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Review

Drug Resistance to EGFR Tyrosine Kinase Inhibitors for Non-small Cell Lung Cancer

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Non-small cell lung cancer (NSCLC) harboring an activating mutation within the epidermal growth factor receptor (*EGFR*) was defined as a clinically distinct molecular group. These lesions show oncogene addiction to EGFR and dramatic responses to the EGFR tyrosine kinase inhibitors (TKIs). Several large Phase III trials have shown that EGFR-TKIs improved the progression-free survival of patients with *EGFR* mutant NSCLC compared to conventional chemotherapy. However, the long-term effectiveness of EGFR-TKIs is usually limited because of acquired drug resistance. To overcome this resistance to EGFR-TKIs, it will be essential to identify the specific mechanisms underlying the resistance. Many investigators have attempted to identify the mechanisms using preclinical models and drug-resistant clinical samples. As a result, several mechanisms have been showed to be responsible for the resistance, but not all of the relevant mechanisms have been uncovered. In this review, we provide an overview of mechanisms underlying drug-resistance to EGFR-TKIs, focusing on results obtained with preclinical models, and we present some possible strategies to overcome the EGFR-TKI resistance.

Key words: non-small cell lung cancer, *EGFR* mutation, tyrosine-kinase inhibitor, drug resistance, cancer stem cell

Lung cancer continues to be the leading cause of death among patients with malignant tumors worldwide [1]. Many patients are diagnosed after the cancer has already spread to distant sites or directly beyond the primary site, resulting in an inoperable stage. In 2004, mutations in the epidermal growth factor receptor (*EGFR*) that cause oncogene addiction to EGFR were discovered in non-small cell lung cancer (NSCLC) [2, 3]. Because these mutations are strongly associated with sensitivity to EGFR-tyrosine kinase inhibitors (TKIs), a great deal of knowledge has been uncovered in regard to both *EGFR* and other genes in the EGFR family and their downstream genes.

EGFR-TKIs have exhibited significant antiproliferative effects against NSCLC with *EGFR*-activating mutations in preclinical studies [2, 3] and their use in the treatment of NSCLC patients has also resulted in prolonged progression-free survival (PFS) in randomized Phase III studies [4–7]. However, patients with *EGFR* mutations who initially respond to EGFR-TKIs eventually acquire resistance, which is a critical problem in the treatment of patients with advanced

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NSCLC. Several mechanisms are believed to be responsible for intrinsic and acquired resistance to EGFR-TKIs, including secondary *EGFR* T790M and minor mutations, *MET* amplification, and activation of the MET/HGF axis, acquiring an epithelial to mesenchymal transition (EMT) signature, and transformation from NSCLC into small cell lung cancer (SCLC) [8–13]. More recently, AXL kinase activation, loss of the EGFR-mutant allele, and emergence of cancer-stem cell (CSC)-like properties have been reported as possible mechanisms of resistance [14–16]. However, it is likely that additional mechanisms remain to be identified.

In this review, we focus on the NSCLCs harboring *EGFR*-activating mutations, and we summarize the mechanisms of drug sensitivity and resistance to EGFR-TKIs. We also describe some possible molecularly targeted strategies for further improving the outcomes of NSCLC patients with *EGFR*-activating mutations.

EGFR-activating Mutations in NSCLC

EGFR (ErbB1) is a member of the ErbB transmembrane receptor family, which includes ErbB2 (HER2/neu), ErbB3 (HER3), and ErbB4 (HER4). These receptors have similar structures and consist of three domains: an extracellular domain, a transmembrane domain, and an intracellular domain. The extracellular domain has a ligand-biding region, and several ligands including EGF bind here. The ligand binding causes receptor homo- or hetero-dimerization between EGFR and other ErbB family members at the cell surface, followed by internalization of the dimerized receptor. The receptor dimerization results in autophosphorylation of the intracellular EGFR tyrosine kinase domain. Subsequently, the phosphorylated tyrosine kinase stimulates an intracellular signal transduction cascade through several downstream pathways (including the Ras-Raf-MEK-ERK, PI3K-AKT-mTOR, and JAK-STAT3 pathways), leading to cell proliferation and apoptosis (Fig. 1) [17, 18].

