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Review Article

Redundant kinase activation and resistance of EGFR-tyrosine kinase inhibitors

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Abstract: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown dramatic effects against that tumors harboring EGFR activating mutations in the EGFR intracytoplasmic tyrosine kinase domain and resulted in cell apoptosis. Unfortunately, a number of patients ultimately developed resistance by multiple mechanisms. Thus, elucidation of the mechanism of resistance to EGFR-TKIs can provide strategies for blocking or reversing the situation. Recent studies suggested that redundant kinase activation plays pivotal roles in escaping from the effects of EGFR-TKIs. Herein, we aimed to characterize several molecular events involved in the resistance to EGFR-TKIs mediated by redundant kinase activation.

Keywords: EGFR, redundant kinase activation, resistance to EGFR-TKIs

Introduction

Epidermal growth factor receptor (EGFR), a member of a family which consists of at least 4 receptor tyrosine kinases, including EGFR (ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4) (**Figure 1**). To date, seven ligands for EGFR have been identified: epidermal growth factor (EGF), transforming growth factor (TGF)-α, heparin-binding EGF-like growth factor (HB-EGF), amphiregulin, betacellurin, epiregulin, and epigen [1]. The EGFR family of cell surface-receptor tyrosine kinases controls the intracellular signaling pathways that promote cell growth, proliferation, differentiation, and migration [2]. The important roles of EGFR in the activation of cancer relevant cellular processes, together with the presence of overexpressed or aberrantly activated EGFR in non-small cell lung carcinoma (NSCLC), suggest that targeting the EGFR may provide a strategy for NSCLC.

Two main anti-EGFR strategies are currently in clinical application: low-molecular-weight TKIs that compete with adenosine triphosphate (ATP) for binding to the tyrosine kinase portion of a mutant EGFR receptor, and monoclonal antibodies (mAbs) that are directed at the ligand-binding extracellular domain, thereby preventing ligand binding, and consequently receptor dimerization, and receptor signaling. Among these, gefitinib and erlotinib were the first EGFR-TKIs to be approved by Food and Drug Administration (FDA) for treatment of NSCLC (**Table 1**). These drugs inhibit kinase activity by competitively bind to the ATP-binding site of EGFR, preventing auto-phosphorylation and consequently blocking downstream signaling cascades of RAS/RAF/MEK/ERK and PI3K/AKT pathway, resulting in proliferation inhibition, cell cycle progression delay, and cell apoptosis [3].

Although EGFR-TKIs treatment shows good response rates and progression free survival (PFS) in NSCLC patients with EGFR gene mutations, acquired resistance of TKIs therapy is common after a median of 12-16 months [4]. To date, various mechanisms of resistance to erlotinib and gefitinib have been identified, including 1) gatekeeper mutations in EGFR, such as the T790M second mutation which is thought to be responsible in over 50% in patients who acquire secondary resistance [5]; 2) activation of redundant kinase signaling pathway such as c-Met [6], insulin-like growth factor receptor (IGFR) [7], HER family members [8, 9], growth

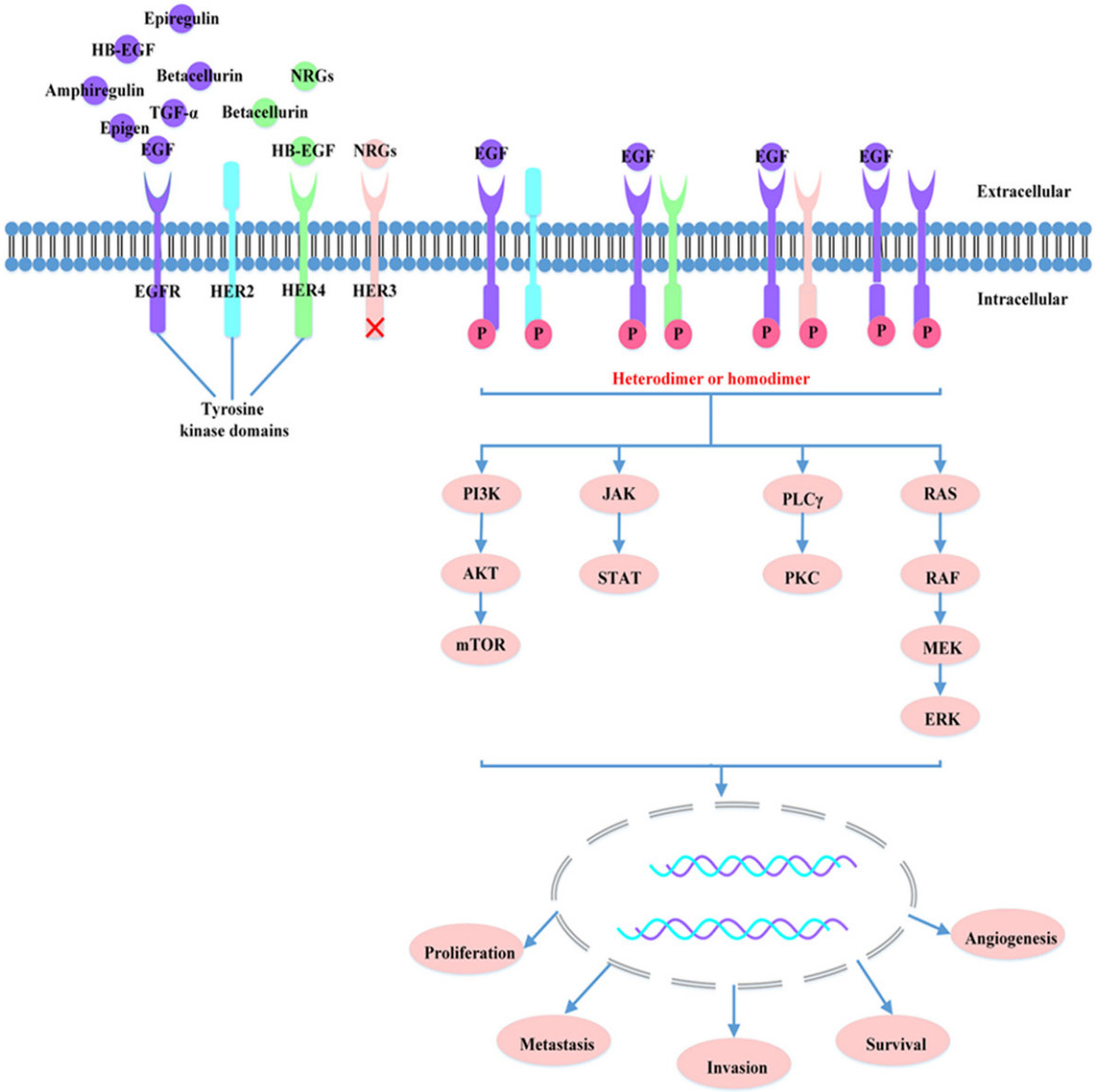


Figure 1. HER family and EGFR signaling pathway. Ligand-bound receptors form functionally active homodimers or heterodimers, resulting in the activation of downstream signaling pathways such as PI3K/AKT, RAS/RAF/MAPK, PLCγ/PKC and JAK/STAT pathway, leading to cell proliferation, invasion, metastasis, survival and angiogenesis.

