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Research on the Resistance Mechanism of Third-generation EGFR-TKIs in Non-Small Cell Lung Cancer

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Abstract: Third-generation epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-Tkis) represented by osimertinib have become the first-line standard treatment option for EGFR-mutated non-small cell lung cancer (NSCLC), significantly improving progression-free survival and overall survival in patients. However, almost all patients eventually develop acquired resistance, which severely limits the long-term efficacy. This article systematically reviews the main molecular mechanisms of resistance to third-generation EGFR-Tkis and the latest research progress. Existing evidence suggests that resistance mechanisms can be roughly divided into two major categories: EGFR-dependent (on-target) and EGFR-independent (off-target). EGFR-dependent resistance mainly includes secondary mutations such as C797S, mutations in other kinase domains, and EGFR gene amplification, which directly affect drug binding to the target. Egfr-independent resistance is more complex, involving bypass signaling pathway activation (such as MET amplification, HER2 or AXL abnormalities), histological transformation (such as adenocarcinoma to small cell lung cancer transformation), downstream signaling pathway abnormalities (RAS/MAPK, PI3K/AKT pathways), and cell cycle regulation imbalance. In addition, recent studies have further revealed the important roles of metabolic reprogramming, epigenetic regulation, tumor-microenvironment interactions, and drug-resistant persistent cells in the formation of resistance. In terms of therapeutic strategies, novel approaches such as combined targeted therapy for resistance mechanisms, next-generation EGFR inhibitors, bispecific antibodies, antibody-drug conjugations, immunotherapy and cell therapy are advancing and showing good clinical prospects in some patients. Overall, third-generation EGFR-TKI resistance shows high heterogeneity and dynamic evolution characteristics, and in the future, multi-omics detection, dynamic molecular monitoring, and individualized combination therapy strategies will be needed to achieve more precise and durable disease control.

Keywords: Non-small cell lung cancer; EGFR mutations; Third-generation EGFR-TKI; Osimertinib; Acquired resistance; Bypass signaling pathways

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1. Introduction

In recent years, there have been revolutionary advancements in precision treatment for non-small cell lung cancer. Third-generation EGFR tyrosine kinase inhibitors, represented by osimertinib, can not only effectively suppress EGFR-sensitive mutations by irreversibly binding to the EGFR kinase domain, but also overcome the most common acquired resistance mutation T790M in first - and second-generation EGFR-Tkis. It is thus established as the standard first-line treatment for advanced EGFR-mutated NSCLC [1,2]. Its extensive use in first-line and subsequent treatments significantly improved patients' progression-free survival and overall survival, leading EGFR-mutated lung cancer into the era of osimertinib-based treatment [1].

However, as with all targeted drugs, acquired resistance is a fundamental challenge for the clinical application of osimertinib. Despite significant initial efficacy, the vast majority of patients experience disease progression approximately 10 to 18 months after treatment [3]. The development of drug resistance is not a single event, but rather the result of tumor cells adapting to drug selection pressure through a variety of complex, dynamic and heterogeneous molecular mechanisms [4]. Resistance mechanisms can be classified into two major categories in general: EGFR-dependent (i.e., in-target resistance) and EGFR-independent (i.e., out-of-target resistance) [2,4]. Understanding these resistance mechanisms is a prerequisite for developing the next generation of effective therapies.

With the advancement of detection technologies, especially the prevalence of next-generation sequencing based on tissue and liquid biopsies in clinical practice, researchers can more accurately map out drug resistance as the disease progresses [5]. This not only reveals a range of known drivers of resistance, such as C797S mutations and MET amplification, but also discovers many rare but potentially intervenable mechanisms [5]. In recent years, the focus of research has expanded from simply describing resistance mutations to exploring non-genetic mechanisms such as adaptive resistance, tumor microenvironment interactions, metabolic reprogramming, and epigenetic regulation [6-7]. This review aims to systematically review the latest research on the mechanisms of resistance to third-generation EGFR-Tkis in recent years and summarize the corresponding preclinical and clinical treatment strategies, with the aim of providing ideas for overcoming resistance and achieving longer-term disease control in the future.