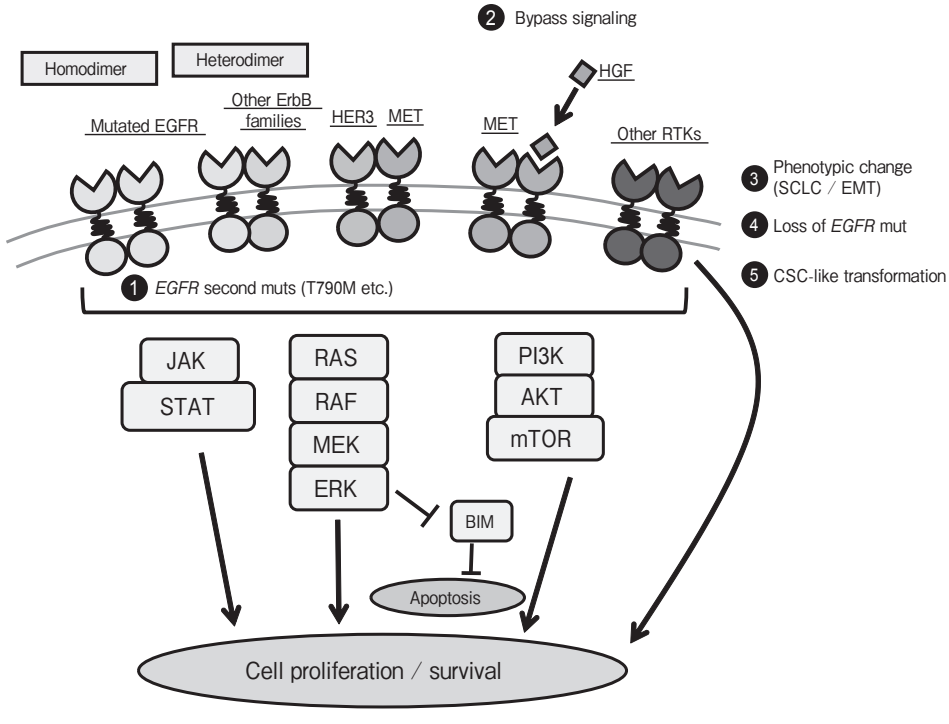

Fig. 1 Signaling pathways and mechanisms of acquired resistance to EGFR-TKIs in *EGFR*-mutated NSCLC. (1) *EGFR* T790M mutations and other less common mutations. (2) Kinase switches and bypass signaling mechanisms. (3–5) Other possible mechanisms related to acquired EGFR-TKI resistance. mut, mutation; RTK, receptor tyrosine kinase; SCLC, small-cell lung cancer; EMT, epithelial to mesenchymal transition; CSC, cancer-stem cell.

When a mutation occurs in exons that encode the EGFR tyrosine kinase protein (*i.e.*, exons 18–21), EGFR is activated ligand-independently, leading to carcinogenesis [2, 3]. About 80%−90% of these *EGFR* mutations are either short in-frame deletions in exon 19 or point mutations that result in a substitution of arginine for leucine at codon 858 (L858R) in exon 21 [19]. Approximately 3% of the mutations occur at codon 719, resulting in the substitution of glycine to cysteine, alanine or serine (G719X) in exon 18. Another approx. 3% are in-frame insertion mutations in exon 20 [19]. These *EGFR*-activating mutations are most common in patients with adenocarcinoma histology, women, never-smokers, and individuals of Asian ethnicity; approx. 40% of lung adenocarcinoma patients in Japan have an *EGFR* mutation [20–22]. *EGFR* mutations have also been detected in normal small bronchial and bronchiolar epithelium obtained from sites adjacent to tumors, suggesting that the EGFR mutations are early events in the pathogenesis of lung adenocarcinomas [23, 24].

