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Editorial

Molecular markers as therapeutic targets in lung cancer

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Abstract

Lung cancer is responsible for 29% of cancer deaths in the United States and has very low 5-year survival rates of approximately 11% in men and 15% in women. Although the early diagnosis of lung cancer may increase the survival rate with adequate treatment, advanced lung cancers are often metastasized and receive limited benefit from therapeutic regimens. As conventional treatments for lung cancer reach their limitations, researchers have attempted to discover novel drug therapies aimed at specific targets contributing to the progression of tumorigenesis. Recent advances in systems biology have enabled the molecular biology of lung carcinogenesis to be elucidated. Our understanding of the physiologic processes of tumor development provide a means to design more effective and specific drugs with less toxicity, thereby accelerating the delivery of new drug therapies to the patient's bedside.

Key words Molecular targets, targeted therapeutics, EGFR-tyrosine kinase inhibitor, *KRAS* mutation

As the leading cause of cancer death, lung cancer claims 1.3 million lives worldwide every year[1], 160 000 of which come from the United States alone[2]. Lung cancer causes more deaths than colon, breast, and prostate cancers combined, accounting for 28% of all cancer deaths[3]. Over half of patients with lung cancer die within one year of diagnosis[4]. While lung cancer can be caused by a variety of genetic and environmental influences, tobacco smoking contributes to 80% to 90% of lung cancer deaths, followed by radon exposure, second-hand smoking, and occupational exposure[5].

There are two major types of primary lung cancer: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Because these two lung cancer types differ histopathologically, they grow and proliferate differently. Histologically, NSCLC is a heterogeneous aggregate that includes squamous cell carcinoma, large cell carcinoma, and adenocarcinoma[6]. SCLC is distinguished from NSCLC by its rapid doubling time, high growth fraction, and early development of widespread metastases[7]. NSCLC accounts for 80% of clinical lung cancer cases, the remaining lung cancer cases are diagnosed as SCLC. Although both NSCLC and SCLC may be caused by tobacco smoking, SCLC is found to occur almost exclusively in smokers[8], with 90% of the patients being smokers or former smokers. Regardless of the cause, variations in the biological behaviors of these two lung cancer cell types impose challenges to their accurate prognosis and medical treatment.

Conventional first-line treatments for lung cancer include surgical resection, chemotherapy, and radiation[9]. Although the former may be suggested to patients during the early stages of NSCLC, the highly proliferative and metastatic nature of SCLC deems operation almost futile because microscopic cells separated from the primary mass may still remain in the body despite surgical resection. However, chemotherapy and radiotherapy serve as cornerstone treatments for SCLC and advanced NSCLC, offering modest survival benefits at the expense of severe and unpleasant side effects[10], despite having improved median survival rates and recurrence when used in combination[11]. As the standard therapy for NSCLC, platinum-based chemotherapy regimens are relatively effective due to their ability to cause DNA crosslinks that inhibit DNA repair or synthesis in cancer cells[12]. However, these regimens have limitations. Their association with severe toxicities, in addition to the

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multiple drug-resistant nature of NSCLC cells, reduce the efficacy of the treatment[13]. As conventional treatments for NSCLC patients reach a therapeutic plateau, research efforts have been made to discover novel agents that target lung cancer-related oncogenes for the optimum treatment.

