Exploiting Synthetic Lethality and Network Biology to Overcome EGFR Inhibitor Resistance in Lung Cancer

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Abstract

Despite the recent approval of third-generation therapies, overcoming resistance to epidermal growth factor receptor (EGFR) inhibitors remains a major challenge in non-small cell lung cancer. Conceptually, synthetic lethality holds the promise of identifying non-intuitive targets for tackling both acquired and intrinsic resistance in this setting. However, translating these laboratory findings into effective clinical strategies continues to be elusive. Here, we provide an overview of the synthetic lethal approaches that have been employed to study EGFR inhibitor resistance and review the oncogene and non-oncogene signalling mechanisms that have thus far been unveiled by synthetic lethality screens. We highlight the potential challenges associated with progressing these discoveries into the clinic including context dependency, signalling plasticity, and tumour heterogeneity, and we offer a perspective on emerging network biology and computational solutions to exploit these phenomena for cancer therapy and biomarker discovery. We conclude by presenting a number of tangible steps to bolster our understanding of fundamental synthetic lethality mechanisms and advance these findings beyond the confines of the laboratory.

Introduction

The discovery over a decade ago that non-small cell lung cancer (NSCLC) patients who harbour epidermal growth factor receptor (EGFR) mutations selectively respond to the EGFR inhibitors (EGFRi) gefitinib and erlotinib brought about an exciting era of personalised medicine in this class of difficult-to-treat cancers [1,2]. These drugs have led to improvements in median progression-free survival (PFS) from 4.6 months to 13.1 months [3], which was unprecedented in lung cancer at the time of its discovery. Despite this success, the overwhelming majority of patients who initially respond to EGFRi therapy relapse within 16 months due to acquired drug resistance [4]. The most frequently observed and well-characterised mechanism of acquired resistance is the T790M gatekeeper mutation in EGFR [5]. In the past year, the approval of the T790M-selective inhibitor osimertinib for the treatment of this cohort of patients demonstrates how a deep understanding of the molecular mechanisms of acquired drug resistance facilitates the development of next-generation therapies for overcoming resistance and delaying tumour recurrence [6]. However, recent clinical data suggest that third-generation inhibitors will be similarly challenged by the emergence of acquired drug resistance [7–9]. In addition, ~10–20% of patients with EGFR mutations fail to respond to first-line EGFRi, and the mechanisms underlying this intrinsic resistance are unclear [10].

In this review, we provide an overview of the synthetic lethal approaches that have revealed signalling network mechanisms that drive both oncogene and non-oncogene addiction in EGFRi-resistant NSCLC [11,12]. We offer a perspective on the challenges faced when directing these findings towards the development of clinical therapies and offer potential solutions to overcome these issues including exploiting signalling plasticity and harnessing the principles of clonal evolution for designing novel strategies to tackle resistance.

NSCLC and EGFR inhibitor therapy

Activating EGFR mutations occur with a frequency of ~15% in lung adenocarcinoma with an enrichment in patients of East Asian descent (10% in Caucasian *versus* 40% in Asian populations) [13]. Of the EGFR activating mutations, 90% are found within the kinase domain, which spans exons 18–21. The exon 21 L858R substitution and in-frame exon 19 deletions between and including residues 746–750 are the most common aberrations making up 85% of EGFR activating mutations [10]. A less frequent exon 20 insertion mutation occurs in 4% of mutant EGFR lung adenocarcinoma patients [14]. While EGFR mutations are present in multiple cancer types [15], this spectrum of kinase domain mutations appears to be exclusive to lung cancer.