arrest specific gene6 (Gas6)-AXL pathway [10], fibroblast growth factor receptor (FGFR) [11], vascular endothelial growth factor (VEGFR) [12], platelet-derived growth factor receptor (PDGFR) [2], and interleukin-6 receptor (IL-6R) signaling pathway [13]; 3) activation of downstream molecules (PTEN loss or K-RAS, PIK3CA mutation) [14, 15]; 4) small-cell lung cancer transformation [16] and 5) epithelial-to-mesenchymal transition (EMT) [17]. Therefore, it is essential to understand the mechanisms of resistance to TKIs for the development of new EGFR-targeted drugs. This review focuses on the mechanisms of resistance to EGFR-TKIs mediated by redundant kinase activation.

Redundant kinase pathways as mechanisms for resistance to EGFR-TKIs

A simple explanation for the insensitivity to EGFR inhibitors is through a “redundant effect” mechanism, the dominant activity of redundant receptor tyrosine kinase (RTK) systems distinct from EGFR [18]. In this regard, it has been observed that a large fraction of the tyrosine phosphoproteome was abundant in erlotinib-

Table 1. Clinical drugs targeting EGFR approved by FDA

Drugs	Trade Name	Target	Category	Times	Application
Erlotinib	Tarceva	EGFR	TKI	2004	NSCLC, pancreatic cancer
Gefitinib	Iressa	EGFR	TKI	2003	NSCLC
Lapatinib	Tykerb	EGFR/HER2	TKI	2007	metastatic breast cancer
Afatinib	Gilotrif	EGFR/HER2	TKI	2013	NSCLC, metastatic breast cancer
Cetuximab	Erbitux	EGFR	Monoclonal antibody	2004	colorectal cancer
Trastuzumab	Herceptin	HER2	Monoclonal antibody	1998	metastatic breast cancer
Panitumumab	Vectibix	EGFR	Monoclonal antibody	2006	colorectal cancer

treated cells [19]. Activation of these receptor tyrosine kinases by growth factors could protect cells against the EGFR-TKIs. Thus, there is no shortage of candidates for RTKs that may function as alternatives to EGFR in signal transduction of growth and transformation in NSCLC.

c-Met pathway

c-Met, a transmembrane tyrosine kinase receptor that binds with HGF, then induces recruitment of the Grb2-associated binder (GAB1) and activation of multiple signaling networks including the phosphoinositide PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways independent of EGFR, HER2, HER3, and HER4 [20]. Deregulation of c-Met signaling due to overexpression of c-Met or HGF has been associated with poor prognosis in advanced gastric carcinomas [21]. A well-documented mechanism is c-Met amplification initially reported in 15-20% of resistant patients [6], but recently another reported in 3-5% [5]. Strong HGF expression was observed in > 60% of tumors with secondary EGFR-TKIs resistance [22]. Activation of c-Met pathway in human tumors can be induced by various means, like HGF overexpression, transactivation by other membrane proteins (including EGFR), and mutations [23, 24]. Accordingly, a recent study suggests that c-Met activation caused by c-met gene amplification is a suitable surrogate marker of resistance to EGFR-TKIs [25]. Interestingly, c-met gene was also found amplify before drug exposure [26] as well as the c-Met activity and protein levels were elevated in nonexposed NSCLC patients [27]. This suggests c-Met overexpression is associated with primary resistance of EGFR-TKIs in NSCLC.

As for transactivation by other membrane proteins, Engelman *et al.* [6] found that there is a cross-talk between EGFR and c-Met mediated by phosphorylation and signaling from HER3 to AKT in lung cancer cell lines, which leads to the resistance of EGFR TKIs. Much to their surprise, even if oncogenic EGFR was fully inhibited, activation of the PI3K/AKT/mTOR pathway could continue through the interaction of c-Met and HER3. Phosphorylation of HER3 by c-Met has been shown to occur via direct as well as indirect mechanisms. With respect to direct phosphorylation, the c-Met receptor may homodimerize with HER3 activates the PI3K/AKT pathway independent of EGFR [28]. This mechanism is analogous to the manner in which EGFR itself activates PI3K-driven signal transduction. Indirect phosphorylation of HER3 include upregulation of EGFR ligands, and activation of other tyrosine kinases (for example, c-Src) [29, 30]. Moreover, when this redundant c-Met signaling via HER3 was simultaneously inhibited, apoptosis increased dramatically among resistant cells [30]. Specific short hairpin RNA (shRNA) and small interfering RNA (siRNA) of c-Met could restore the ability of gefitinib in resistant cells [31]. However, Rho *et al.* [32] found that there was no cross-talk between c-Met and EGFR. These phenomena may be explained by a previous report [27], in which it was shown that mutated and amplified EGFR can activate c-Met. Likewise, enhanced levels of HGF, active the c-Met/PI3K/AKT signaling pathway, thus induce gefitinib resistance of lung cancer cells harboring EGFR-activating mutations [33]. An anti-HGF neutralizing antibody or an HGF antagonist (NK4), when combined with EGFR-TKIs, dramatically reversed HGF-induced resistance *in vitro* and *in vivo* [34]. Moreover, transient but intensive inhibition of PI3K/AKT by PI3K inhibitors and gefitinib successfully overcame HGF-induced EGFR-TKIs resistance *in vitro* and *in vivo* [35]. 17-DMAG (an HSP90 inhibitor) has efficacy for HGF-triggered erlotinib resistance in cell lines and animal models [36]. Another research found

that through promoting c-Met-integrin association, HGF-FN (fibronectin) and HGF-VN (vitronectin) complexes coordinated and enhanced endothelial cell migration through activation of the PI3K pathway [37]. There is also an important cross-talk between c-Met and the α2β1 integrin in mast cell, resulting in the release of the pro-inflammatory cytokine, IL-6 [38], which can activate the IL-6R/JAK/STAT signaling related with EGFR-TKI resistance [13].

Many of these mechanisms above are thought to be critical for the contribution of c-Met to tumorigenesis and may be involved in both primary and acquired resistance to gefitinib, meanwhile provide a rationale for targeting HGF/c-Met pathway. The c-Met inhibitor PHA-665752 [39] and NPS-1034 [40] has great effect against lung cancer cells resistant to EGFR-TKIs. Mueller *et al.* [25] have shown that inhibiting c-Met kinase activity in breast cancer cell lines with constitutive c-Met activation sensitizes these cells to EGFR-TKIs.

