Review Article

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Molecular genetics of lung cancer

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Abstract:

Lung cancer is one of the most common cancers with high mortality and is described as one of the leading causes of cancer-related deaths worldwide. Lung cancer is classified into two main histological groups: small cell lung cancer (SCLC) and non-SCLC (NSCLC). Using tobacco products is the most important risk factor for lung cancer development and appears to be responsible for 80%–90% of total lung cancers. It is thought that lung cancer is the end result of exposure to environmental risk factors in people with genetic susceptibility. Lung cancer cells contain many genetic alterations such as mutation, amplification, insertion, deletion, and translocation. The information obtained from research suggests that these genetic changes are also associated with characteristics such as smoking status, race, and gender. Significant progress has been made in the last 10–15 years to understand the molecular basis of lung cancer, and the discovery of oncogenic precursor mutations has created new pathways in the NSCLC classification and has also provided new therapeutic targets for anticancer therapy. With the introduction of targeted agents such as epidermal growth factor receptor and anaplastic lymphoma kinase in the treatment of adenocarcinomas in an effective manner, personalization of treatment strategies has become especially important for advanced lung cancer patients. The 2015 World Health Organization guideline for the classification of lung cancer recommends the preservation of pathologic specimens for molecular examinations and emphasizes the importance of molecular testing in the individualized treatment of advanced lung cancer patients.

Keywords:

Lung cancer, molecular alterations, mutation

Introduction

Lung cancer is a cancer with high mortality rate, which is the most common cause of cancer-related deaths worldwide, and causes approximately 1.6 million deaths each year.[1,2]

Lung cancers are traditionally classified into two main histologic groups (small cell lung cancer [SCLC] and non-SCLC [NSCLC]) according to differences in the natural course of the disease and the treatment approaches. NSCLC constitutes approximately 85% of all lung cancers, and the most common subtypes are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[3] It has been determined that these lung cancer subtypes are not only morphologically different but also have different molecular bases and have different therapeutic targets. Recent advances in molecular biology of cancer indicate that in approximately 60% of adenocarcinomas and 20% of squamous cell carcinomas, there is a defined genetic change *(gene signature)* and these changes allow for the successful development and implementation of treatments that target the appropriate molecules.[4]

In the revised World Health Organization guidelines on the classification of lung cancer (2015), some changes have been made in the classification of lung cancer, and molecular typing has been emphasized especially in adenocarcinomas. It has been recommended that the pathologic specimens undergo molecular testing (epidermal growth factor receptor [EGFR] mutation, anaplastic lymphoma kinase [ALK], and ROS-1 rearrangement) for precursor mutations in tumor tissues.[5]

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This review aims to investigate molecular changes in lung cancer and recent studies on this subject.

Molecular Genetics of Lung Cancer

Lung cancer is one of the most common genetic disorders, and the molecular pathogenesis of lung cancer is quite complicated and heterogeneous. Lung cancer can develop as sequel to several genetic and epigenetic changes (e.g., point mutation, amplification, insertion, deletions, and translocations); it is particularly associated with the activation of the pathway that promotes growth and the inhibition of the tumor suppressor pathways [Figure 1].[6,7]

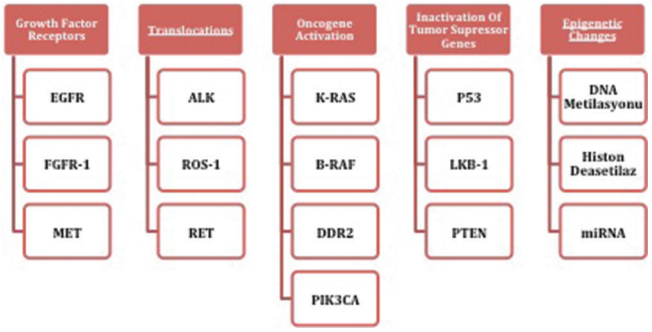

Figure 1: Molecular alterations in lung cancer

Studies indicate that adenocarcinomas and squamous cell carcinomas, both subtypes of NSCLC, are quite different regarding their molecular features. The precursor mutations and the prevelances of these mutations in NSCLC by histologic subtype are presented in Figures 2 and 3.

