	115	CR or PR, 10% (95% CI, 4.9–16.5%). Median OS, 7.6 months (95% CI, 6–9.7 months).	[165]
Xentuzumab	Afatinib	Previously treated *EGFR* mutation-positive NSCLC	I	32	ORR, 0. Median SD, 2.3 months (95% CI, 0.8–10.9 months).	[166] NCT02191891
Xentuzumab	Everolimus, exemestane	Hormone receptor-positive/ HER2-negative locally advanced and/or metastatic breast cancer	Ib/II	II 140	Median PFS, 7.3 months, with HR = 0.21 (95% CI, 0.05–0.98, $p = 0.0293$), compared to everolimus plus exemestane.	[153] I, NCT02123823 II, NCT03659136

Table 3. Continued.

Drugs	Combination	Cancer type	Phase	Participants	Results[1]	Ref. or trial ID
Linsitinib	None	Locally advanced or metastatic adrenocortical carcinoma	III	139	Median OS, 323 days (95% CI, 256–507 days). No significant difference, compared to placebo.	[151] NCT00924989
Linsitinib	None	Wild type gastrointestinal stromal tumors	II	20	ORR, 0. CBR at 9 months was 40%. 9 months PFS, 52%. 9 months OS, 80%.	[152]
Picropodophyllin	None	Advanced solid tumors	Ia/b	Ia 20 Ib 39	For 15 NSCLC patients, the median PFS was 31 weeks and the OS was 60 weeks.	[172] NCT01062620
Picropodophyllin	None	Previously treated, locally advanced or metastatic NSCLC	II	99	12-weeks PFS, 29%, ORR, 0. Estimated median OS, 38.7 weeks. No improvement, compared to docetaxel.	[167]
Cixutumumab	Capecitabine, lapatinib	HER2-positive metastatic breast cancer previously treated with trastuzumab	II	68	Median PFS, 5.0 months. Median OS, 21.9 months. No improvement, compared to capecitabine plus lapatinib.	[168] NCT00684983
Cixutumumab	Bevacizumab	Stage IV or recurrent non-squamous, NSCLC	II	175	Median PFS, 7.0 months. ORR, 58.7%. Median OS, 16.1 months. The addition of cixutumumab increased toxicity without improving efficacy.	[169] NCT00955305
Cixutumumab	Doxorubicin	Advanced soft tissue sarcoma	I	30	Estimated PFS, 5.3 months (95% CI, 3.0–6.3 months).	[173] NCT00720174
Cixutumumab	Androgen deprivation (AD)	New metastatic hormone-sensitive prostate cancer	II	210	NO statistical difference between AD and AD plus Cixutumumab in OS or PFS.	[171]
Cixutumumab	Cetuximab	Recurrent/metastatic head and neck squamous cell carcinoma	II	91	Median PFS, 2.0 months. CBR, 15.3%. No improvement, compared to cetuximab alone.	[170]

[1] ORR, objective response rate; CBR, clinical benefit rate; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; HR, hazard ratio; CI, confidence interval; Trial ID registered number at https://ClinicalTrials.gov.

inhibitors that target both the IGF and EGFR pathways, to improve efficacy and reduce toxicity. This will require more in-depth basic and clinical research studies.

Author Contributions

YP wrote the original draft, draw the figures, and acquired, initially analyzed, and visualized data from the reviewed literature. JT edited the review, conceptualized and interpreted the data from the reviewed literature. Both authors have read and agreed to the published version of the manuscript. Both authors contributed to editorial changes in the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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