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Mini-review

Drug combination approach to overcome resistance to EGFR tyrosine kinase inhibitors in lung cancer

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ABSTRACT

The discovery of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) has led to unprecedented clinical response in a subset of lung cancer patients carrying the sensitizing EGFR mutations (L858R or exon 19 deletion). However, disease progression invariably occurs within a year after the initial TKI treatment, predominantly due to the development of acquired resistance caused by the secondary EGFR T790 M mutation. Numerous second generation irreversible and third generation EGFR T790 M selective EGFR TKIs have been developed to overcome resistance. Besides developing new EGFR TKIs, combination therapy represents another promising strategy to combat resistance. This approach aims at circumventing drug resistance through a so-called bypass signaling mechanism by targeting horizontal pathways or vertical pathways or both. The logical combinations of different molecular targeted drugs inhibiting various oncogenic signaling have been studied. On the other hand, the repurposing of drugs with indications other than oncology has also emerged as a promising approach. In this review, we focus on the effectiveness of combination therapy of EGFR-TKIs with different agents in advanced lung cancer.

Introduction

Lung cancer is currently the second most common cancer and the leading cause of cancer-related mortality worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 83% of all lung cancer cases [1]. Most NSCLC patients (up to 84%) present with advanced stage and metastasis at first diagnosis.

The biological basis of epidermal growth factor receptor (EGFR)

EGFR is a cell surface receptor and plays a pivotal role in regulating survival and apoptosis of epithelial cells and tumors of epithelial cell origin. It is a member of the ErbB family, a group of four receptor tyrosine kinases sharing similarities in structures and functions: ErbB1 (EGFR or HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4). Upon activation by its growth factor ligands, such as epidermal growth factor (EGF) and transforming growth factor α (TGFα), EGFR undergoes a conformational change that induces a homo- or hetero-dimerization. This is followed by autophosphorylation of the receptor itself, which subsequently serve as binding sites for the recruitment of signal transducers and activators of intracellular substrates to drive cell transformation and tumor progression [2].

Lung cancer, its conventional treatment and molecular targeted therapy

Until a decade ago, conventional chemotherapy with a two-drug combination consisting of a platinum drug and another chemotherapeutic agent, such as pemetrexed, gemcitabine, vinorelbine, and a taxane, was the only treatment option for advanced NSCLC. However, its effectiveness is limited and the median survival is less than a year [3]. In 2004, an evolutional breakthrough in the treatment of NSCLC was discovered where specific activating mutations within the tyrosine kinase domain of EGFR were first identified and

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shown to correlate with the favorable clinical responsiveness to EGFR tyrosine kinase inhibitors (TKIs) in patients with advanced NSCLC [4,5]. About 90% of these activating mutations are either short in-frame deletions in exon 19 or point mutations in exon 21 resulting in a substitution of arginine for leucine at amino acid 858 (L858R) [4,5]. The mutant EGFR have higher affinity over ATP to bind with, leading to "addictive" oncogenic signaling. These sensitizing mutations occur in approximately 10%–20% of NSCLC tumors, predominantly in adenocarcinomas, Asians, women, and non-smokers [6]. EGFR TKIs target this "addictive" signaling and disrupt the downstream pathways to selectively kill cancer cells. Advanced NSCLC patients bearing the sensitizing EGFR mutations demonstrated remarkably longer progression-free survival (PFS) when treated with EGFR TKIs, compared with those on conventional chemotherapy [7–9]. Molecular targeted therapy using EGFR-TKIs is now recognized as a promising strategy to treat NSCLC.

EGFR-TKIs

The two major first-generation EGFR-TKIs approved by United States Food and Drug Administration (US FDA) for advanced NSCLC are gefitinib and erlotinib. They reversibly compete with ATP binding at the tyrosine kinase domain of EGFR. This inhibits ligand-induced tyrosine phosphorylation, EGFR activation and subsequent activation of its downstream signaling pathways [10]. Unfortunately, despite harboring EGFR-mutant diseases, approximately 30% of NSCLC patients do not respond and importantly, all responders eventually relapse due to primary and acquired resistance, respectively [11].

Drug resistance to EGFR-TKIs

Primary resistance

Primary resistance, defined as immediate inefficacy of EGFR-TKIs, have been observed in the presence of non-classical sensitizing EGFR mutations (other than exon 19 deletion and L858R), non-sensitizing EGFR mutations (mostly exon 20 insertion), and concurrent molecular or genetic alterations that could demolish the responsiveness of patients with sensitizing EGFR mutations to EGFR-TKIs (Fig. 1). Among them, the last type is the most common and mainly includes mutation of K-Ras, an isoform of Ras, and PTEN loss. Activating K-Ras mutation, often associated with a history of tobacco use, constitutively stimulates the Ras-Raf-MEK-ERK pathway downstream of EGFR to drive cell survival. On the other hand, PTEN loss leads to the hyperactivity of the PI3K/Akt pathway, thus maintaining a high level of Akt activity independent of EGFR tyrosine kinase status to drive the downstream cancer survival pathways [12].