Cancer cells with mutant *EGFR* are physiologically dependent on the continued activity of specifically activated or overexpressed oncogenes for the maintenance of their malignant phenotype, in a phenomenon called 'oncogene addiction' [25]. This addiction, at the same time, results in a greater sensitivity to small-molecule inhibitors that target the kinase domain of EGFR. In first-line treatment, EGFR inhibitors showed approx. 75% response rate in patients with typical *EGFR* mutations. Randomized trials have also demonstrated improved PFS for *EGFR*-mutant patients receiving EGFR-TKIs compared to chemotherapy [4–7].

Molecular Mechanisms in Resistance to EGFR-TKI

Primary resistance to EGFR-TKIs. There are some cancer cell populations that exhibit intrinsic resistance to EGFR-TKIs although they have *EGFR*-activating mutations. Multiple clinical trials have shown a disease control rate of approx. 90% for patients with *EGFR* mutations, suggesting that 10% of the patients harboring *EGFR* mutations are intrinsically resistant to EGFR-TKIs [4–7]. Some molecular mechanisms of this primary resistance have been uncovered in recent research.

1. EGFR-TKI-resistant mutations. It has been shown that the most prevalent *EGFR* exon 20 insertion mutation, which accounts for up to 4% of all *EGFR* mutations, is resistant to reversible (gefitinib and erlotinib) and irreversible (neratinib, afatinib, and dacomitinib) EGFR-TKIs in preclinical models and clinical samples [26, 27]. Another mutation that contributes to primary TKI resistance is T790M, a point mutation that results in the substitution of methionine for threonine at codon 790 in exon 20. They show TKI resistance through steric hindrance to EGFR-TKIs in crystal structure analyses or by increased affinity for adenosine triphosphate (ATP) [8, 28]. T790M has been identified as a minor clone in treatment-naïve tumor specimens with *EGFR*-activating mutations [29–31]. Su *et al.* reported that T790M was detected in 2.8% by direct sequencing, 25.2% by matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS), and 34.2% by next-generation sequencing (NGS) in TKI-naïve NSCLC tumors harboring *EGFR*-activating mutations [31].

2. EGFR signal-related alteration. Some EGFR signal-related gene alterations have been reported to contribute to primary EGFR-TKI resistance. It has been reported that *EGFR* mutations and *PIK3CA* mutations could co-occur and result in EGFR-TKI resistance [32–34]. *PIK3CA* mutations have also been shown to be acquired after EGFR-TKI treatment and to induce acquired TKI resistance [13]. Loss of phosphatase and tensin homolog (PTEN) similarly contributes to primary resistance to EGFR-TKIs [34, 35]. The pro-apoptotic protein BIM is known to be a mediator of TKI-induced apoptosis, and it is upregulated in some *EGFR* mutant cancer cells [36]. The inhibition and downregulation of BIM expression promoted intrinsic resistance to EGFR-TKIs in a preclinical model and clinical samples [37]. A recent report suggests that a genetic polymorphism in *BIM* results in alternative splicing and altered BIM function, which may contribute to intrinsic TKI resistance [38].

3. Non-EGFR signal-related alteration. Hepatocyte growth factor (HGF), a ligand of MET receptor tyrosine kinase, was reported to induce the EGFR-TKI resistance of cancer cells harboring *EGFR* mutations by restoring the PI3K-AKT signaling pathway via the phosphorylation of MET [12]. HGF was overexpressed in approx. 30% primary resistant

NSCLC harboring *EGFR* mutations, suggesting the activation of the MET signal pathway through HGF stimulation might be associated with primary TKI resistance.

Acquired resistance to EGFR-TKIs. All patients with *EGFR* mutations who initially respond to the first-generation EGFR-TKIs gefitinib or erlotinib ultimately develop acquired resistance to EGFR-TKIs over time (median 6–12 months). Acquired resistance to EGFR-TKIs is strongly associated with patient mortality, and thus further investigations of the mechanisms of acquired resistance to EGFR-TKIs are of great importance.

