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Review Article

Role of Molecular Biomarkers in Non-Small Cell Lung Carcinoma in Diagnosis and Treatment Prediction

Rami Abdullah Ali Al Daghreer[1*], Hamad Aldaghreer[2], Smita Sharma[3]

[1]Masters in Biotechnology, Ministry of Health, Nejran, KSA
[2]Nejran Health cluster, Director of Integration, Health care Department.
[3]MD, DTCD, Astt. Prof. Biochemistry, Ajay Sangaal Institute of Medical Sciences & Research, Jhinjhana, UP, India

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***Corresponding Author:** Rami Abdullah Ali Al Daghreer
Masters in Biotechnology, Ministry of Health, Nejran, KSA

Abstract

Lung cancer is leading cause of mortality worldwide. About 80-85% of lung cancers are nonsmall cell lung carcinomas (NSCLC). The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large cell carcinomas. These NSCLC are grouped together as their treatment and prognosis is often similar. Diagnosis depends on symptoms, histopathology and molecular biomarkers. Even treatment in late stages of NSCLC requires appropriate testing with predictive molecular biomarkers as it provides information that is essential for establishing appropriate treatment options for each patient. This review paper provides current molecular biomarkers in NSCLC which are useful in diagnosing as well predicting treatment.

Keywords: NSCLC, Molecular Biomarkers.

INTRODUCTION

In NSCLC mutations in EGFR, KRAS and ALK rearrangements. New molecular biomarkers BRAF mutations, HER2, PIK3CA and new translocations such as ROS, RET1.For patients with histologically or cytologically confirmed metastatic non-squamous NSCLC, the current Clinical Practice Guidelines of the European Society for Medical Oncology (ESMO) for oncogene-addicted advanced-stage NSCLC (2023) recommend to perform molecular testing for the following predictive biomarkers: *EGFR, KRAS (G12C), BRAF (V600), ERBB2*, and *MET* (exon 14 skipping) mutations, *MET* amplifications, *ALK, ROS1, RET*, and *NTRK1/2/3* fusions, and PD-L1 expression [1]. These ESMO guidelines are in line with the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (2022) and the American Society of Clinical Oncology (ASCO) guidelines (2022) [2, 3].

Epidermal growth factor receptor (EGFR)

It is Tyrosine kinase receptor member of ERBB family. It is overexpressed in 62% cases of NSCLC and associated with poor prognosis. EGFR mutations are present in lung tumor patients. These mutations are present in exon 18-21. Activating mutations in the kinase domain of EGFR trigger ligand-independent tyrosine kinase activation, leading to hyperactivation of downstream antiapoptotic signaling pathways. Treatment with tyrosine kinase inhibitors (TKIs), such as gefitinib, erlotinib and afatinib, in patients with *EGFR*-mutant tumors, and the significantly greater progression-free survival (PFS) of these patients. But these patients also develop resistance due to new mutations. *EGFR* mutations are identified mostly with the use of gene sequencing methodologies and real-time polymerase chain reaction (PCR)-based assays.

Anaplastic Lymphoma Kinase (ALK)

It is tyrosine kinase receptor for insulin receptor family. ALK gene rearrangements consists of fusion of *ALK* and echinoderm microtubule-associated protein-like 4 (*EML4*) genes [4]. This rearrangement encodes for a chimeric protein with constitutive kinase activity, which promotes malignant growth and proliferation [5]. ALK fusion responsive (57%-74%) to ALK inhibitors such as crizotinib. However, despite initial responses, a fraction of the patients develop acquired resistance to crizotinib, owing to secondary mutations. Current diagnostic approaches to detect *ALK* fusion genes and their results include break-apart fluorescence in situ

hybridization (FISH), IHC, and reverse-transcription PCR (RT-PCR) [6].

Kirsten rat sarcoma viral oncogene (KRAS)

Because *KRAS*, *EGFR*, and *ALK* molecular alterations are mutually exclusive there are no targeted therapies approved for patients with lung cancer.

ROS proto-oncogene 1, receptor tyrosine kinase (*ROS1*)

ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) is a tyrosine kinase receptor member of the insulin receptor family. 1% to 2% of NSCLCs harbor *ROS1* rearrangements [8], *ROS1*-rearranged NSCLC typically occurs in young, female, never smokers with a histologic diagnosis of adenocarcinoma [7, 8]. Clinical trials have reported that patients with advanced NSCLC harboring *ROS1* rearrangement have benefited from crizotinib treatment [7, 9]. Currently available diagnostic methods include FISH, RT-PCR, and IHC [10].