2. EGFR-dependent (on-target) resistance mechanisms

Egfr-dependent resistance mainly refers to secondary mutations that occur in the EGFR gene itself, which interfere with the interaction between the drug and the kinase binding domain, and is an important category of osimertinib resistance [2,8]. Among them, the serine-substituted cysteine mutation at locus 797 of the kinase domain in exon 20 of the EGFR gene is the most common and is called the C797S mutation [2,8]. C797 is a key covalent binding site for osimertinib, and the C797S mutation causes the drug to fail to effectively bind to EGFR by introducing steric hindrance and eliminating the covalent binding site, resulting in resistance [2,9]. This mutation can occur alone or coexist with the T790M mutation, and its cis or trans alignment with T790M has a decisive impact on subsequent treatment options. A retrospective study of 365 patients in 2024 classified patients into four subtypes based on the allelic background of the C797S/T790M/ sensitive mutation: cis-trans, cis-trans coexistence, and only C797S [10]. Different subtypes have heterogeneous genomic maps and distinct clinical outcomes. For example, patients with coexisting cis-trans subtypes have the worst prognosis, while patients with cis-type subtypes may have longer progression-free survival when treated with brigatinib combined with cetuximab [11]. This suggests that fine

stratification of the C797S allelic background is crucial for guiding subsequent precision treatment.

In addition to C797S, other point mutations located in the EGFR kinase domain also constitute an important part of in-target resistance. Mutations at sites such as L718, G724, L792, and G796 have also been reported [12]. These mutations mediate resistance by altering the conformation of the kinase domain or by influencing the affinity of the drug-binding pocket. These secondary mutations are not uniformly distributed and their occurrence is associated with the initial EGFR-sensitive mutation type, such as exon 19 deletion or L858R. For example, the C797 and G724 mutations are more likely to occur in the context of exon 19 deletion, while the L718, G796 and L792 mutations are more associated with the L858R mutation context [11]. This specificity suggests that different EGFR mutations may have unique structural characteristics that lead to different paths of drug resistance evolution.

In addition, amplification of the EGFR gene itself is also identified as a mechanism of resistance. Tumor cells amplify the driver signal by increasing the copy number of the EGFR gene, thereby maintaining survival under drug stress [12]. Although the overall detection rate of EGFR amplification in samples after drug resistance is not high, it is associated with a poorer prognosis. Overall, the characteristics of the EGFR-dependent resistance mechanism are relatively clear, which provides a clear target for the development of a new generation of inhibitors (such as fourth-generation EGFR-Tkis) capable of overcoming these specific mutations [13,14].

3. EGFR-off-target resistance mechanisms

The EGFR-independent resistance mechanism is more complex and diverse, involving the activation of bypass signaling pathways, histological type transformation, and alterations of downstream signaling molecules, which are major components of acquired resistance [3,15].

Bypass signal activation is the most common type among them. MET gene amplification is recognized as the primary mechanism of bypass resistance, with an incidence of approximately 15-25% in patients who progress after first-line osimertinib treatment [8,16]. MET amplification bypasses the EGFR signaling axis suppressed by osimertinib by continuously activating downstream survival signaling pathways such as PI3K/AKT and MAPK/ERK. Clinical studies have confirmed that osimertinib in combination with MET inhibitors such as savolitinib or tepotinib can effectively overcome such resistance. INSIGHT 2 studies showed that the combination of tepotinib and osimertinib achieved an objective response rate of 50% in patients who were resistant to first-line osimertinib due to MET amplification, providing a promising oral targeted treatment option for this population [17]. In addition, amplification or activation of other receptor tyrosine kinases such as HER2 and AXL is also an important bypass for resistance. AXL activation not only promotes resistance by directly driving downstream signals such as PI3K-AKT, but also its palmitoylation modification enhances its membrane localization and constitutive activity [18]. Studies have shown that AXL inhibitors combined with osimertinib can reverse AXL-mediated resistance [19]. In addition to amplification, kinase domain mutations such as MET Y1230C can also drive resistance [20].