1. EGFR T790M "gatekeeper" mutation and other less common mutations. The most common mutation associated with acquired resistance to EGFR-TKIs is *EGFR* T790M, a secondary point mutation in exon 20 [8, 9]. T790M is associated with over 50% of adenocarcinoma cases with acquired resistance [13, 39]. *EGFR* T790M is analogous to the *ABL* T315I, *KIT* T670I, and *ALK* L1196M "gatekeeper" mutations observed in imatinib-resistant chronic myelogenous leukemia, gastrointestinal stromal tumors (GISTs), and crizotinib-resistant NSCLCs, respectively [40–42]. Interestingly, among patients with acquired resistance to EGFR-TKIs, although the molecular basis is unclear, the presence of T790M is associated with a favorable prognosis relative to acquired resistance via other processes [43]. Other less common mutations associated with EGFR-TKI resistance include *EGFR* D761Y (in TKI-naïve and acquired-resistant tumors) [30, 44], L747S [45], and T854A [46].

2. "Kinase switch" and bypass signaling mechanisms. Acquired resistance to EGFR-TKIs can develop through a "kinase switch" mechanism. One major bypass signaling is the MET, the receptor of HGF. *MET* amplification was observed in 5%–20% of tumor samples with acquired resistance to EGFR-TKIs [10, 11, 13, 47]. The cancer cells with *MET* amplification undergo a kinase switch through an ErbB3-mediated activation of downstream PI3K-AKT signaling that bypasses the inhibited EGFR [10, 11]. Other bypass signaling tracts through *HER2* amplification [48], *CRKL* amplification [49], *MAPK1* amplification [50], *PIK3CA* mutations [13], and *BRAF* mutations [51] have been described as possible mechanisms of acquired EGFR-TKI resistance. Moreover, in several preclinical models, the loss of IGF binding proteins (IGFBPs) with the subsequent activation of IGF1R signaling [52], FGFR1 activation through FGF2 autocrine [53], increased FAS expression and NFκB pathway activation [54], and upregulation of integrin beta1 [55] caused by EGFR-TKI treatment have also been reported to result in acquired EGFR-TKI resistance.

3. Phenotypic change: small-cell transformation and EMT. Examinations of re-biopsied samples revealed that phenotypic changes could occur and be responsible for acquired resistance after EGFR-TKI treatment. Some studies observed the transformation from NSCLC to small-cell lung cancer (SCLC) after EGFR-TKI treatment [13, 56]. These tumors maintained the *EGFR*-activating mutation with the expression of neuroendocrine markers and, surprisingly, they responded to conventional chemotherapy for SCLC.

Another well-known phenotypic change related to acquired resistance involves EMT. EMT is a phenomenon in which cells with epithelial phenotypes acquire mesenchymal characteristics, and EMT plays an important role in cancer metastasis and drug resistance. In preclinical models and clinical samples, EMT features were observed after the acquisition of resistance to EGFR-TKIs [13, 16, 57–59]. The activation of several pathways including the TGF-β -IL-6 [60], Slug [61], Notch-1 [62], and PDGFR [63] pathways were reported to be associated with EMT and EGFR-TKI resistance. Possible mechanisms such as Axl upregulation [14] and MED12 downregulation [64] were reported as key molecules in EMT-related EGFR-TKI resistance. In addition, we reported the relation between epigenetic alteration and EGFR-TKI treatment [16]. We showed that the CpG island hypermethylation-associated silencing of the miR-200 family in acquired resistance to EGFR-TKI cells with EMT features.

4. Loss of activating mutation. We and another group reported that the loss of the activated *EGFR* mutant allele could result in acquired EGFR-TKI resistance [15, 16]. We established an EGFR-TKI-resistant cell line using the *EGFR*-mutated and -amplified cell line HCC827 under exposure to a high concentration of gefitinib, and the results revealed that the cells showed a progressive decrease in the *EGFR*-mutated and -amplified allele through the course of

passages. We confirmed in clinical samples obtained from before and after EGFR-TKI failure that the *EGFR* 19del mutation had disappeared in recurrent tumors [16].

5. Stem-cell like transformation and other mechanisms. We have established many cell lines with acquired EGFR-TKI resistance under different cell culture conditions, and these cell lines showed that the manner of drug exposure could influence the mechanism of their acquired resistance [16]. In general, drug-resistant cell lines were established under a stepwise escalation of concentration. However, we established the EGFR-TKI-resistant cell lines under an initially high concentration of EGFR-TKI (but similar to the plasma concentration after an oral administration of EGFR-TKIs). As a result, some established resistant cells under a high concentration of EGFR-TKI showed CSC-like features with EMT features (including CSC-related marker upregulation), increased side-population, and self-renewal capability (Fig. 2). The cells showed extremely high drug resistance to not only multiple EGFR-TKIs but also conventional chemotherapeutic agents.