HER pathway

Recent studies have suggested that overexpression of other members of the EGFR receptor family, namely HER2 and HER3 are involved in EGFR-TKIs resistance [41, 42]. Activation of HER2 signaling was recently reported to cause resistance to cetuximab alone in patients with colorectal cancer [43]. The recent role of HER2 amplification in the acquisition of resistance to TKIs, reported in 12-13% of patients [5]. HER2 can be actived by IGFR1 through a physical association between the two receptors [44]. Importantly, IGFR1 signaling via the PI3K/AKT pathway is associated with resistance to trastuzumab (an anti-HER2 monoclonal antibody) in breast cancer, it also demonstrate evidence of the existence of a physical interaction between IGFR1 and HER2 [45]. Furthermore, activated IGFR1 can also physically associate with HER3 and HER4 [46]. Cretella *et al.* [8] found that targeting HER2 with trastuzumab-DM1 can improve the treatment of HER2 positive breast cancer. It offers a new therapeutic approach in lung cancers expressing HER2 even when resistant to EGFR-TKIs. The combination of afatinib plus cetuximab could be efficacious in overcoming acquired resistance in lung cancer [47]. HER2 mutations are present in about 2-4% of NSCLC, especially in women, never-smokers, Asian patients and in adenocarcinomas without EGFR or K-ras mutations [48]. These mutations render the receptors activation, resulting in proliferation and metastasis of tumor cells. Alternatively, through study of receptor down-regulation, data suggests that mutant EGFRs, especially the L858R/T790M variant, have a propensity to heterodimerize with HER2, which allows for evasion of Casitas B-cell lineagelymphoma (CBL) mediated ubiquitinylation and subsequent lysosomal degradation [49].

Likewise, HER3 overexpression was previously reported to be associated with impaired survival in breast cancer [50]. Almost all *de novo* resistant NSCLC tumors the HER3 receptor is strongly phosphorylated [51]. HER3 lacks tyrosine kinase activity but it can be trans-phosphorylated efficiently by c-Met [6] or other RTKs such as HER2 and HER4 [52]. HER3 interacts with the other HER family members to active intracellular pro-survival signaling due to several tyrosine residues in its intracytoplasmic domain, which can be phosphorylated and become high affinity docking sites for the catalytic subunit of PI3K. High surface HER3 expression correlates with AKT phosphorylation in lung adenocarcinoma primary cultures [10]. Byun *et al.* [53] reported that genetic silencing of USP8 led to the downregulation of several RTKs including EGFR, HER2, HER3, and c-Met, markedly decreased the viability of gefitinib-resistant and -sensitive NSCLC cells by decreasing RTKs expression while having no effect on normal cells. Furthermore, erlotinib with either HER2 or HER3 knockdown by their cognate siRNAs also inhibited PI3K/AKT activation [54]. This indicates that the loss of addiction to mutant EGFR results in the gain of addiction to both HER2 and HER3. Antibodies against HER3 only work in cells overexpressing surface HER3 [9]. And combination of anti-HER3 antibodies with EGFR-TKIs synergistically affect cell proliferation *in vitro*, resulting in cell cycle arrest, p21 expression upregulation and tumor growth inhibition in mouse xenografts [9]. Hence surface HER3 may be considered a predictive marker of efficacy if appropriately validated in a more number of cases. In light of these considerations, HER3 might be a central node in the resistance to EGFR-TKIs, and agents targeting this molecule are being developed (NCT01-211483) [55].

VEGFR pathway

Vascular endothelial growth factor (VEGF) is an important survival factor of vascular endotheli-

al cells that activates tyrosine kinase after binding to VEGFR. VEGFR2 is the key mediator of VEGF-mediated angiogenesis, and VEGFR1 and VEGFR3 are involved in vasculogenesis, and lymphangiogenesis, respectively [12]. Recent studies showed that VEGF overexpression was associated with clinical response to EGFR-TKIs in patients with lung cancer [56, 57]. It suggested the VEGF may play a key role in resistance to EGFR-TKIs. EGFR and VEGFR signaling pathways are independent but are closely interlinked, both EGF and TGF-α can induce VEGF expression via activation of EGFR in cell culture models [58].

HGF is also associated with VEGFR signaling pathway. High serum HGF is relevant to short progression-free survival in a clinical trial of a VEGFR inhibitor, sorafenib, for the treatment of hepatocellular carcinoma [59]. Overexpression of HGF conferred resistance to lenvatinib (a VEGFR inhibitor) and it was cancelled by golvatinib (a c-Met inhibitor) [60]. In renal cell carcinoma, HGF was also reported to induce resistance to sunitinib, an inhibitor of multiple kinases, including VEGFR2, by compensating for inhibited angiogenesis [61]. Previous study showed HGF stimulated VEGF production by activation of the c-Met/Gab1 signaling pathway in EGFR mutant lung cancer cell lines [62]. Silencing of Gab1 successfully canceled HGF-stimulated VEGF production and HGF-induced EGFR-TKIs resistance. These findings suggest that Gab1 may be a novel ideal target for controlling EGFR mutant lung cancer. Though inhibition of VEGFR shrinked the tumor, meanwhile it made the tumor more aggressive with more metastatic behavior in a model of pancreatic neuroendocrine cancer [63]. Maybe the blockade of VEGFR signaling caused hypoxia and that hypoxia is likely to enhance HGF/c-Met pathway that promotes tumor survival and metastasis [64]. Therefore, dual inhibition of HGF and VEGF may be therapeutically useful for EGFR-TKIs resistant lung cancer. Golvatinib is an orally active dual TKI for c-Met and VEGFR2, it exerts effect by inhibiting the c-Met/Gab1/PI3K/AKT pathway [65].