Histological transformation is another unique pattern of resistance, mainly referring to the transformation of lung adenocarcinoma to small cell lung cancer. This transformation is often accompanied by EGFR signal-dependent loss and the acquisition of neuroendocrine features. A spatial transcriptomics study found that most of the transformed small cell lung cancer components presented neuroendocrine subtypes, and EGFR expression was significantly reduced at both mRNA and protein levels [21]. The transformation process is closely associated with epigenetic changes such as histone deacetylation. Restoring EGFR expression with histone deacetylase inhibitors and combining it with osimertinib showed synergistic anti-tumor effects in preclinical models [21]. In addition,

epithelial-mesenchymal transition is also considered an important phenotypic basis for resistance and invasion and metastasis, often driven by signaling axes such as PIM1/GSK3β/SNAIL [22].

Alterations in downstream signaling pathways should not be overlooked either. Activation of the RAS/MAPK pathway (KRAS, NRAS, BRAF mutations) and the PI3K/AKT/PTEN pathway (PI3KCA mutations, PTEN deletion) can directly maintain the transduction of pro-survival signals downstream of EGFR, leading to drug resistance [15]. At the same time, variations in cell cycle regulatory genes (such as CDK4/6, CCNE1) also occur frequently, prompting tumor cells to evade cell cycle arrest induced by targeted therapy [12]. Different resistance mechanisms often coexist or occur sequentially, constituting a high degree of heterogeneity in tumor evolution. Co-mutations in TP53 and RB1 have been found to be associated with shorter treatment response times and faster resistance evolution, possibly by promoting genomic instability and cellular plasticity to accelerate the production of multiple drug-resistant clones [12,23].

4. The role of novel resistance mechanisms in the tumor microenvironment

Beyond traditional gene mutations and amplifications, recent studies have deeply revealed the core role of metabolic reprogramming, epigenetic regulation, and the tumor microenvironment in driving resistance to third-generation EGFR-Tkis.

Metabolism and epigenetic remodeling are key adaptive mechanisms for maintaining the survival of drug-resistant cells. Osimertinib-resistant tumor cells often show enhanced oxidative phosphorylation and glycolytic activation, studies have found. Branched-chain amino acid transaminase 1 drives H3K27 demethylation by promoting the production of α -ketoglutarate, thereby epigenetically activating glycolysis-related genes and ultimately leading to resistance [24]. Similarly, nicotinamide N-methyltransferase reduces the methylation levels of histone H3K9 and H3K27 by consuming the methyl donor S-adenosylmethionine and forms a double positive feedback loop through lactic acid-mediated histone lactation modification to promote resistance [25]. In addition, NUAK1 kinase reduces osimertinib-induced reactive oxygen species accumulation by phosphorylating NADK, thereby helping cells evade drug-induced apoptosis [26]. These findings reveal therapeutic potential targeting key metabolic and epigenetic nodes.

The tumor microenvironment plays an active role in shaping drug resistance. Cancer cells do not evolve in isolation but interact continuously with the surrounding fibroblasts, immune cells, and extracellular matrix. Studies have found that osimertinib treatment induces cancer cells to secrete TGF-β1, thereby promoting the accumulation of cancer-associated fibroblasts [27]. These CAFs induce resistance to amitinib (another third-generation EGFR-TKI) by secreting factors that activate the Hippo/YAP/TAZ signaling pathway within tumor cells [27]. Time-derived cytokines can upregulate the expression of interferon-induced transmembrane protein 3 in tumor cells. IFITM3 promotes osimertinib resistance by interacting with MET and activating the AKT pathway [28]. This suggests that targeting the communication interface between the TME and tumor cells may be an effective intervention strategy.

Drug-resistant persistent cells are a core concept for understanding the origin of acquired resistance. Even when initial treatment is effective, a small portion of tumor cells can enter a reversible, slow-proliferating DTP state to survive under drug stress [7]. These cells are a “reservoir” for generating fully drug-resistant clones. DTP cells have unique molecular characteristics such as upregulation of ribosome biosynthesis and protein translation pathways, as well as enhanced anti-apoptotic signaling [7]. Among them, the cell surface protein TROP2 was found to be significantly enriched in DTP cells. CAR-T cell therapy targeting TROP2 was able to efficiently

clear osimertinib-induced DTP cells in preclinical models, significantly prolong recurrence-free survival, and even achieve a "cure" effect, opening up new avenues for preventing drug-resistant recurrence through cellular immunotherapy [29].

