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Review

AKT inactivation causes persistent drug tolerance to EGFR inhibitors

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ABSTRACT

Drug resistance is a major obstacle to the success of EGFR-targeted therapy. We recently studied the mechanism by which a small subset of EGFR mutant lung cancer cells remains viable after EGFR inhibition. We found that this drug-tolerant subpopulation develops because EGFR inhibition prevents AKT activity and thus inactivates Ets-1 function. In this article, we discuss how changes in intrinsic cell signaling after EGFR inhibition open a new avenue to drug resistance in NSCLCs, and comment on combined TKI and MEK inhibitor treatment to reduce the probability of emergent resistance to EGFR TKIs.

Contents

Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small-cell lung cancer; TKIs, tyrosine kinase inhibitors; RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor; IGF-1R, insulin-like growth factor 1 receptor; FGFR1, fibroblast growth factor receptor 1; HGF, hepatocyte growth factor; FGF, fibroblast growth factor; NRG1, neuregulin 1; DUSP6, dual specificity phosphatase 6; PTEN, phosphatase and tensin homolog; EMT, epithelial-mesenchymal transition.

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1. Introduction

Lung cancer is the leading cause of cancer death worldwide and approximately 85% of lung cancers are composed of the non-small cell (NSCLC) histologic type [1,2]. 10–20% of NSCLCs harbor mutations in epidermal growth factor receptor (EGFR), a receptor tyrosine kinase (RTK). Although targeted therapy of these mutated NSCLCs with EGFR TK inhibitors (TKIs) has shown progress, drug resistance has limited the ultimate success of EGFR TKIs in the treatment of NSCLC. In a recent study, we sought to investigate the mechanism by which a small subset of NSCLC cells remains viable after EGFR TKI treatment, despite rapid cell death of the vast majority of NSCLC cells (Fig. 1) [3]. These residual surviving NSCLC cells comprise a tumor cell reservoir from which drug resistant tumors subsequently emerge.

Our study demonstrated that EGFR inhibition in lung cancer cells generates a drug-tolerant subpopulation by preventing AKT activity and thus inactivating Ets-1 function. These cells enter a dormant, non-dividing state through the inhibited transactivation of Ets-1 target genes: cyclins D1, D3, and E2. Moreover, Ets-1 inactivation inhibits transcription of dual specificity phosphatase 6 (DUSP6), a negative regulator specific for ERK1/2 [4,5]. As a result, ERK1/2 is activated, which enhances cell survival by accelerating Bim protein turnover [6,7]. Thus, a small subset of quiescent cells tolerates TKIs and constitutes the observed acquired drug resistance.

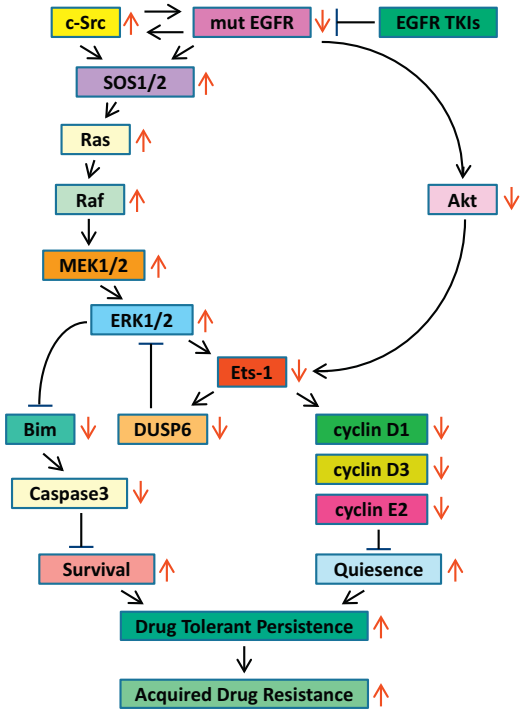

Fig. 1. Summary of the molecular mechanism of EGFR inhibition and persistent drug resistance in EGFR-mutated NSCLC cells. Increases and decreases in activity/expression of signaling molecules or biological outcomes resulting from EGFR inhibition are indicated by red arrows.

In this article, we discuss how changes in PI3K/AKT- and Ras/MAPK-signaling pathways after EGFR inhibition open a new avenue to drug resistance in NSCLCs, and we comment on the combination of TKI and MEK inhibitor to reduce the probability of emergent resistance to EGFR TKIs.

2. Drug resistance to EGFR TKIs

2.1. Heterogeneous clinical responses to EGFR TKIs in NSCLCs

Many cancer cells develop a dependency on an oncogene [8], referred to as oncogene addiction. This prompted the development of targeted therapies, of which specific treatment of EGFR mutations in NSCLCs represent an example [2]. However, although EGFR TKIs had shown promise, a recent randomized phase-3 clinical trial with erlotinib found tumor reduction >90% in only 5% of patients [9]. The remainder responded only partially, even though they too had TKI-sensitive EGFR mutations, either exon 19 deletions or L858R missense mutation in exon 21 (an amino acid substitution at position 858 from leucine to arginine). The heterogeneous nature of this primary response raised questions of its causation–whether attributable to resistance inherent in the tumor cells or to acute drug-tolerance, or both.

2.2. Primary and acquired drug resistance

Based on tumor response to the initial therapy, drug resistance is classified as either primary (also called innate or intrinsic) or acquired (adaptive or secondary) [2]. Patients with primary resistance do not respond at all to treatment, while those with acquired resistance may respond initially, only to fail to do so over time [10].

Primary resistance to EGFR TKIs in NSCLCs is associated with wild-type EGFR, activation of KRAS mutations, or loss of function of the apoptotic Bim gene [11–13]. Recent studies demonstrated that RTK ligands secreted through paracrine, autocrine, and endocrine mechanisms in the tumor microenvironment are also important determinants of primary therapeutic responses to anticancer kinase inhibitors [14–16]. Indeed, hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and neuregulin 1 (NRG1) confer primary drug resistance to a large number of cancer cell lines by activating RTKs and thus stimulating the Ras/MAPK- or PI3K/AKT pro-survival pathways, or both. HGF-mediated activation of the RTK MET is suspected as the most important cause of primary resistance to anticancer agents [14–16]. Additionally, intrinsic signaling pathways become paradoxically activated after RTK inhibition or blockade of other signaling pathways, presenting another mechanism that contributes to primary resistance [17,18].

In contrast, acquired resistance to EGFR TKIs is predominantly mediated by the development of the T790 M secondary mutation in EGFR (an amino acid substitution from threonine to methio-