CSCs have been attracting interest as a source of cancer cells, and the significance of stem cell-like properties in lung cancer has been investigated in both basic and clinical research [65–67]. Many of the relationships between CSCs and EGFR-TKI resistance remain unclear and the biological meaning of CSC-related markers such as ALDH1A1, ABC-transporters ABCB1 and ABCG2, and CD44 is unknown. Further research is needed to obtain additional clarification.

Overcoming Molecular Mechanisms of Resistance to EGFR-TKIs

The first-generation EGFR-TKIs gefitinib and erlotinib have been used as first-line or second-line therapy for advanced *EGFR*-mutant NSCLCs, although sequential drug resistance has been inevitable. Many investigators have attempted to delay or overcome this resistance through preclinical examinations and clinical trials, and some promising strategies have been reported.

Beyond progressive disease (PD) strategies and the re-challenge of TKIs. The repetitive use of EGFR-TKIs in *EGFR*-mutant patients with acquired resistance to gefitinib or erlotinib might be clinically beneficial in select patients. Several reports have demonstrated that patients who acquire resistance could re-respond to EGFR-TKIs after a drug

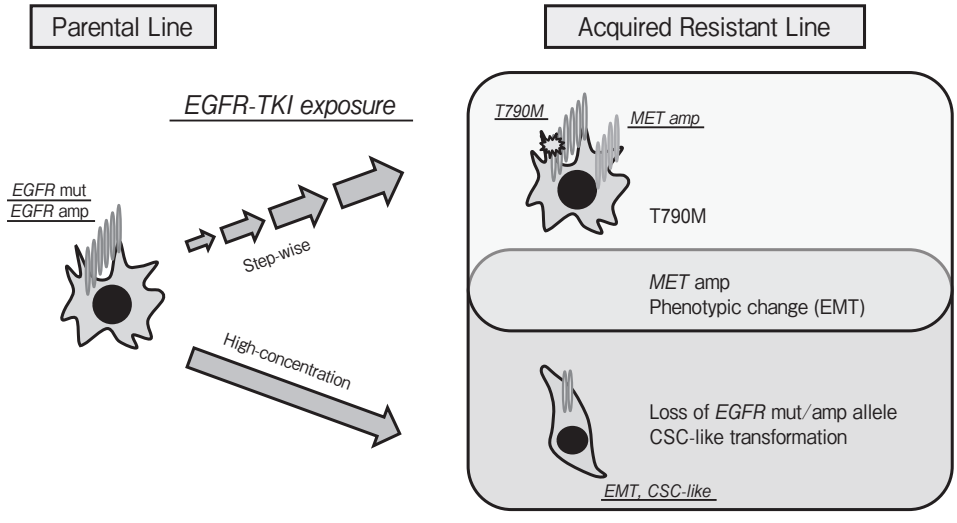

Fig. 2 Preclinical model of acquired resistance to EGFR-TKIs. The drug exposure method could affect the acquisition mechanisms of EGFR-TKI resistance. Under a conventional step-wise concentration of EGFR-TKI exposure, cancer cells with the *EGFR* T790M mutant or *MET* amplification were observed. In contrast, under a high (but similar to the plasma) concentration of EGFR-TKI exposure, cancer cells with wild-type *EGFR* or cancer stem cell (CSC)-like feature appeared. mut, mutation; amp, amplification; EMT, epithelial to mesenchymal transition; CSC, cancer-stem cell.

holiday [68, 69]. A prospective trial is being conducted to test whether an EGFR-TKI in addition to chemotherapy beyond progression is better than chemotherapy alone at the time of resistance (NCT01544179).