5. Research progress and treatment strategies for overcoming resistance

In the face of the complex pattern of drug resistance, a range of novel treatment strategies aimed at preventing, delaying or reversing resistance are being explored, covering multiple frontier directions such as combination therapy, next-generation targeted drugs, immunotherapy and cell therapy.

Targeted combination strategies based on drug resistance mechanisms are currently the field with the fastest clinical progress. For clear bypass activation, osimertinib in combination with the corresponding inhibitor has become the standard direction of exploration. As mentioned earlier, clinical trials of osimertinib in combination with tepotinib or savolitinib for MET amplification have confirmed its efficacy and feasibility [17,30]. For patients with EGFR C797S mutations that are trans-arranged with T790M, theoretically, a combination of first-generation and third-generation EGFR-Tkis could be adopted, but the clinical efficacy varies and more precise patient selection is needed [10]. For HER2 amplification or mutation, antibody-drug conjugations such as trastuzumab and detrastuzumab show potential. Rare fusion mutations such as RET and NTRK have also been reported as mechanisms of resistance, in which case the combination of corresponding TRK or RET inhibitors may be effective [31,32]. Real-world studies such as COMPOSIT have confirmed that osimertinib combined with targeted therapy guided by re-biopsy results, despite varying efficacy, is a feasible and potentially clinically beneficial strategy in specific populations, such as MET amplification [33].

The development of a new generation of targeted drugs is the fundamental way out to overcome drug resistance. Fourth-generation EGFR-TKIs are designed to address in-target resistance mediated by mutations such as C797S. These drugs often employ novel mechanisms such as allosteric inhibition to overcome dependence on covalent binding sites. At present, several fourth-generation EGFR-TKIs have entered the early clinical trial stage, and although not yet approved, their preliminary data show the prospect of overcoming triple mutations such as C797S [13,14]. Bispecific antibodies represent another class of innovative drugs. Amivantamab, a bispecific antibody targeting both EGFR and MET, has been approved for the treatment of EGFR exon 20 insertion mutations with a unique mechanism that has shown efficacy in multiple osimertinib resistance scenarios, regardless of the presence or absence of MET abnormalities, and is being extended to later-line treatment for acquired resistance [16,34]. Antibody-drug conjugates offer a "bystander effect" to overcome tumor heterogeneity by precisely delivering cytotoxic drugs to tumor cells expressing specific targets. ADCs targeting HER3, TROP2, c-MET, etc. have shown encouraging activity in overcoming EGFR-TKI resistance. For example, the MET-targeted ADC drug REGN5093-M114 effectively suppressed multiple types of resistance, including PTEN deletion and MET mutation, in preclinical models [20]. ADCs targeting MUC1-C have also been shown to reverse resistance driven by the protein [35].

Anti-angiogenic combination therapy, as a non-specific combination strategy, has shown potential to overcome resistance by reshaping the tumor microenvironment, improving drug delivery, and modulating the immune response. A retrospective study showed that osimertinib combined with anlotinib in patients resistant to osimertinib had significantly better median progression-free survival and overall survival than regimens such as chemotherapy alone [36]. Single-cell sequencing analysis revealed that the combination therapy increased CD8+ T cell infiltration and remodeled tumor-associated macrophages, partially reversing the immunosuppressive

microenvironment [36]. The ETOP-BOOSTER Phase II randomized trial explored the efficacy of osimertinib combined with bevacizumab versus osimertinib monotherapy in T790M-positive patients. Although the primary endpoints did not show significant differences, potential advantages of the combination therapy were observed in specific subgroups, such as smokers [37]. Another study also confirmed that afatinib in combination with bevacizumab had some clinical activity after osimertinib resistance, especially in patients with non-T790M and rare EGFR mutations [38].