Smoking is the most important risk factor for lung cancer worldwide; 85% of lung cancers are caused by the carcinogens found in tobacco smoke. The differences in smoking habits are found to be associated with the molecular differences.[6]

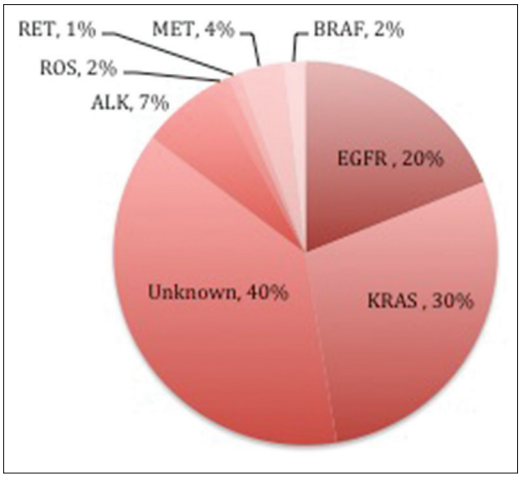

Figure 2: Common mutations in lung adenocarcinomas[6,9,10]

Growth Factor Receptors

Epidermal growth factor receptor

EGFR is a tyrosine kinase receptor that is a member of the ErbB family, and it is abnormally activated in many types of epithelial cancers. EGFR activation leads to the activation of several important pathways, such as phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR, RAS/RAF/MAPK, and JAK/STAT, which are responsible for cell proliferation, differentiation, angiogenesis, invasion, and metastasis.[7,8]

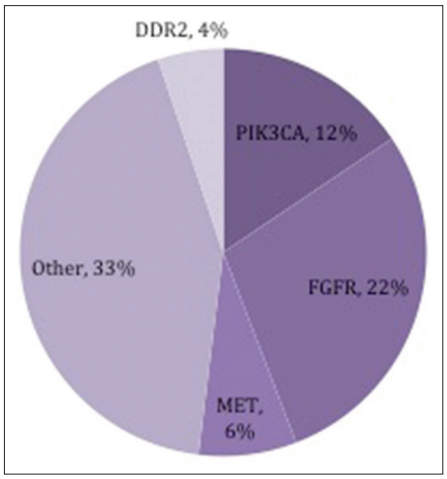

Figure 3: Common mutations in lung squamous cell carcinomas[6,9,10]

EGFR mutations are seen in approximately 20%–30% of lung adenocarcinomas; however, it is very rarely seen in squamous cell carcinomas. EGFR mutations are more common among women, nonsmoker patients, and Asian populations.[1]

EGFR gene is formed from 28 exons; the tyrosine kinase domain is encoded by exons 18–21. Activating mutations in exon 18, deletions in exon 19, and L858R point mutations in exon 21 make up 90% of all EGFR mutations. The response rate of the tumors that have these mutations to EGFR tyrosine kinase inhibitors (TKIs) is approximately 70%. The mutations on exon 20 are rarer and they are thought to cause resistance against EGFR inhibitors.[8,9]

EGFR TKIs, i.e., erlotinib, gefitinib, and afatinib are used for the treatment of EGFR mutant adenocarcinomas.[10] In general, the diseases tend to develop a resistance after 1 year of treatment. The most important underlying cause is a second mutation in the EGFR gene, which occurs in approximately 60% of cases that develop resistance. The most common secondary mutation is the T790M mutation in exon 20.[9,11] Osimertinib is a third-generation EGFR-suppressing agent that suppresses both the

mutations that are sensitive to EGFR TKIs and the T790M mutations. It has been approved by the USA Food and Drug Administration (FDA) (2015) and the European Medicines Agency (2016) for the treatment of EGFR T790M mutation-positive NSCLC patients after EGFR TKI treatment.[12]

It has also been shown that the amplifications of fibroblast growth factor receptor-1 (FGFR1), MET, and HER2 play a role in EGFR TKI resistance. It is thought that the cell can continue its growth proliferation despite EGFR blockage through these alternative tyrosine kinases. This indicates that EGFR is not a single dominant tyrosine kinase in the autocrine growth of NSCLC and that other tyrosine kinases also play a part. For this reason, the autocrine and paracrine signaling in NSCLC should be effectively blocked, and the other tyrosine kinases should also be evaluated to plan the appropriate treatment.[13]

Fibroblast growth factor receptor-1

The FGFR tyrosine kinase family consists of four kinases: FGFR-1, FGFR-2, FGFR-3 and FGFR-4. These function as cell surface receptors for fibroblast growth factors, playing a critical role in embryonic development, cell proliferation, differentiation, and migration control. This FGFR tyrosine kinase family also has an important role in the tumor pathogenesis, and it can be dysregulated by amplification, point mutation, or translocation.

