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Journal of Genetics and Genomics 43 (2016) 3−10

JGG

REVIEW

The Impact of Genomic Profiling for Novel Cancer Therapy − Recent Progress in Non-Small Cell Lung Cancer

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Received 14 June 2015; revised 2 September 2015; accepted 7 September 2015
Available online 15 September 2015

ABSTRACT

There is high expectation for significant improvements in cancer patient care after completion of the human genome project in 2003. Through pains-taking analyses of genomic profiles in cancer patients, a number of targetable gene alterations have been discovered, with some leading to novel therapies, such as activating mutations of *EGFR*, *BRAF* and *ALK* gene fusions. As a result, clinical management of cancer through targeted therapy has finally become a reality for a subset of cancers, such as lung adenocarcinomas and melanomas. In this review, we summarize how gene mutation discovery leads to new treatment strategies using non-small cell lung cancer (NSCLC) as an example. We also discuss possible future implications of cancer genome analyses.

KEYWORDS: Targeted therapy; Lung cancer; Gene mutation

INTRODUCTION

Targeted therapy is a special type of chemotherapy that targets the specific difference between cancer and normal cells. The concept of targeted therapy has been evolving over the years. In early years, targeted therapy means to selectively kill cancer cells based on a high cell proliferation rate of the cancer cells. In the last ten years, significant progress in cancer therapeutics has been made through identification of novel genetic alterations in the cancer genome. Strategies in targeted therapy are largely based on gene mutation, pathway activation and alterations in the immune system. The most significant progress is the use of inhibitors for mutant kinases.

Discovery of BCR-ABL tyrosine kinase inhibitor STI571 (other names include imatinib mesylate and Gleevec) by Novartis scientists and successful clinical trials in chronic myelogenous leukemia (CML) patients by Dr. Druker and his collaborators (Druker et al., 2001a, 2001b) established a major milestone for targeted therapy, and promoted imatinib mesylate as the first-line drug for treatment of CML with *BCR-ABL* gene fusion. Because imatinib mesylate also targets several other kinases, such as c-kit and PDGFRA, it has been shown to be effective for treatment of gastrointestinal stromal tumor (GIST) (Demetri et al., 2002) and neurofibromatosis type 1 (NF1) (Robertson et al., 2012), as well as a subset of melanoma with c-kit expression (Carvajal et al., 2011; Guo et al., 2011).

MAJOR GENETIC ALTERATIONS IN NON-SMALL CELL LUNG CANCER (NSCLC)

Lung cancer is the leading cause of cancer-related death, claiming ~158,000 American lives every year, which exceeds the combined mortality from breast, prostate and colorectal cancers (Siegel et al., 2015). However, research in lung cancer

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http://dx.doi.org/10.1016/j.jgg.2015.09.003

has been under-funded for years, with $1442 per lung cancer death in comparison of $6849, $13419 and $26398 for colon, prostate and breast cancer respectively (Foundation, 2015). Currently, the 5-year survival rate for all types of lung cancer is ~17%. The majority of all newly diagnosed cases are patients with advanced lung cancer, which have a median survival of ~12 months following the first-line chemotherapy.

Common genetic alterations in lung cancer include *p53* mutations/deletion, *p16* gene silencing through methylation, *LKB1* loss-of-function mutations and activating *KRAS* gene mutations. Overall, three major signaling pathways are affected in lung cancer: p53 signaling, the RB/p16 signaling axis and the RAS signaling. Mutations or deletions of *p53* occur in 50% of NSCLC (Robles et al., 2002; Cooper et al., 2013). Although there are several strategies to target p53 signaling for cancer therapies, no p53-related drugs are now available for cancer treatment. P53 is regarded as the guardian of the genome, and *p53* gene mutations result in many changes in the cancer genome (Lane, 1992; Khoo et al., 2014).