First-generation EGFRi gefitinib and erlotinib target the ATP binding site of the EGFR kinase by competitive reversible inhibition and are used to exploit the oncogene dependency on activating EGFR mutants in lung adenocarcinoma. These drugs are currently approved for first-line treatment in patients harbouring activating EGFR mutations and have a remarkable objective response rate (ORR) of ~80% [5]. In the remaining ~20% of patients, the reasons for a lack of response are largely unclear, but amongst these, EGFR exon 20 insertions and BIM and PTEN deletions have been associated with resistance to EGFRi therapy [16–18]. In patients who do initially respond to EGFRi therapy, resistance invariably develops and relapse occurs within 16 months [4]. Acquisition of a secondary substitution gatekeeper mutation in EGFR (T790M) is the dominant mechanism of resistance in ~60% of treated patients [19]. In addition to T790M, other mechanisms of acquired resistance include MET and human epidermal growth factor receptor 2 (HER2) amplification, and PIK3CA and BRAF mutations [20]. Activation of insulin-like growth factor receptor 1 (IGF1R) has also been observed in preclinical models of resistance to first-generation inhibitors [21,22]. Histological alterations such as transformation to small cell lung cancer (SCLC) and epithelial–mesenchymal transition (EMT) have additionally been reported as mechanisms of acquired EGFRi resistance [23,24]. Likewise, the AXL receptor has been shown to contribute to acquired EGFRi resistance in lung cancer [25]. AXL upregulation in tumour xenografts is accompanied with an EMT signature, hinting at a potential role of AXL in promoting EMT as a mechanism of resistance in lung cancer. An in-depth discussion of the distinct mechanisms of EGFRi resistance is out of the scope of this article, and interested readers should read these excellent reviews for a comprehensive discussion on this topic [20,26,27].

Unlike the first-generation drugs, second-generation EGFRi, such as afatinib, bind irreversibly to EGFR via a cysteine residue (C797) in the kinase domain. While afatinib has good activity in the first-line setting, it has limited clinical efficacy in the context of acquired T790M EGFR mutation with <10% ORR observed in relapsed patients [28]. The reason for this lack of efficacy is due to dose-limiting toxicities caused by non-selective activity of afatinib towards wild-type EGFR and limited inhibition against the T790M gatekeeper mutant, thereby reducing its relevance as a second-line treatment [28]. In response to the ineffectiveness of second-generation inhibitors, third-generation therapies that also bind irreversibly to the C797 residue but are capable of binding to sensitising EGFR mutations and the T790M gatekeeper mutation were developed. Osimertinib (AZD9291) is currently the only third-generation irreversible EGFRi approved by the FDA, with an ORR of 61% in patients harbouring a T790M mutation [6,29]. The most common mechanism of osimertinib resistance is a single amino acid substitution of C797S, acting as a blanket resistance mechanism to block all irreversible EGFR inhibitors [8]. A fourth-generation allosteric inhibitor, EAI045, to combat the C797S mutation is currently under development [30]. Additional minor resistance mechanisms to osimertinib identified include HER2 amplification and SCLC transformation, which overlap with mechanisms driving resistance to gefitinib and erlotinib [31,32]. As seen with previous generations of EGFRi, a proportion of patients display intrinsic resistance to osimertinib, despite the presence of EGFR mutations predictive of drug response [8].

Although there have been significant advancements in lung cancer treatment with EGFRi therapy, overall survival has not improved in these patients [33]. The clinical pathway for the treatment of patients who are resistant to EGFRi therapy is limited (Fig. 1). This is due to the lack of salvage therapies to combat acquired EGFRi resistance in the non-T790M setting and also the patients who harbour intrinsic resistance to this class of drugs. The quest for developing new therapies to overcome both acquired and intrinsic resistance is moving away from single mutations towards exploiting alternative signalling pathways that drive oncogene and non-oncogene addiction in EGFRi-resistant cancer. With each successive generation of EGFRi, the variety, heterogeneity, and complexity of these signalling networks broaden. The manner in which resistance is managed has to adapt to engage this rapidly evolving landscape where mutational analysis may no longer be sufficient to fully address the challenge of resistance in the clinic. Adaptive signalling networks that reinforce EGFR downstream effectors or promote non-oncogene addiction pathways to subvert EGFRi therapy need to be mechanistically defined for effective translation into clinical applications. A useful strategy to uncover these signalling networks in EGFRi resistance is through large-scale synthetic lethality screens.