The FGFR1 gene on chromosome 8 is one of the most common genes that are amplified in human cancers. The results of various studies indicate that the FGFR1, FGF2, and FGF9 ligands have a combined expression in human lung cancers.[14,15]

It was determined that FGFR1 amplification had an incidence of 21% in squamous cell carcinoma, and it was also associated with a low survival rate and a history of smoking.[10] Furthermore, it has been determined that FGFR1 amplification was present in 3% of adenocarcinomas and 5%–6% of SCLCs. There are ongoing studies concerning the efficacy of the new FGF1 inhibitor ponatinib.[9,14]

MET

MET is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor for the hepatocyte growth factor ligand and that takes part in several carcinogenic processes, such as cell proliferation, survival, invasion, motility, and metastasis.[16]

MET amplification is seen in 5%–10% of NSCLCs. High gene copy numbers are more common in squamous cell carcinoma than in adenocarcinoma. High MET protein expression has been shown to be associated with poor prognosis.[9]

Translocations

Anaplastic lymphoma kinase

Insulin receptor protein is an ALK protein that is a member of the tyrosine kinase superfamily and a transmembrane tyrosine kinase receptor.[17]

ALK protein was first discovered in 1997 as a chimeric protein that resulted from the t(2; 5) (p23; q35) chromosome translocation in anaplastic large cell lymphoma. In 2007, another ALK translocation was found in NSCLC. A part of ALK, located on chromosome 2, inverted and fused with a part of the EML-4 gene *(Echinoderm Microtubule-Associated protein-like 4 gene)*.[18] This new ALK fusion protein can be activated in the cytoplasm without requiring a ligand to activate the RAS/RAF/MEK, PI3K/AKT/mTOR, and JAK/STAT signal pathways.[19] The ALK-EML-4 fusion is observed in 4%–7% of NSCLCs often young, nonsmokers and clinic, mostly among younger patients, patients without a history of smoking, and patients with clinically advanced disease.

Crizotinib is an oral small-molecule TKI of the ALK, MET, and ROS-1 kinases. It is a first-generation ALK inhibitor. The use of crizotinib was approved by the FDA (2011) and the Committee for Medicinal Products for Human Use European Commission (2015) in ALK-positive NSCLC.[17]

ROS-1

ROS-1 is a proto-oncogene that is located on chromosome 6 that encodes the transmembrane tyrosine kinase receptors of the insulin receptor family. The protein kinase domain is similar to ALK.[7]

ROS-1 translocations are observed in 1%–2% of adenocarcinoma patients. In lung adenocarcinomas, the ROS-1 gene may be fused with several different genes, but the most common is the CD74-ROS-1 fusion. ROS-1 fusion is more commonly seen among younger patients, women, and nonsmokers. Crizotinib is structurally similar to the kinase regions of ROS-1 and ALK proteins; thus, it inhibits the ROS-1 protein.[20]

RET

RET is a proto-oncogene that encodes a receptor tyrosine kinase that takes part in neural crest formation.[21]

The translocation of the RET gene can result in a number of fusion proteins. The fusion of the RET gene with 6 different genes has been identified in approximately 1%–2% of adenocarcinomas. These oncogene fusions are seen majorly in nonsmokers, and it has been shown that the tobacco-independent double-helix disruptions probably trigger the development of RET fusion.[20]

Oncogene Activation

KRAS

KRAS is a member of the RAS proto-oncogene family; it encodes the G protein, which has critical functions in the signal pathways that regulate cell proliferation, differentiation, and survival.[7] The structural activation of the protein eliminates the need for growth factor-mediated signaling.[22]

KRAS mutations are the most common oncogenic change in adenocarcinoma; it is seen in 25%–40% of adenocarcinomas. However, it is very rarely seen in squamous cell carcinoma or small cell cancer.[7] KRAS mutations are associated with a poor prognosis.

Among KRAS mutations, G12C, G12V, G12D, and G12A mutations are most commonly seen and these mutations are more frequent in Western societies, males, and smokers.[23] The most common mutation among smokers is G12C (41%), while the most common mutation among nonsmokers is G12D (56%).[24]

There is not a developed agent that specifically targets KRAS; it is thought that MEK inhibitors can be used in the inhibition of the downstream targets.[23]

BRAF

BRAF encodes a serine/threonine protein kinase that is a downstream effector protein of KRAS. It activates the MAPK signal transduction pathway that regulates cell proliferation and survival.[7]

BRAF mutations are seen in 8% of all human cancers. They are most common among the following cancers: hairy cell leukemia (100%), melanoma (50%), papillary thyroid carcinoma (45%), colorectal cancer (10%), and rarely in ovarian and lung cancers (3%). The T1799 point mutation in exon 15 of the BRAF gene leads to the addition of a glutamate to the valine in codon 600 (V600E). The is the most common carcinogenic precursor mutation in melanoma (90%).[25] Approximately half of all lung cancers contain the V600E mutation, while the other half contain non-V600E mutations, such as the L596R and G468A mutations.[9] Vemurafenib and dabrafenib are Type I BRAF serine/threonine kinase inhibitors that have higher selectivity for the V600E BRAF protein. The use of vemurafenib and dabrafenib has been approved for the treatment of patients with BRAF V600E-mutation melanoma. The studies concerning its activity in NSCLC resume.[25]