IGFR pathway

IGFR is a member of the class II receptor tyrosine kinase family. It has two distinct ligands (IGF1 and IGF2) plus insulin, and two receptors (IGFR1 and the insulin receptor). The two receptors are capable of homo- and hetero-polymerization, leading to receptor auto-phosphorylation and subsequent phosphorylation of substrate proteins, the insulin receptor substrate-1 (IRS-1) [66]. Similar to the EGFR pathway, IGFR1 activation triggers the RAS/RAF/MAPK pathway and the PI3K/AKT/mTOR pathway [67]. Overexpression of IGFR1 was detected in 33% of HCCs and increased activation of IGFR1 was observed in 52% of tumors [68]. A report indicated that IGF1R activation is a molecular mechanism that confers acquired resistance to erlotinib in lung cancers with the wild-type EGFR [69]. Overexpression of the igfr1 gene constitutes a common theme in many human cancers including NSCLC [70]. Interestingly, IGFR1 expression in NSCLC specimens was associated with a history of tobacco smoking, squamous cell carcinoma histology, mutant (mut) K-Ras, and wild-type (wt) EGFR, all of which have been strongly associated with poor response to EGFR-TKIs [71]. Kim et al. [72] found that activation of IGFR1 caused by IGF1 overexpression led to spontaneous lung tumor development that progressed to adenocarcinoma upon exposure to tobacco carcinogens. It was suppressed by a selective IGFR1 inhibitor, cis-3-[3-(4-methyl-piperazin-I-yl)-cyclobutyl]-1-(2-phenyl-quinolin-7-yl)-imidazo [1, 5-a] pyrazin-8-ylamine (PQIP) on the early stage. Jameson *et al.* [7] found that IGFR1 activation partially reverses the cell cycle arrest caused by gefitinib in oral squamous cell carcinoma (OSCC) cells. Importantly, IGFR1 stimulation does not eliminate the gefitinib-induced increase in total p27 (cyclin kinase inhibitor), its phosphorylation state and subcellular localization are altered. This suggested that the IGFR1 can rescue OSCC cells from EGFR-TKIs treatment. Knockdown of IGFR1 with siRNAs, mammary tumor growth was strongly delayed *in vitro* [73]. And lung adenocarcinoma cell lines responded to combined therapy with erlotinib and NVP-AEW541, an IGF1R-TKI [69]. Thus, it has been proposed that reduction of IGFR signaling in some cancer types may have therapeutic benefit to EGFR-TKI treatment.

In addition to the level of IGFR1 and IGF, the degree of IGFR1 activation is dependent on the abundance of insulin like growth factor binding proteins (IGFBPs) [74]. Epidemiological studies have shown that decreasing levels of IGF-1 and increasing levels of IGFBP-3 are independently associated with a high risk of colorectal cancer [75]. IGFBP-3 is a potent negative regulator of IGFR1 activation by binding with IGF-1 and then

regulates the mitogenic and anti-apoptotic actions of IGFs independent of IGF [76]. Choi *et al.* [77] showed significant downregulation of IGFBP-3 expression in resistant cells, and addition of recombinant IGFBP-3 restored the ability of gefitinib to downregulate PI3K/AKT signaling and to inhibit cell growth. On the other hand, adenovirus-mediated overexpression of or recombinant IGFBP-3 slightly inhibited the growth of HCC cells *in vitro* [78]. A report showed that in breast cancer, trastuzumab regulates IGFBP-2 and -3 expressions, which impacts IGFR1 downstream signaling [79]. Collectively, these results suggest that loss of expression of IGFBPs in tumor cells treated with EGFR-TKIs results in the activation of IGFR1 signaling, which in turn mediates resistance to EGFR-TKIs.

Hurbin *et al.* [80] observed a cross-talk between EGFR and IGFR1 and their ligands, amphiregulin and IGF1 under gefitinib treatment in resistant mucinous cells. It is reported that amphiregulin and IGFR1 mediate gefitinib resistance through increasing the interaction between the proapoptotic protein BAX and Ku70 [81]. The inhibition of Ku70 acetylation enhances BAX/Ku70 binding and prevents gefitinib-induced apoptosis. In contrast, the acetylation of Ku70 releases BAX from Ku70 and restores the sensitivity to gefitinib. Indeed, amphiregulin is a principal activator of the ligand-receptor autocrine pathway, members of the HER family (HER 1-4) can form heterodimers with IGFR1 and InsR, leading to the formation of hybrid receptors through physical associations between heterologous families [80]. Morgillo *et al.* [82] also reported that increased levels of EGFR/IGFR1 heterodimers activated IGFR1 and its downstream signaling mediators, leading to acquired resistance to erlotinib. Co-treatment of erlotinib and an IGFR1 inhibitor induced both apoptosis and cell cycle arrest, while either agent or EGFR-TKI alone only induced cell cycle arrest in some EGFR mutant NSCLC cells [83].

FGFR pathway

FGFs bind with members of a family of RTKs (FGFR1-4), then lead to receptor dimerization and activation of the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways [84]. Recently, FGFR was regarded as an important autocrine growth factor pathway for resistance to EGFR-TKIs in NSCLC [85]. FGFR1 amplification is associated with poor prognosis in NSCLC [86]. A plenty of *in vitro* studies revealed overexpression of FGF2, FGFR1 and FGFR2 mRNA and protein in primary NSCLC specimens [87, 88]. Recently, two independent groups reported that FGFR1 was amplified in approximately 10% to 20% of squamous cell lung cancers [89, 90]. However, another study found only 3 of 41 NSCLC cell lines showed evidence for activated FGFR1 [91]. And amplification of the fgfr gene has been detected in bladder cancer, albeit at a very low frequency [92]. It is suggested that FGF/FGFR pathway activation is one of the important mechanisms to escape from EGFR-TKIs. Terai *et al.* [11] found that the expression of FGFR1 and FGF2 were increased in gefitinib-resistant cells and that the phosphorylation status of EGFR itself was not affected by FGF2/FGFR1 activation and completely inhibited by gefitinib. Ware and colleagues reported on rapid acquired resistance to EGFR-TKIs in NSCLC cell lines through derepression of expressions of FGFR2 and FGFR3 [93]. They demonstrated that FGFR2 and FGFR3 can mediate FGF2 and FGF7 stimulated ERK activation as well as FGF stimulated transformed growth in the setting of EGFR-TKIs. It means that FGF2 or FGF7 rescues NSCLC cells from treatment with an EGFR-TKI. Also, co-culture of H322c cells with human fibroblasts rescues EGFR-TKIs induced growth inhibition in an FGFR-dependent manner [93]. Interestingly, FGFR2 and FGFR3 expression was induced in all gefitinib-sensitive NSCLC cells and correlated with cells that co-express EGFR and EGF ligands or bear gain-of-function EGFR. However, NSCLC cells that do not express EGFR or are gefitinib-resistant did not exhibit FGFR2 and FGFR3 mRNA induction in response to gefitinib [94]. Much to surprise, FGFR2 and FGFR3 induction occurs quickly (1-2 days) compared with met gene amplification in response to gefitinib (~6 months) [6]. It suggests that the fgfr2 and fgfr3 gene are not amplified but are being regulated at the transcriptional level. Thus, increased FGFR2 mRNA is partially mediated by transcriptional induction of the fgfr2 gene following gefitinib treatment. Importantly, the application of siRNA and neutralizing FGF antibodies is an efficient therapy against tumor growth [95, 96]. Also, RO4383596 (an FGFR inhibitor) inhibited basal fibroblast growth factor receptor substrate-2 (FRS2) and ERK phosphorylation as well as tumor proliferation and growth [94].