Human epidermal growth factor receptor 2 (*HER2*)

The human epidermal growth factor receptor 2 gene *HER2* (*ERBB2*) is protooncogene it expression and/or encodes for a tyrosine kinase receptor member of the ERBB receptor family. Overexpression of HER2 has been reported in 7% to 34.9% of NSCLCs and has been associated with poor prognosis in patients with these tumors [11]. Activating mutations of *HER2* have been found in 1.6% to 4% of lung cancers [11, 12]. Many studies showed adenocarcinomas for *HER2* mutation as a method to select patients who could benefit from *HER2*-targeted therapies (afatinib and trastuzumab), which have shown response rates of approximately 50% [13]. HER2 mutations are usually assessed via sequencing approaches.

***RET* proto-oncogene**

The *RET* proto-oncogene encodes for a tyrosine kinase receptor for the glial cell line–derived neurotrophic factor family of ligands and is involved in cell proliferation, migration, and differentiation, as well as neuronal navigation [14]. *RET*-rearranged NSCLC typically occurs in adenocarcinomas with more poorly differentiated solid features in young never smokers, and it is mutually exclusive with known driver oncogenes [15, 17]. In vitro studies showed that *RET* fusions lead to oncogenic transformation, which can be inhibited by multitargeted kinase inhibitors such as vandetanib, sorafenib, and sunitinib [17]. Preliminary studies with cabozantinib (MET and vascular endothelial growth factor receptor 2 inhibitor) in *RET*-rearranged lung adenocarcinoma are promising [16].

FISH is currently the standard diagnostic assay for detection of *RET* chromosomal rearrangements.

MET proto-oncogene

The *MET* gene oncogene encodes for a tyrosine kinase receptor (hepatocyte growth factor receptor), which activates multiple signaling pathways that play fundamental roles in cell proliferation, survival, motility, and invasion [4]. Pathologic activation of *MET* includes mutation, gene amplification, and protein overexpression [18]. In lung cancer, *MET* mutation occurring in 3% of squamous cell lung cancers and 8% of lung adenocarcinomas [18]. *MET* amplifications are found in 4% of lung adenocarcinomas and 1% of squamous cell lung cancers and are associated with sensitivity to MET inhibitors Activating point mutations affecting splice sites of exon 14 of the *MET* gene (*MET*ex14), which occur in 4% of lung adenocarcinomas, represent a possible oncogenic driver and identify a subset of patients who may benefit from MET inhibitors such as capmatinib and crizotinib [18]. This alteration is usually assayed by NGS methodology.

The B-RAF proto-oncogene

It encodes for a serine/threonine kinase, which is involved in the RAS/RAF/MEK/ERK signaling pathway [19]. *BRAF*-mutated NSCLC has been reported to be mostly adenocarcinoma, patients with *BRAF* mutations are mostly current or former smokers [20]. Nevertheless, patients with NSCLC and *BRAF* V600E mutations have a worse prognosis and lower response to platinum-based chemotherapy than patients with wild-type *BRAF*. These patients have benefited from treatment with BRAF and MEK inhibitors [21]. BRAF inhibitors, such as vemurafenib and dabrafenib, have high and selective activity against the V600E-mutant BRAF kinase, with overall responses rates from 33% to 42% [21, 22]. BRAF and MEK inhibitors targeting *BRAF* mutation–positive NSCLC, such as trametinib, selumetinib, and dasatinib, among others, are currently under evaluation in clinical trials. Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*).

PI3Ks are heterodimeric lipid kinases involved in cell growth, transformation, adhesion, apoptosis, survival, and motility [23]. *PKI3CA* amplifications, deletions, and somatic missense mutations have been reported lung cancers.

Mutations are found in 1% to 4% of patients with NSCLC, usually affecting exons 9 and 20 (80%) [4, 23-29]. These mutations are not mutually exclusive with other driver alterations and have been reported more frequently in lung squamous cell carcinoma compared to adenocarcinoma (6.5% vs 1.5%) [26].

Studies have shown that *PIK3CA* mutations in *EGFR*-mutated lung cancer confer resistance to EGFRTKIs and are a negative prognostic predictor in patients with NSCLC treated with EGFR-TKIs [27]. *PI3KCA* alterations and their downstream effectors, such as phosphatase and tensin homolog

(PTEN), mTOR, and AKT, are potential therapeutic targets for NSCLC therapy and are being evaluated in clinical trials for lung cancer [28]. Alterations in *PI3KCA* are detected using sequencing approaches, mostly NGS assays.