Discoidin domain receptor-2

Discoidin domain receptor-2 (DDR2) is a membrane-bound tyrosine kinase receptor that binds collagen, a major component of the extracellular matrix in the lung. It has been shown that DDR2 activates several important signal components, such as SHC, SRC, JAK, Erk1/2, and PI3K. DDR2 is associated with a number of cancer types, and it has been shown to play a role in proliferation and the redirection of metastasis.

DDR2 mutations are seen in 3%–4% of squamous cell carcinomas. It is predicted that DDR2 can be a potential new target for the treatment of lung squamous cell carcinoma.

Multiple kinase inhibitors, i.e., dasatinib, imatinib, and nilotinib ATP competitively blocks DDR2 kinase activity at various levels.[26] A study has shown that the DDR2 mutant lung squamous cell carcinomas are selectively sensitive to these inhibitors; further research regarding DDR2 inhibitors is in progress.[27]

Phosphoinositide-3-kinase, catalytic, alpha polypeptide

PI3K protein families are lipid kinases that take part in the PI3K/AKT/Al pathway. The main catalytic subunit, p110alpha isoform, is encoded by the phosphoinositide-3-kinase, catalytic, alpha polypeptide (PIK3CA) gene. The amplification of PIK3CA and the activating mutations lead to the ligand-independent signal pathway activation.[7,10]

PIK3CA mutations are found in approximately 1%–3% of NSCLCs. They are commonly found together with other oncogenic mutations, especially EGFR, KRAS, and ALK. PIK3CA amplifications are more common in squamous cell carcinomas (33%) than adenocarcinoma (6%) and SCLC (4%).[28] A variety of PI3K inhibitors are under clinical development.[29]

Inactivation of Tumor Suppressor Genes

TP53

TP53 is located in the short arm of chromosome 17. It is a tumor suppressor gene that takes part in the control of the cell cycle, DNA repair, and apoptosis. Mutations in the TP53 gene are among the most common genetic alterations, seen at high frequency in human cancers, and approximately 80% of the TP53 gene mutations are missense mutations.

Inactivation of TP53 is seen in 90% of small cell carcinomas and in approximately 65% of NSCLCs.[7,30] The mutational spectrum of TP53 mutations differs for smokers and nonsmokers.[31] Abnormal p53 is found to be a negative prognostic factor in lung NSCLC; also, the genetic changes in TP53 are associated with treatment resistance.[30]

LKB-1

LKB-1 (STK11) encodes serine/threonine kinase and regulates biological processes such as the cell cycle, cell

polarity, and energy metabolism through the inhibition of mTOR.[6]

The mutations that inactivate LKB-1 lead to the Peutz–Jeghers syndrome. The biallelic inactivation of LKB-1 is the third most common genetic disorder in NSCLC after TP53 and KRAS and is found in 30% of primary tumors. Inactivating mutations are more common in adenocarcinomas than in squamous cell cancers; they are also more common among males and smokers and in poorly differentiated adenocarcinomas.[7,32]

PTEN

PTEN is a tumor suppressor gene localized on chromosome 10, which encodes lipid and protein phosphatase that inhibits the PI3K/AKT/mTOR signaling pathway. PTEN inactivation leads to the unrestricted ligand-independent activation of AKT/protein kinase.[7,10]

PTEN mutations are seen in approximately 5% of NSCLC. It is more common in squamous cell carcinoma compared to adenocarcinoma and is associated with a history of smoking.[29] Decreased PTEN expression levels are seen in approximately 75% of NSCLC. Vandetanib, a TKI, has been reported to be efficacious against EGFR mutation-positive lung cancer cell lines showing loss of PTEN.[10]

Epigenetic Changes

Epigenetic changes are defined as "the regulation of gene expression through the hereditary changes in the chromatin structure, without changing the DNA sequence." They are known to take part in the pathogenesis if several different cancers. Furthermore, epigenetic changes are thought to play a role in the drug resistance in cancer treatment.[33,34]

DNA methylation

DNA methylation is one of the most important epigenetic changes; it is catalyzed by DNA methyltransferase (DNMT) enzymes and takes place with the help of proteins that bind methyl-CpG (MBD1, MBD2, MeCP2, etc.).[34]