In addition to inappropriate expression of FGF ligands and FGFRs, FGFR mutations could participate in oncogenesis. FGFR2 mutations are mainly located within the hinge between Ig-like domains (exon 7), around the 3rd Ig-like domains and within the kinase domain [97]. FGFR2 mutations are observed gain-of-function in 10% of primary endometrial cancers as well as endometrial tumor cell lines [98]. In urothelial cancers, FGFR3 mutations in the ligand binding domain lead to ligand-independent dimerization or stabilization of the active conformation of the receptor while mutations in the kinase domain can render the receptor constitutively active [92]. FGFR4 mutations have been observed in lung adenocarcinoma with a potential contributing role to carcinogenesis [99]. One study [18] suggested that epithelial to mesenchymal transition (EMT) can mediate EGFR-TKIs resistance by kinase switch, such as those activated by FGFR, PDGFR or α5β1 integrin. Their results were provided by primary lung cancer cells without exposure to EGFR-TKIs and cells with wild-type EGFR. FGFRs have also been shown to be physically associated with N-cadherin in mammary cancer cells, resulting in cell survival, invasion, proliferation and metastasis [100]. Maybe the N-cadherin promotes ERK and AKT phosphorylation resulting in sustained signaling.

PDGFR pathway

PDGFR is a member of the class III receptor tyrosine kinase family. PDGFR can activate the PI3K, PLCγ, and mitogen-activated protein kinase (MAPK) signaling pathways [101]. High expression of PDGFRβ is a predictor of poor prognosis [102]. The PDGFRβ isoform has been shown to mediate EGFR transactivation, suggesting this class of receptors may play a role in the response to TKIs. Importantly, phosphorylated PDGFRβ was observed in glioblastoma that lacked of EGFR signaling [103]. The contribution of PDGFRβ signaling to drug resistance remains incompletely understood. PDGFRβ amplifications and/or mutations are exceedingly rare events in glioblastoma [104]. In mouse genetic models, PDGFβ ligand overexpression can promote gliomagenesis by enhancing cellular proliferation [105]. Kassouf *et al.* [106] revealed that PDGFRβ was undetectable or expressed at very low levels in gefitinib-sensitive cell lines, but was expressed at higher levels in all resistant cell lines. Akhavan *et al.* [2] first demonstrated that mTORC1 inhibition mediates EGFR-TKIs resistance in glioblastoma through transcriptional regulation of PDGFRβ, a mechanism which could also be active in other cancer types. In mouse embryonic fibroblasts, PDGFRβ was shown to be a target of mTOR-dependent negative transcriptional downregulation [107]. Also, PDGFRβ has been shown to mediate vemurafenib resistance through transcriptional upregulation in melanoma [108]. Akhavan *et al.* [2] identified that EGFR inhibitors derepress PDGFRβ transcription, providing a potent mechanism underlying RTK switching. Thomson *et al.* [18] suggested that a switch to PDGFR signaling occurs in concert with EMT. Recently, PDGFRβ has been shown to promote glioma stem cell self-renewal [71], suggesting a more definitive role in tumorigenesis and/or maintenance. Moreover, a PDGFRβ inhibitor significantly reduced PDGFR and MAPK phosphorylation [71]. Although these observations indicate that PDGFRβ can active EGFR/MAPK pathway, there is still not any clinical data suggesting a relationship between PDFGR expression and acquired resistance to EGFR-TKIs.

In addition, Yeh *et al.* [109] showed that PDGFRα have a functional interaction with c-Met *in vitro* and *in vivo*. Previously, Black and his colleagues reported co-expression of c-Met/PDGFRα in all of 9 human bladder cancer cell lines [110]. The interaction between c-Met and PDGFRα was further corroborated by HGF stimulation and siRNA silencing experiments *in vitro* [109]. The interaction may be initiated by signal regulation. That PD98059 rather than FTI-277 (RAS inhibitor) or PP2 (Src inhibitor) successfully inhibited c-Met activation, suggests transactivation of PDGFRα is independent of RAS or Src. Consistent with this, Kina *et al.* [111] showed that PDGFα-mediated signaling plays a key role in c-Met upregulation, which in turn is relevant with chemotherapy resistance. And PDGFα receptor inhibition eliminates cisplatin-dependent c-Met expression in cervical cancer cell lines [111]. Future studies are required to explore the mechanism of PDGFR pathway in resistant cancers.

AXL pathway

AXL is a member of the tyro3 tyrosine kinase receptor family of RTKs, which also includes MER and TYRO-3. After binding with growth arrest-specific gene 6 (GAS6), it activates the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways to promote proliferation, survival, and

migration of cancer cells *in vitro* [112] and tumor angiogenesis and metastasis *in vivo* [113]. Recently, the activation of AXL kinase confers acquired resistance mechanism of EGFR-TKIs [10]. Overexpression of AXL and/or GAS6 is the main mechanisms of activation in a wide range of human cancers, and it often correlates with poor prognosis [114]. In a small cohort of NSCLC patients refractory to EGFR-TKIs, higher expression of AXL and GAS6 was detected in 20% and 25% of cases, respectively [10]. High levels of AXL in EGFR mutant lung cancer cell lines induced erlotinib resistance [52, 80]. Zhang *et al.* [10] shows that AXL upregulation is the second most common mechanism of EGFR-TKIs acquired resistance (after EGFR T790M) in EGFR-mutant NSCLCs. In some erlotinib resistance cell lines, GAS6 is not indispensable because AXL overexpression can promote downstream signaling and induce transformation in the absence of GAS6 expression [10].

Resistant cells with AXL overexpression are more inclined to migrate and adhere, which is the same with EMT and c-Met [115]. AXL was also activated in this cell line with T790M and c-Met amplification, whereas a report [10] found increased activation of AXL in EGFR-mutant lung cancer models with erlotinib acquired resistance in the absence of EGFR T790M or c-Met activation. Even so, c-Met was shown to interact with AXL, and promote signal transduction downstream of AXL [116]. Increased expression and coactivation of c-Met and AXL have been described in NSCLC [91]. Both c-Met and AXL was involved in HER2-positive breast cancer resistant to lapatinib [117, 118] and resistance to AKT inhibition in preclinical models [119]. Salian-Mehta *et al.* [120] showed HGF/c-Met signaling modulated neuron migration dependent and independent of AXL coexpression and p38MAPK. Conversely, AXL controls gonadotropin-releasing hormone (GnRH) neuronal survival via HGF/c-Met signaling. When altering the levels of AXL, the bi-directional cross-talk between AXL and c-Met was affected. The kinase dead mutant of AXL expression reduced the phosphorylation of AKT and p38-MAPK induced by c-Met, but with no effect on ERK or STAT3 [120]. It confirmed the cell specific pathways downstream of the interaction between AXL and c-Met in GnRH neurons. Similarly, either deletion of the intracytoplasmic domain or mutating the tyrosine kinase domain of AXL reduced HGF- induced activation of c-Met. Interestingly, the AXL pathway was also associated with increased levels of tumor vimentin, thus suggesting that AXL may mediate EMT in EGFR-TKIs resistant patients [16, 17]. Consistently, a prior study showed vimentin upregulation was associated with AXL overexpression in breast cancer cells [40]. AXL and MER also regulate tumor stromal cell interactions via secretion of proinflammatory cytokines [114]. Only MER (but not AXL or TYRO-3) inhibits IL-6 secretion by lipopolysaccharide (LPS)-stimulated U937 cells and monocytes/macrophages [121].