Neurotrophic receptor tyrosine kinase 1(*NTRK1*)

The neurotrophic receptor tyrosine kinase 1 (*NTRK1*) proto-oncogene *NTRK1* is involved in the regulation of cell growth and differentiation via activation of several signal transduction pathways including MAPK, PI3K, and phospholipase C-gamma.

In lung cancer, approximately 3% of adenocarcinomas harbor *NTRK1* fusions, and some fusion partners, including myosin phosphatase RHO-interacting protein (*MPRIP*)-*NTRK1* and *CD74-NTRK1*, have been reported [29]. All of these fusions result in constitutive TRKA kinase activity, which has been reported to be oncogenic [29]. In early phase 1 studies, NTRK inhibitors, such as entrectinib and LOXO-101, have shown promising results in patients with solid tumors harboring NTRK fusions [30].

Fibroblast growth factor receptor (*FGFR*)

The fibroblast growth factor receptor **(***FGFR*) encodes for a tyrosine kinase receptor belonging to the FGFR family. In cancer, *FGFR* gene amplifications, somatic missense mutations, and chromosomal translocations are the most frequent mechanisms of activation [31]. In addition, *FGFR* amplifications may be found in concurrence with other tumor genetic alterations including *TP53* and *PIK3CA* mutation and platelet-derived growth factor receptor A (*PDGFRA*) amplification [32]. Multiple FGFR inhibitors, such as ponatinib, a multitargeted kinase inhibitor that displays potent pan–anti-FGFR activity, are in development, with promising results in cell lines and xenograft models [33]. Phase 1 and 2 clinical trials of FGFR inhibitors (dovitinib, nintedanib, ponatinib, and AZD4547, among others) are ongoing in patients with NSCLC. *FGFR* gene copy number is usually assayed by FISH.

Discoidin domain receptor tyrosine kinase 2 (*DDR2*)

The discoidin domain receptor tyrosine kinase 2 gene (*DDR2*) encodes for a tyrosine kinase receptor that is expressed in mesenchymal tissues and which binds fibrillar collagen as ligand. DDR2 activates important signaling pathways including SRC, SRC homology domain-containing (SHC), Janus kinase (JAK), ERK1/2, and PI3K and promotes cell migration, proliferation, and survival [35].

In lung cancer, *DDR2* mutations occur in 3% to 4% of lung squamous cell carcinomas [36] compared to 0.5% of adenocarcinomas [37] and are only present in smokers [38].

DDR2 mutations have been associated with response to dasatinib (a multitargeted kinase inhibitor) in preclinical models and early phase clinical trials. Phase 2 clinical trials of dasatinib in patients with lung squamous cell carcinoma are under way [34, 36].

Emerging predictive biomarkers in non-squamous NSCLC

ERB2 MUTATION: Predictive response **to** to HER2-targeted therapy (e.g., trastuzumab deruxtecan)
ERB2 AMPLIFICATION: Predictive value for response to HER2-targeted therapy (e.g., ado-trastuzumab)
NRG1 fusion: Predictive value for response to NRG1-targeted therapy.
MAP2K1 mutation: Predictive value for response to MEK inhibitors.
BRAF non-V600 mutation: Predictive value for response to BRAF/MEK inhibitors.
TP53 mutation + *KRAS* mutation: Predictive value for response to immunotherapy **[**39].

Emerging biomarkers associated with primary resistance to targeted therapy

PIK3CA mutation + *EGFR* mutation: Negative prognostic value for response to EGFR TKI.
KEAP1 mutation + *KRAS* mutation: Negative predictive value for response to $KRAS^{G12C}$-inhibitor treatment.
CDKN2A mutation + *KRAS* mutation: Negative predictive value for response to $KRAS^{G12C}$-inhibitor treatment.
SMARCA4 mutation + *KRAS* mutation: Negative predictive value for response to $KRAS^{G12C}$-inhibitor treatment.

These emerging biomarkers under trial [39].

CONCLUSION

Molecular biomarkers play an important role in thoracic oncology. They are helpful not only diagnosis but also in treatment prediction. So it is essential Molecular tumor profiling for all clinically relevant biomarkers in patients with advanced stage NSCLC, including biomarkers for which targeted therapies are available through clinical trials, off-label use, or compassionate use programs, should be performed. It is necessary to implement routine large-panel next-generation sequencing (NGS) for all patients with advanced stage NSCLC to enable testing of all clinically relevant biomarkers, both for biomarkers relevant today as well as biomarkers relevant in the (near) future.

Conflict of Interest: There is no conflict of interest.

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