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Review

New strategies for targeting drug combinations to overcome mutation-driven drug resistance

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ABSTRACT

Targeted therapies are suggested as an effective alternative for patients with cancer that harbor mutations, but treatment outcomes are frequently limited by primary or acquired drug resistance. The present review describes potential mechanisms of primary or acquired drug resistances to provide a resource for considering how to be overcome. We focus on strategies of targeted drug combinations to minimize the development of drug resistance within the context how resistance develops. Strategies benefit from the combined use of "omics" technologies, i.e., high-throughput functional genomics data, pharmacogenomics, or genome-wide CRISPR-Cas9 screening, to analyze and design targeted drug combinations for mutation-driven drug resistance. We also introduce new insights towards pathway-centric combined therapies as an alternative to overcome the heterogeneity and benefit patient prognoses.

Contents

Abbreviation: EGFR, Epidermal growth factor receptor; TP53, Tumor protein p53; KRAS, Kirsten rat carcoma viral oncogene; ALK, Anaplastic lymphoma kinase; RTK, Protein receptor tyrosine kinase; TKI, Tyrosine kinase inhibitor; PI3K, Phosphatidylinositol 3-kinase; NSCLC, Non-small cell lung cancer; EMT, Epithelial-mesenchymal transition; PXN, Paxillin; PTEN, Phosphatase and tensin homolog on chromosome 10; NF1, Neurofibromatosis type 1; FOXO3a, Forkhead box O3; MAGE-A, Melanoma-associated antigens family A; CTLA-4, CTL antigen 4; PD-L1, Programmed cell death protein ligand; MAPK, Mitogen-activated protein kinases; STAT3, Signal transducer and activator of transcription 3; GAS6, Growth arrest-specific 6; TGF-beta, Transforming growth factor beta; SCLC, Small cell lung cancer; FGFR, Fibroblast growth factor receptor; IGF-1R, Insulin-like growth factor-1 receptor; DDR1, Discoidin domain receptor 1; KIT, Proto-oncogene receptor tyrosine kinase; CDC25A, Cell division cycle 25A; CCLE, Cancer Cell Line Encyclopedia; CNV, DNA copy number variation; CGP, Cancer Genome Project.

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1. Introduction

The efficiency of targeted therapies is limited by the existence or development of drug resistance following treatment, although gene-targeted therapies are beginning to show promise. We present a functional framework representing the causes and mechanisms of drug resistance where we look at both direct and indirect effects on drug and on target, as detailed in Fig. 1. Additionally we have begun to associate the specific observations from the literature to begin to identify patterns of behavior for use in predictive analysis. For example, patients with non-small cell lung cancer (NSCLC) initially responded to EGFR-TKIs and then develop acquired resistance [1]. A phase-3 clinical trial demonstrated that erlotinib could reduce >90% tumor size only in 5% of the patients [2,3]. After treatment with the BRAF V600E inhibitor vemurafenib, 30% of the patients developed drug resistance [4]. Patients with primary resistance failed to respond to target treatment completely, while those with acquired resistance loss the initial respond over time [5]. While we commonly associate primary drug resistance with alterations of gene function in cell apoptosis, tumor microenvironment, or signaling pathways [6–8], drug resistance is mainly acquired by secondary mutations in the drug target itself or other genes, or initiation of epithelial-mesenchymal transition or transfer in histological phenotype during reactivation of drug target signaling pathways [9], as explained in Fig. 2. We believe that the potential for a more systematic analysis of the mechanisms and processes, based on the existing global databases, can provide new opportunities for improving both drug development and patient response to treatment.

Clearly there are many discrete observations. A number of mutations in epidermal growth factor receptor (EGFR), tumor protein p53 (TP53), kirsten rat sarcoma viral oncogene (KRAS), BRAF, anaplastic lymphoma kinase (ALK), have been commonly reported In lung cancer as drivers of the tumorigenic process [10–13]. Protein receptor tyrosine kinase pathway is recognized to play a key role in lung cancer development with mutation events, where targeted EGFR-tyrosine kinase inhibitors (TKIs)[14–16], e.g. Cetuximab as a monoclonal antibody that binds to EGFR extracellular domain, blocks ligand-dependent receptor activation [17]. Erlotinib and gefitinib inhibit the activity of the EGFR protein by binding to the ATP-binding site and blocking ATP hydrolysis [18]. Phosphatidylinositol 3-kinase (PI3 K)/mTOR pathway and cell cycle-associated pathways also play important roles in lung cancer process [19]. Other targeted therapies (e.g., Polo-Like Kinase inhibitor [20], BRAF inhibitor [21] and Src inhibitor [22], etc.) have also been used to treat lung cancer patients.

In this review, we highlight potential mechanisms of primary or acquired drug resistance. We discuss potential strategies for targeted drug combinations to minimize the development of drug resistance through the use of high-throughput functional genomics data, pharmacogenomics profile, or genome-wide CRISPR-Cas9 screening. The present review provides new insights towards pathway-centric combined therapies to overcome patient and tumor heterogeneity and prevent from drug resistance.

Table 1
Potential pairings by which co-occurrence of gene mutations may result in primary drug resistance in lung cancer.

Gene	Co-mutant Gene	Gene	Co-mutant Gene
EGFR	c-Met	STK11	SRC
	KRAS		PIK3CA
	ROS1	CDKN2A	TP53
	PXN	KRAS	BRAF
	PIK3CA		STK33
	IGF1R		TBK1
	ERBB2		PLK1
	ALK		PIK3CA
	BCL211		TP53
	BRAF		FGFR3
	FGFR1		CTTNB
	NRAS		NRAS
	RET		CDK4
	TP53		SYK
			RON
ALK	KRAS		STK11
	BRAF		NF-1
	RET		APC

2. Primary drug resistance

2.1. Activation of signaling pathways

Potential pairings by which co-occurrence of gene mutations may result in primary drug resistance in lung cancer were proposed in Table 1. The efficacy of EGFR-TKIs in patients with EGFR mutations was over-shadowed by co-occurrence of KRAS mutations that result in re-activation of downstream signaling in the EGFR pathway, while combination therapies of EGFR and KRAS inhibitors were able to overcome this form of drug resistance [23]. Co-occurrence of more than 2 mutated genes requires an even more complex and comprehensive strategy. For example, Crizotinib, an ALK and ROS1 inhibitor, had no effect on the patient exhibiting EGFR mutations, KRAS mutations and ROS1 rearrangement [24]. Gene amplification or overexpression can also activate signaling pathways and result in primary resistance. For example, Paxillin (PXN) overexpression confers TKIs resistance in EGFR-mutant lung cancer cells by mediating extracellular ERK activation [25].

2.2. Loss function of the apoptotic protein or cancer suppressor gene

The BIM deletion polymorphism has been associated with dysfunction of BIM, an apoptosis-associated protein, and decreased apoptosis induced by EGFR-TKIs in EGFR mutation-positive lung cancer [26,27]. BCL2-a as an anti-apoptotic protein is up-regulated in erlotinib- and gefitinib-resistant cells [28]. Cancer suppressor genes such as the phosphatase and tensin homolog on chromosome 10 (PTEN) are important regulators in TKIs inhibition of lung cancer, evidenced by the fact that low expression of PTEN induced the development of drug-resistance to TKIs [29]. Neurofibromatosis type 1 (NF1), known as neurofibromin, could confer resistance to erlotinib in experimental lung cancer [30]. The strategy of the combination between up-regulation of apoptotic proteins and tumor

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