Pharmacologically or genetically inhibiting AXL restored erlotinib sensitivity both *in vitro* and *in vivo*. Rho *et al.* [40] investigated the antitumor activity of NPS-1034, a newly developed drug that targets both c-Met and AXL, in gefitinib or erlotinib resistant NSCLC cells. Combining gefitinib or erlotinib with NPS-1034 effectively induced cell proliferation delay and cell apoptosis in both resistant cell lines. Combining AXL siRNA or NPS-1034 with EGFR-TKIs is also effective, suggesting that AXL is a key role in EGFR-TKIs resistance. Importantly, whether GAS6 might induce EGFR-TKIs resistance via AXL pathway and whether somatic alterations (amplifications, rearrangements, point mutations) in AXL or GAS6 occur in human EGFR-mutant NSCLCs needs further study to fully elucidate.

IL-6R pathway

IL-6 was hypothesized to reduce the dependence of EGFR pathway through the IL-6/gp130/STAT3 axis [122]. Serum IL-6 levels are elevated in patients with lung cancer than in normal individuals [123]. Also, IL-6 is detected at higher levels in tumor-associated stroma than in normal bone marrow stroma [124]. Recently, it has been reported that STAT3 activation via IL-6R is relevant with multidrug resistance in cancer cells [125]. Afatinib can promote the secretion of IL-6 by activating a positive feedback loop for IL-6/STAT3 axis. Among soluble factors secreted from stromal cells in tumor microenvironment, IL-6 is the most widely studied factor to induce resistance to anticancer drugs in many cancers [126]. Kim *et al.* [13] found that AKT and ERK were dramatically inactivated due to afatinib treatment, but STAT3 was paradoxically hyperactivated via increase of autocrine IL-6 production. Moreover, overexpression or addition of IL-6 to TKI-sensitive cells induced TKI resistance, which could be

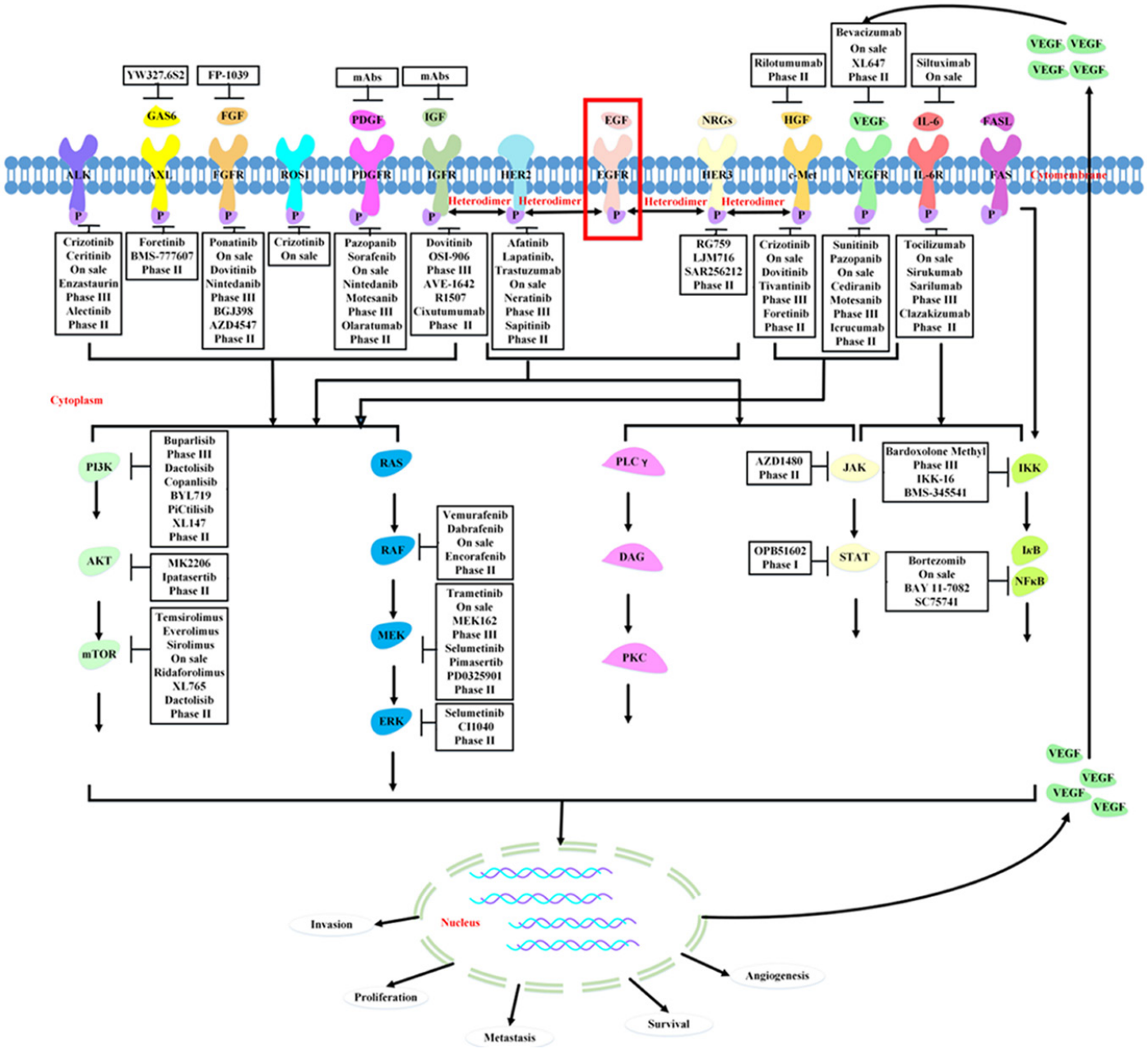
overcome by metformin [127]. Finally, metformin-based combinatorial therapy effectively blocked tumor growth in TKI-resistant cancer cells, which was associated with decreased IL-6 secretion and decreased IL-6-signaling activation *in vivo*. In addition, activation of NF-κB is another possible explanation for the autocrine IL-6 production by afatinib [13]. IL-6 is a well-known downstream target of NF-κB. Recently, it was reported that increased IL-6 production via NF-κB activation mediated resistance to docetaxel in prostate cancer [128]. These reports support the hypothesis that NF-κB activation is involved in autocrine IL-6 production upon afatinib treatment. Because IL-6 is mainly secreted from fibroblasts *in vivo* [129], there may be a cross-talk between fibroblasts and IL-6, which leads to afatinib resistance through activation of the IL-6R/JAK1/STAT3 signaling pathway in cancer cells. Co-culturing cancer cells and MRC5 fibroblasts (secrete IL-6), afatinib-induced STAT3 activation was enhanced in the presence of MRC5-CM [13]. And treating with IL-6R neutralizing antibody or IL-6R siRNA completely suppressed afatinib-induced STAT3 activation and significantly restored the effect of afatinib. However, the treatment of MRC5-CM did not affect the inactivation of AKT and ERK by afatinib in both cells. These findings indicate that interaction with fibroblasts is important for *de novo* resistance of NSCLC cells to afatinib through activation of the IL-6R/JAK1/STAT3 signaling pathway.