Targeted cancer therapies focus on blocking the growth and spreading of cancer by interfering with specific molecules involved in tumor growth and progression. Research endeavors in targeted cancer therapy have focused on studying proteins that govern basic cellular functions that interfere with cell growth signaling, tumor blood vessel development, selective apoptosis, immunity stimulation, and drug delivery to specific target sites. With the advance of experimental techniques, systems biology has become an emerging approach to map the complex interactions within biological systems that may broaden our understanding of metabolic and cell signaling networks[6]. Coupled with bioinformatics and proteomics, protein-protein interaction (PPI) analyses enable the identification and discovery of previously unknown protein functions. Not only does PPI network facilitate our understanding of the molecular mechanisms underlying lung cancer, it may serve as an important tool for identifying diagnostic molecular markers to predict patient susceptibility and detect early stages of lung cancer. PPI network allows several molecular targets to be identified. Ray *et al.*[9] discussed several novel agents that target different molecular sites involved in the signaling pathways of lung cancer, particularly those associated with apoptosis, angiogenesis, and tumor growth. A widely studied target for NSCLC therapeutics is epidermal growth factor receptor (EGFR) because aberrant activation of this gene is associated with bypassed apoptotic cell death, self-sufficient growth, a lack of response to anti-growth signals, sustained angiogenesis, and tumor metastasis[14-16], all of which are characteristics of cancer formation. Furthermore, results from immunohistochemistry and real-time quantitative polymerase chain reaction (PCR) analyses have indicated EGFR overexpression in NSCLC tumors. The clinical use of EGFR-tyrosine kinase inhibitor (TKI) treatments utilizes the knowledge that EGFR kinase mutations sensitize the mutated receptor tyrosine kinase to EGFR-TKIs and has resulted in dramatic tumor responses [17]. Although research efforts have endeavored to discover molecules that bind EGFR tyrosine kinases, the volatile nature of the EGFR gene results in the acquisition of resistance to TKI treatments as a result of secondary mutations. New-line agents have been greatly studied to circumvent such limitations. MET tyrosine kinase, a multifaceted receptor kinase, is an emerging molecular target currently being tested in clinical trials. When activated, it induces tumor cell activities such as cell proliferation and angiogenesis, epithelial-mesenchymal transition (EMT), and cell scattering, leading to tumor cell invasion and metastasis[18]. Because MET receptors and EGFR in lung cancer are often co-expressed and co-activated, the simultaneous targeting of MET and EGFR pathways may be an effective strategy to overcome secondary resistance to EGFR-TKIs with an enhanced primary response to targeted therapy [19]. Patients with nonsquamous NSCLC have demonstrated improved progression-free survival and overall survival rates when treated with combined inhibitors targeting both the EGFR and MET pathways[20]. Nonetheless, the long-term clinical success of such targeted therapeutics remains questionable until the mechanisms of resistance are further understood.

Although some literature has focused on the theory of "cancer stem cells" to explain drug resistance to therapy, the relationship between the tumor microenvironment and lung cancer stem cells is too poorly characterized to draw any profound conclusions. A growing body of evidence indicates that NSCLC exhibits stem cell behaviors, such as self-renewal, proliferation, and multipotency [21]. When induced by genetic or epigenetic factors, these tumor cells are believed to take on stem cell properties and to drive growth and drug resistance. However, cell surface markers, such as CD44 and multidrug resistance 1 (MDR-1), have been identified in a series of SCLC cells[21]. Tellez *et al.*[22] have suggested that cells expressing CD44 are highly associated with lung cancer progression and metastasis via EMT. In their study, cells exposed to carcinogens gained stem cell-like properties. These cells not only lose cell-cell adhesion mediated by E-cadherin down-regulation but also gain mobility and invasive properties. Despite these findings, no targeted therapies are currently available to target cells with CD44 and MDR1 expression. Nevertheless, similarities between tumor cells and stem cells may be helpful for revealing certain molecular mechanisms underlying lung cancer.

Adenocarcinoma is the most common form of NSCLC in smokers [23]. Adenocarcinoma patients have nucleotide transversion mutations in the *KRAS* gene [24]. In heavy smokers, *KRAS* oncogene mutations are the dominant promoter of the activation of oncogenic signaling pathways. *KRAS* mutations have been associated with constitutively activated KRAS protein, which stimulates the downstream pathways by altering other receptors' signals, such as c-Raf and PI3 kinase, both of which are crucial signal transducers. Although KRAS is downstream to EGFR, EGFR-TKIs have shown to be ineffective in blocking the activities of mutated KRAS protein [25]. The specific type of KRAS mutation may provide insight into disease aggressiveness or drug sensitivity, thereby making the KRAS status in patients

with mutant *KRAS* a significant marker for predicting therapeutic responses[26]. The essential role of *KRAS* for survival is evident due to the embryonic lethality observed in *KRAS* -/- mice and suggests that mutant *KRAS* may be a potent oncogene. Transgenic mice with a *KRAS* mutation were significantly more susceptible to carcinogen-induced lung carcinogenesis than their wild-type counterparts[27]. Interestingly, wild-type *Kras* mice have been found to be capable of inhibiting lung tumor development. Although efforts in developing therapies against mutant *KRAS*-driven cancers have met with disappointment, their non-responsiveness to EGFR-TKI therapies allows us to gain insight into the complexities of the KRAS signaling network, directing us to discover more effective therapies for these targets.

As conventional therapies for lung cancer reach their limitations, targeted therapy will become an important field for scientists searching for personalized targeted treatments with maximum effectiveness. The availability of advanced experimental techniques and high-throughput methods allows us to better understand the molecular mechanisms underlying lung cancer. Using real-time quantitative PCR, we are capable of measuring gene expression and hence the effectiveness of drug treatments. In addition, the accessibility of microarray-based assays enables gene expression profiling and the identification of cancer development stages. By coupling our knowledge of signaling pathways via systems biology with efficient experimental tools, optimum therapeutics may be possible for each individual. With greater knowledge of molecular targets, the development of novel agents directed at these markers will open the doors to personalized medicine.

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