Strategies targeting new resistance mechanisms are moving from the laboratory to the clinical setting. Targeting metabolic and epigenetic targets, such as the combination of BCAT1 inhibitors, NNMT inhibitors, or histone deacetylase inhibitors with osimertinib, has been shown to reverse resistance in preclinical models [21,24,25]. Inhibiting MCL-1, targeting the MDM2-FBW7 axis to restore apoptotic sensitivity, or inhibiting the NUAK1-NADK axis to increase ROS accumulation are all promising strategies [26,39]. For TME, blocking immunosuppressive signals with TGF-β inhibitors or modifying CAR-NK cells to express dominant negative TGF-β receptor II can effectively enhance the efficacy of cell therapy in drug-resistant models [40].

Chemotherapy and local treatment remain the cornerstone of the later line of therapy. For patients with no clear intervention mechanism for resistance identified, platinum-based dual-drug chemotherapy with or without anti-angiogenic drugs is the standard option [41]. For patients with oligoprogression or central nervous system progression, the combination of local radiotherapy or surgery on the basis of continuing osimertinib is an effective means to prolong disease control time. The FLAURA2 study pioneered a forward strategy for "preventing resistance", confirming that first-line osimertinib combined with chemotherapy significantly prolonged progression-free survival compared to osimertinib monotherapy, providing a new intensive treatment option for patients at high risk or expecting deeper remission [42].

6. Conclusion

The widespread use of third-generation EGFR-TKIs has greatly improved the prognosis of patients with EGFR-mutated non-small cell lung cancer, but acquired resistance remains the "Achilles' heel" that restricts long-term efficacy [3]. The current study reveals that the resistance mechanism is a highly heterogeneous and dynamically evolving complex ecosystem, not limited to secondary mutations in the EGFR gene itself, but more broadly involves bypass signal activation, histological transformation, epigenetic remodeling, metabolic reprogramming, and close interaction with the tumor microenvironment [4,43]. This complexity determines that a single "one-size-fits-all" solution is unlikely to succeed, and the future must rely on more precise and dynamic individualized treatment strategies.

To crack the road to drug resistance precisely, one must first rely on precise drug resistance typing. As the disease progresses, comprehensive molecular profiling should be carried out through tissue re-biopsy and/or liquid biopsy as much as possible, which is the cornerstone for identifying intervenable targets and guiding subsequent treatment decisions [11,12]. With the advancement of detection technologies, multi-omics analyses that combine genomics with transcriptomics, proteomics, metabolomics and even single-cell sequencing will be able to reveal more deeply the driving mechanisms of drug resistance and the evolutionary trajectory of tumors [43]. Secondly, the concept of dynamic monitoring and early intervention is becoming increasingly important. Through continuous monitoring of circulating tumor DNA, the budding of drug-resistant clones can be detected earlier, providing an opportunity for intervention (such as combination therapy) before macroscopic progression [4]. Therapeutic

strategies targeting DTP cells, such as TROP2 CAR-T therapy, are at the forefront of this idea [29].

Future treatment modalities will focus more on the forward application of novel combination strategies. From the FLAURA2 study to the exploration of various bispecific antibodies, ADCs and osimertinib combinations, it is suggested that delaying or preventing drug resistance through initial intensive treatment may be more effective than treatment after multi-drug resistance occurs [42]. Meanwhile, treatments targeting common nodes of resistance, such as apoptotic pathways, epigenetic regulators, or the tumor microenvironment, are expected to overcome resistance caused by a variety of different mechanisms and have broader application prospects [35,44].

Looking ahead, with the deepening understanding of resistance biology and the successive emergence of innovative drugs such as the fourth-generation EGFR-TKI, novel ADCs, bispecific antibodies, and cell therapies, we are entering a new era of more refined management and overcoming of EGFR-TKI resistance [14,45]. By integrating multi-omics information, using artificial intelligence to assist decision-making, and conducting innovative clinical trial designs, the ultimate goal is to tailor the best treatment sequence for each EGFR-mutated lung cancer patient, transforming incurable diseases into chronic diseases that can be managed for a long time, and truly realizing the ultimate vision of precision treatment for lung cancer.

Disclosure statement

The authors declare no conflict of interest.

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