Other pathways

Several recent studies demonstrated that the FAS-NFκB signaling pathway can promote tumor growth [130, 131]. NFκB signaling has been broadly associated with inflammation and cancer [132]. A recent report showed activated NFκB pathway rescued NSCLC cells bearing a mutant EGFR from EGFR inhibitors. Bivona *et al.* [133] identified activation of NFκB signaling as a new mechanism of *de novo* resistance to erlotinib treatment. Of the 36 shRNAs recovered from the pooled screen, 18 targeted genes that are involved in NFκB signaling directly or indirectly. Interestingly, one of the top hits in the pooled screen was CD95/FAS, the ligand of the FAS death receptor, it functions upstream of NFκB to promote cell survival and tumor growth [131]. They also observed increased FAS expression and NFκB pathway activation in resistant cells [133]. And knockdown of FAS and several components of the NFκB pathway enhanced cell death in EGFR-mutant lung cancer cells treated with EGFR-TKIs. Low expression of the NFκB inhibitor IκB (high NFκB activation state) was predictive of a poor clinical outcome in patients treated with EGFR-TKIs [133]. IκB status was not a predictive outcome in EGFR mutant lung cancer patients treated with surgery or chemotherapy, indicating NFκB signaling is specific biomarker of EGFR-TKIs response in this patient population. Presumably more data about this pathway and its clinical relevance will become available in the near future.

The echinoderm microtubule-associated protein-like (EML) 4-ALK (anaplastic lymphoma kinase) fusions gene that encodes a cytoplasmic chimeric protein with constitutive kinase activity have been found in 5-7% of NSCLC patients, more frequently in those with young age, adenocarcinoma histology, and never or light smokers [134]. The resulting protein carries a coiled-coil basic domain from the upstream fusion partner, which may promote dimerization to activate the ALK tyrosine kinase [135]. EML4-ALK overexpression activated ERK and STAT3, but not AKT [136]. Moreover, ALK gene rearrangements are often mutually exclusive with EGFR mutations, even if there were cases of patients harboring both EGFR activating mutations and ALK translocation [137]. Activating mutations or translocations of the alk gene have been identified in anaplastic large-cell lymphoma, neuroblastoma, inflammatory myofibroblastic tumor and NSCLC [135]. Activated alk gene initiates signaling mostly through RAS/RAF/ERK and PI3K/AKT pathway. ALK inhibition results in downregulation of both AKT and ERK phosphorylation [138], and cell apoptosis mediated by ERK-dependent BIM upregulation and STAT3-dependent survivin downregulation [136].

Rearrangements of the receptor tyrosine kinase c-ros oncogene 1 (ROS1) appeared to occur in approximately 1% to 2% of NSCLC [139]. ROS1 is located on chromosome 6 and has a high degree of amino acid homology with ALK (49% within the kinase domain and 77% within the ATP-binding site). Clinicopathologic features of ROS1-positive cases are the same as ALK-rearranged NSCLC, including younger age, never smokers, and adenocarcinoma histology [140]. Multi-targeted ALK/MET/ROS1 inhibi-


YW327.6S2
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NRGs
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IL-6
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ALK
AXL
FGFR
ROS1
PDGFR
IGFR
HER2
EGFR
HER3
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VEGFR
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Crizotinib Ceritinib On sale Enzastaurin Phase III Alectinib Phase II
Foretinib BMS-777607 Phase II
Ponatinib On sale Dovitinib Nintedanib Phase III BGJ398 AZD4547 Phase II
Crizotinib On sale
Pazopanib Sorafenib On sale Nintedanib Motesanib Phase III Olaratumab Phase II
Dovitinib OSI-906 Phase III AVE-1642 R1507 Cixutumumab Phase II
Afatinib Lapatinib, Trastuzumab On sale Neratinib Phase III Sapitinib Phase II
RG7592 LJM716 SAR256212 Phase II
Crizotinib On sale Dovitinib Tivantinib Phase III Foretinib Phase II
Sunitinib Pazopanib On sale Cediranib Motesanib Phase III Icrucumab Phase II
Tocilizumab On sale Sirukumab Sarilumab Phase III Clazakizumab Phase II
Cytoplasm
PI3K
AKT
mTOR
Buparlisib Phase III Dactolisib Copanlisib BYL719 PiCtilisib XL147 Phase II
MK2206 Ipatasertib Phase II
Temsirolimus Everolimus Sirolimus On sale Ridaforolimus XL765 Dactolisib Phase II
RAS
RAF
MEK
ERK
Vemurafenib Dabrafenib On sale Encorafenib Phase II
Trametinib On sale MEK162 Phase III Selumetinib Pimasertib PD0325901 Phase II
Selumetinib CI1040 Phase II
PLC γ
DAG
PKC
AZD1480 Phase II
JAK
OPB51602 Phase I
STAT
Bardoxolone Methyl Phase III IKK-16 BMS-345541
IKK
IκB
NFκB
Bortezomib On sale BAY 11-7082 SC75741
VEGF VEGF
VEGF VEGF
Nucleus
Invasion
Proliferation
Metastasis
Survival
Angiogenesis

Figure 2. Redundant kinase signaling pathway. The activation of redundant kinase leads to downstream pathway such as PI3K/AKT, RAS/RAF/MEK and JAK/STAT signaling actived, which offsets the blockade of EGFR pathway by TKIs.

tors, such as crizotinib, have demonstrated efficacy in this population [141].