Although retinoblastoma (*Rb*) gene mutations are not frequent in lung cancer, inactivation in *p16*, through methylation or chromosomal deletion as well as point mutation, occurs frequently in NSCLC (~50%) (Otterson et al., 1994; Liggett and Sidransky, 1998; Sanchez-Cespedes et al., 1999). The p16 protein binds to CDK4 (inhibitor of kinase 4, or INK4) and inhibits Rb protein phosphorylation (Liggett and Sidransky, 1998). It was found that *p16* hypermethylation is associated with poor prognosis (Jin et al., 2001; Kim et al., 2001; Ng et al., 2002). In addition, Cyclin D1 overexpression occurs in nearly half of NSCLCs and is associated with a poor treatment outcome (Jin et al., 2001). Cyclin D1 acts to inhibit Rb function by inducing its phosphorylation through CDK4. A second protein p14ARF is transcribed from an alternate reading frame that largely overlaps that of p16INK4 (Sanchez-Cespedes et al., 1999). The p14ARF protein prevents MDM2-mediated p53 protein degradation, resulting in elevated p53 signaling. The *p14ARF* gene inactivation is found in 19%−37% of NSCLCs with variable results from different patient populations (Sanchez-Cespedes et al., 1999; Sherr, 2001; Sherr and McCormick, 2002).

The RAS signaling pathway is frequently activated in lung cancer through mutations of several genes, including activated gene mutations in several growth factor receptors (see more below), KRAS and PIK3CA, as well as loss-of-function gene mutations in *PTEN* and *LKB1*. While PTEN loss increases PIK3CA activity, LKB1 loss-of-function promotes mTOR signaling. Taken all together, almost all lung cancer cells have elevated RAS signaling (Cooper et al., 2013). Furthermore, in tumors with *LKB1* inactivation, metabolism inhibitors, such as phenformin, are predicted to be more effective in cancer treatment (Liu et al., 2013; Shackelford et al., 2013).

In the last few years, several targetable oncogenic mutations have been discovered in lung adenocarcinomas, including *EGFR, HER2, FGFR1* and *c-MET* (reviewed in Thomas et al., 2015). Additionally, several gene fusions involving *ALK*, *RET*, and *ROS-1* have been reported. Other gene mutations include activating mutations in the PI3K/AKT pathway (PIK3CA and AKT) and the BRAF/MEK signaling (BRAF and MEK1/2).

EGFR gene mutation is often mutually exclusive from *KRAS* gene mutation. The same is true for ALK fusion and *KRAS* gene mutation, indicating that these are the driving mutations for NSCLC. While the specific inhibitors for KRAS are not clinically available, several specific small molecule inhibitors have been developed to target RAS downstream molecules, and have been approved for cancer treatment.

It is worth noting that the frequency of gene mutation varies among different patient populations (Couraud et al., 2012). For example, *EGFR* gene mutation occurs only in 5% of American cancer patients who are current smokers, in 28% of never-smoking American patients, but ~50% of never-smoking Asian women. Similarly, *ALK* fusion occurs more frequently in never-smoking Asian women than in current smoking American men. The exact molecular mechanisms underlying the gene mutation for *EGFR* and *ALK* are still elusive. It is known that *p53* gene mutations are often associated with smoking history, particularly G to T transversions. Furthermore, squamous cell carcinomas are different from adenocarcinomas in gene mutations. The frequency of *p53* gene mutation is more common in squamous cell carcinomas (~90%) (*vs.* <50% in adenocarcinomas), while *KRAS* mutations occur in ~36% of lung adenocarcinomas but rarely in squamous cell carcinomas. Silencing of *p16* is common in squamous cell carcinomas (~45%) but rare in adenocarcinomas. Mutations of *EGFR*, *ALK*, *cMET* and *ROS-1* are rare in squamous cell carcinomas but commonly found in lung adenocarcinomas (8%−50% depending on smoking history and gender). Below, we summarize specific clinical drugs targeting on specific gene alterations.

INHIBITORS FOR MUTANT KINASES

Mutant tyrosine kinase inhibitors

EGFR inhibitors

Identifying novel gene mutation has revolutionized treatment of NSCLC. The best example is EGFR. Initial studies using EGFR inhibitor gefitnib (Iressa) showed tumor-inhibitory effects in only 10%−19% of patients with NSCLC (Fukuoka et al., 2003). Later analyses indicate that most patients with activating *EGFR* mutations had better responses to gefitnib than those without such mutations (Lynch et al., 2004; Paez et al., 2004). Initial observation indicates that treatment with the EGFR kinase inhibitor gefitinib causes tumor regression in some patients with NSCLC, more frequently in Asian population. *EGFR* activating gene mutations occur in 14% of lung adenocarcinomas. However, lung cancers from Asian women without smoking history have a much higher percentage of *EGFR* gene mutations (~50%), twice of the rate in cancer patients from the US and Europe. Following FDA approval of gefitinib in 2003, a similar drug, erlotinib (Tarceva®) was approved in 2004 (Fig. 1 for details).