Acquired resistance

Progression of advanced NSCLC was found to invariably occur within a year after the initial EGFR TKI treatment due to acquired resistance. The most prominent mechanism, which occurs in 50% of NSCLC tumors harboring resistance to EGFR-TKIs, is secondary EGFR T790 M mutation-a substitution of threonine with a bulkier residue, methionine, at position 790 in exon 20 of EGFR (Fig. 1). It not only sterically hinders drug binding, but also increases the EGFR kinase affinity for ATP over EGFR-TKIs. Other resistance mechanisms include activation of bypass or alternative pathways, such as MET amplification (Fig. 1); and phenotypic transformation, such as epithelial to mesenchymal transition (EMT) and transformation into other lung cancer histological type [12].

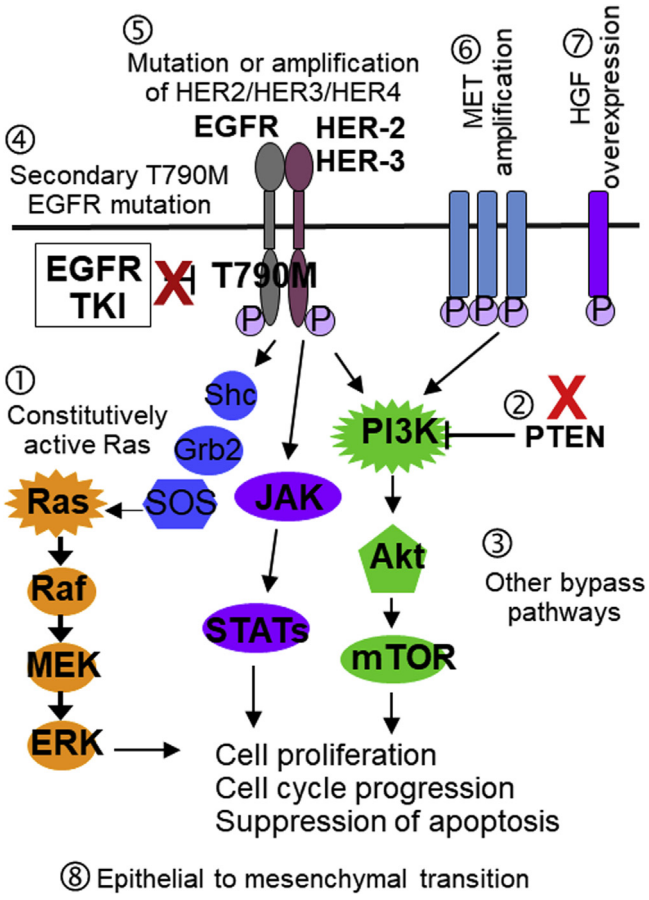

Fig. 1. Mechanisms contributing to primary and acquired resistance to EGFR-TKIs. Primary resistance is mainly due to the activation of EGFR downstream molecules (KRas mutation ① or PTEN loss ②) or the overexpression of other parallel signaling pathways ③, thereby bypassing the inhibition of EGFR activation by EGFR TKIs. On the other hand, acquired resistance is mainly caused by the induction of a secondary EGFR T790 M mutation ④, which reduces the affinity of the kinase to EGFR TKIs. Mutation or overexpression of other ErbB family receptor tyrosine kinases (HER2, HER3, or HER4) may allow the *trans*-phosphorylation of EGFR even in the presence of EGFR TKIs ⑤. The amplification of parallel oncogenic pathways (MET ⑥ and HGF ⑦) has also been reported, thereby driving cancer growth. Epithelial to mesenchymal transition has also been reported to mediate acquired resistance to EGFR TKIs ⑧.

Strategies to overcome drug resistance

Development of new generations of EGFR-TKIs

The emergence of acquired resistance after treatment with first-generation EGFR-TKIs led to the development of new generations of EGFR-TKIs. Thus far, second-, third-, and fourth-generations of EGFR-TKIs have been further developed for the treatment of advanced NSCLC.

Second-generation EGFR-TKIs include afatinib and dacomitinib. Afatinib was approved by US FDA for the treatment of late stage NSCLC in 2013. Most recently, the first phase III study (ARCHER 1050) comparing dacomitinib and gefitinib reported a significant improvement in efficacy of dacomitinib versus gefitinib in first-line treatment of NSCLC patients with EGFR activating mutations (30.6% of patients in the dacomitinib arm were progression free versus 9.6% in the gefitinib arm at 24 months) [13]. Theoretically, second-generation EGFR-TKIs have advantages over the first-generation ones: irreversible binding, with higher affinity for the EGFR kinase domain; additional HER2 and/or HER4 inhibition, preventing dimerization of EGFR with HER2 or HER4 and *in vitro* activity