Strategies

Targeting redundant kinase and its ligands

There are many inhibitors and anti-bodies targeting both receptors and ligands of these redundant kinases (**Figure 2**). For example, adding a c-Met inhibitor (PHA-665752 or NPS-1034) may be beneficial to EGFR mutant lung cancer patients whose tumors harbor c-Met amplification as a mechanism of EGFR-TKIs resistance. Antibodies targeting the HGF (NK4) are currently in clinical development. Besides, 17-DMAG (an HSP90 inhibitor) has efficacy for HGF-triggered erlotinib resistance in cell lines and animal models [36]. Likewise, as an inhibitor of IGFR1 and AKT phosphorylation, PQ401 is reported to mimic IGFBP-3 and an IGFR1-blocking antibody that does not bind the InsR [142]. Amphiregulin might also be a therapeutic target. Amphiregulin inhibition combined with gefitinib strongly reduced tumor growth of mucinous cells with wild-type EGFR and mutated K-ras *in vivo* [81]. It is also noteworthy that inhibition of the InsR along with the IGFR1 may be clinically desirable due to InsR can substitute for IGFR1 when IGFR1 is selectively inhibited [143]. Importantly, targeting multiple receptors with a single agent may potentially overcome molecular heterogeneity and improve efficacy. HKI-272 (neratinib) is an irreversible inhibitor with activity against both EGFR and HER2 [144]. Idacomitinb, a pan-HER inhibitor that irreversibly and covalently binds to the ATP domain of each of three kinase-active member of the HER family (EGFR, HER2 and HER4) [145]. BMS-690514 is a TKI targeting both EGFR and VEGFR that has shown interesting phase II data with patients with NSCLC [146]. Likewise, AZD2171 (cediranib) was developed as a VEGFR inhibitor [147], but exhibits good potency for FGFRs and has been employed as an effective inhibitor of growth of FGFR2-driven gastric cancer cell lines [148]. Additionally, a multi-kinase targeted TKI, dovitinib, has been used to inhibit activated FGFR3 in multiple myeloma [149]. Sorafenib is a multi-targeted tyrosine kinase inhibitor acting on PDGFR, VEGFR, RAF, c-Kit, and fms-like tyrosine kinase-3 (FLT3), and has been shown to inhibit hepatic cellular cancer (HCC)-induced proliferation and angiogenesis [150, 151].

Inhibition of downstream molecules

Since a lot of redundant kinase signaling share the same downstream signaling, PI3K/AKT/mTOR or RAS/RAF/MEK/ERK or JAK/STAT pathway, the inhibitors of these downstream molecules may be of a great efficency to block the activation of various redundant kinase (**Figure 2**). At the present time, several drugs that inhibit activated RAF, MEK, PI3K, AKT and mTOR are available and clinical trials with these agents are actively recruiting patients, some of them selecting therapy based on the genetic profile of the tumor. Addition of PI3K inhibitors to standard treatment is an interesting approach already being explored in multiple phase- I/II trials [152]. Besides, mTOR is a key mediator of PI3K/AKT downstream signaling and is commonly activated in NSCLC. To date, several mTOR inhibitor rapamycin analogs are available, including temsirolimus and everolimus, which show effect in renal cell carcinomas and pancreatic neuroendocrine tumors [153]. Rapamycin and its analogs bind FK506-binding protein-12 (FKBP12) inhibits mTOR activity and halting the translation of proteins critical for cell proliferation and survival [154]. Moreover, mTOR, PI3K, and dual PI3K/mTOR inhibitors are being evaluated in early-stage clinical trials of lung cancer, either alone or in combination with EGFR inhibitors. The MEK inhibitors, such as CI-1040 and AZD6244, reversed the resistance both *in vitro* and *in vivo* [155]. Several agents, OPB-31121 (STAT3 decoy oligonucleotides) [156], or AZD1480 (a small molecule inhibitor for JAK) [157] has been developed, it can block the IL-6R and EGFR pathway, may be suitable candidates for future combined therapy with irreversible EGFR-TKIs.

Combination therapy

A number of studies provided increasing evidences supporting the dual inhibition of two or more receptors rather than single receptor targeting. Combining a reversible EGFR-TKI and an anti-EGFR antibody may be a relevant strategy for overcoming EGFR-TKIs resistance. Afatinib

(BIBW 2992), an irreversible inhibitor of EGFR, HER2, and HER4 [158], in combination with cetuximab, was reported to have significant activity in patients with acquired resistance to EGFR-TKIs [47]. Due to the cross-talk between EGFR family and other kinase receptors, such as EGFR-VEGFR, HER2-IGFR, HER3-c-Met, as well as the interaction between c-Met and other redundant kinases, combination therapy is indispensable for overcoming the resistant tumors. Dual blockade of the EGFR and VEGFR axes may be valuable for overcoming not only EGFR-TKIs resistance but also angiogenesis inhibitor resistance. Combining drugs targeting HER2 or HER3 with inhibitors of IGFR or c-Met can cause both two pathways blocked, respectively. Dual inhibition of c-Met and VEGFR pathway, resulting in the blockage of two signaling and better effect if combined with EGFR-TKIs. The combination of small molecule kinase inhibitors targeting AXL (XL880 or MP-470) or an AXL neutralizing antibody with an EGFR-TKI is a potential approach to overcome resistance. In addition, NPS-1034 inhibited cell proliferation as well as ROS1 activity in HCC78 cells with ROS1 rearrangement. Rho *et al.* [40] established the efficacy of NPS-1034 in NSCLC cells resistant to EGFR-TKIs because of AXL activation or ROS1 rearrangement. Combining inhibitions of receptor kinases and downstream molecules is also applicable for treatment. Kim *et al.* [71] provide a rationale for the therapeutic use of IGF-1R TKIs, either singly or in combination with MAPK/ERK inhibitors, particularly in tumors with K-ras mutations. In patients with resistance to first-generation EGFR-TKIs generated by c-Met, it is unlikely that an irreversible EGFR inhibitor alone would be effective, but the combination of an irreversible EGFR inhibitor and an mTOR inhibitor may be an effective strategy for overcoming resistance [159].

Conclusion

Clinical and biological evidence suggests that the EGFR does not function as a single dominant receptor tyrosine kinase in autocrine growth of NSCLC, but that multiple redundant kinases will participate in (**Figure 2**). Cancers harboring EGFR mutations depend on constitutive activation of these kinases for survival independent of EGFR. Explanations for the EGFR-TKIs resistance of redundant kinase activation, up to now, have not been fully clarified. Thus, effective blockade of these signaling in primary NSCLC tumors will require precise identification of the active receptor tyrosine kinase pathways through appropriate biomarkers. The development of multi-TKIs with the capacity to inhibit several different receptor tyrosine kinases should also be pursued, as these drugs would represent a more optimal choice than a combination of several different TKIs. It is likely, that specific combinations of selective TKIs will be required to completely inhibit signaling and cell transformation.

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Disclosure of conflict of interest

Authors have no relevant, potential conflicts of interest to declare.

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