Next-generation kinase inhibitors and the blockade of bypass signaling. To delay or overcome EGFR-TKI resistance, second- and third-generation EGFR-TKIs which are more potent than first-generation TKIs and could affect other receptors/pathways are being developed. Second-generation irreversible EGFR-TKIs such as afatinib (BIBW-2992) and dacomitinib (PF-299804) are ATP mimetics that covalently bind to the Cys-797 of EGFR, and they are reported to be able to inhibit T790M in cis to *EGFR* activating mutation at lower concentrations than first-generation TKIs in preclinical models. In addition, third-generation EGFR inhibitors such as WZ-4002, CO-1686, and AZD-9291 have been developed as EGFR inhibitors specifically selected to target *EGFR* mutations with T790M [70-72]. Several prospective clinical trials evaluating these drugs are currently ongoing. At the same time, T790M status is becoming important to predict patient response. Therefore, an examination of the T790M status in addition to *EGFR*-activating mutation before and during EGFR-TKI treatment is important. It will also be necessary to establish methods to repeatedly quantitate the T790M population using noninvasive techniques such as a circulating DNA analysis (the so-called "liquid-biopsy").

Other approaches to overcome resistance are combination treatment with TKIs and other conventional chemotherapies, antibodies, and immunotherapies. The combination of both irreversible EGFR-TKI BIBW-2992 and the EGFR-specific antibody cetuximab was reported to induce the dramatic shrinkage of erlotinib-resistant tumors harboring the T790M mutation, because together BIBW-2992 and cetuximab efficiently depleted both phosphorylated and total EGFR [73]. Such strategies like this method blocking both the intracellular and the extracellular domains of the EGFR, a so-called "vertical blockade", might be an additional strategy to effectively overcome EGFR-TKI resistance.

As mentioned above, acquired EGFR-TKI resistance can develop through kinase switches and alternative bypass signal activations. The blockade of each activated signal consonant with individual resistant cells could contribute to the delay and overcoming of acquired resistance. In this sense, the most promising strategy in preclinical modes may be the dual use of MET and EGFR-TKIs in cells with *MET* amplification [10, 74].

Novel agents against EGFR-TKI resistance: epigenetic drugs, immuno-gene therapy, and others. It has been reported that epigenetic alterations are a key determinant in the maintenance of cancer cells, especially with high-level resistance to cytotoxic therapy and potent tumorigenic capacity [75]. Among these epigenetic alterations, DNA methylation and chromatin deacetylation are the most fundamental alterations. Whereas genetic alterations are usually fixed in the genome, epigenetic alterations are potentially reversible, offering a therapeutic opportunity. Histone deacetylate (HDAC) is an enzyme that regulates chromatin remodeling and is crucial in the epigenetic regulation of various genes. In preclinical studies, HDAC inhibitors such as trichostatin A and vorinostat (SAHA) showed an anti-tumor effect in EGFR-TKI resistant cells due to *BIM* polymorphism [76] and CSC-like features [16].

Heat shock protein (HSP) 90 inhibitors may also overcome EGFR-TKI resistance. A number of signaling molecules in the EGFR pathway are processed for activation and degradation by the HSP family of enzymes. Because the increased expression of these HSP clients mediates resistance to EGFR inhibitor therapy, HSP90 inhibitors represent a promising class of agents [77-79]. In addition, we found that the proteasome inhibitor bortezomib had an anti-tumor effect in both parental and acquired EGFR-TKI-resistant cells harboring T790M, *MET* amplification, and CSC-like features in a preclinical model [16].

In a recent preclinical study, we demonstrated that gene therapy using REIC/Dkk-3-expressing adenovirus vector (Ad-REIC) showed a potent anti-tumor effect in many NSCLC cells, even after they harbored acquired resistance to EGFR-TKIs [80]. A clinical trial to test the anti-tumor effect of Ad-REIC against NSCLC showing resistance to conventional drugs is in preparation. This new type of therapeutic strategy that may not target EGFR or other oncogene pathways could be a breakthrough to overcome EGFR-TKI resistance.

Conclusions

We provided an overview of drug resistance mechanisms in EGFR-TKI treatment and presented some possible strategies to overcome EGFR-TKI resistance. Both cancer cell autonomous mechanisms and the tumor microenvironment could contribute to primary and acquired EGFR-TKI resistance.

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