The inactivation of tumor suppressor genes through promoter hypermethylation is seen in the early stages of lung cancer, and the majority of these genes are known to be associated with prognosis. The genes that are most widely studied in the context of promoter methylation in lung cancer are p16INK4a, RASSF1A, APC, RARβ, CDH1, CDH13, DAPK, FHIT, and MGMT.[35]

Studies have found that the levels of the DNMT1 and DNMT3b enzymes and MBD2 (which bind methyl, CpG-DNA) had increased in lung cancer patients. It is thought that these contribute to the development of lung cancer through the hypermethylation of tumor suppressor genes.[34,36,37] It is expressed that increased TRDMT1, which takes part in the recognition of DNA damage, DNA recombination, and repair, can influence RNA methylation and affect the development of lung cancer.[34]

Another mechanism of cancer development is genomic hypomethylation. In lung adenocarcinoma, global hypomethylation can be seen in advanced stages. It is reported that in NSCLC, hypomethylation can activate the inactive oncogenes and cause genomic instability, which leads to cancer formation. It has been shown that in lung cancer, there is hypermethylation in nuclear elements, LTR elements, segmental duplicates, and subtelomeric regions.[35]

Histone deacetylase

Histone deacetylases catalyze the removal of the acetyl groups on the histone tail. Thus, they lead to a heterochromatic condition that is not transcriptionally active.

It has been shown that histone deacetylases (HDAC) are overexpressed in lung cancer. Various global histone modifications have been associated with survival in lung cancer.[35] It has been shown that the SIN3A mRNA, a component of the HDAC repressor complex, is downregulated in NSCLC.[38]

The use of HDAC inhibitors, vorinostat and romidepsin, has been approved by the FDA for the treatment of cutaneous T-cell lymphoma. Nevertheless, although a recently completed clinical trial demonstrated promising results in the combination of an HDAC inhibitor, Entinostat, and DNA-demethylating agent, 5-azacytidine, in advanced chemorefractory NSCLC, there is not a HDAC inhibitor that is approved for lung cancer treatment.[35,39]

Micro RNA

Micro RNAs (miRNAs) are small RNA molecules which are encoded by the microRNA (mir) genes that are not translated into proteins. miRNAs can negatively regulate hundreds of mRNA targets. They are usually dysregulated in lung cancer, as with many other types of cancer.

Many studies have reported an association between lung cancer and miRNA expression, the most commonly studied ones being miR-21 and miR-155.[35] In a recent meta-analysis, high miR-21 expression was associated with low survival in NSCLC.[40]

Histology-specific miRNA expression patterns have also been demonstrated. For example, it was reported

that miR205 was specific to squamous cell carcinoma,[41] whereas miR-124a was reported to be specific to adenocarcinoma.[42]

Conclusion

Lung cancer is a common type of cancer and is one of the most common causes of mortality among cancer types. Most lung cancer cases are diagnosed in stages where the patients can be offered limited treatment options.

In the last decade, many molecular alterations which are effective in the development of lung cancer have been discovered. In adenocarcinoma, TKIs were developed for EGFR mutations and ALK and ROS1 translocations and were approved for use in the treatment of advanced stage adenocarcinomas. For squamous cell cancers, part of the determined precursor mutations is at the level of drug development; however, the evaluation of these mutations is not yet used in clinical practice. In addition, there are ongoing studies concerning many potential therapeutic molecular targets, such as ROS, MET, FGFR, DDR-2, and RET.

The signal pathways which are regulated by oncogenes and tumor suppressor genes and which take part in carcinogenesis are interconnected and complicated. Furthermore, the tumors can undergo mutational evolution during the natural prognosis of the disease. These indicate the heterogeneity and complexity of the molecular biology of lung cancer and make it difficult to develop target-oriented treatments. For this reason, the multiple biochemical pathways that take part in the molecular pathogenesis of lung cancer should be better understood for the determination of diagnostic and prognostic markers of lung cancer and for the development of personalized specific treatment strategies.

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Conflicts of interest
There are no conflicts of interest.

References

1. Diniz G, Ünlü I, Kömürcüoğlu B. Histopathological and molecular features of lung cancer. Tepecik Eğit Hast Derg 2017;27:77-87.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A, *et al*. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
3. Forde PM, Ettinger DS. Targeted therapy for non-small-cell lung cancer: Past, present and future. Expert Rev Anticancer Ther 2013;13:745-58.
4. Thunnissen E, van der Oord K, den Bakker M. Prognostic and predictive biomarkers in lung cancer. A review. Virchows Arch 2014;464:347-58.
5. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, *et al*. The 2015 world health organization classification of lung tumors: Impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 2015;10:1243-60.
6. Larsen JE, Minna JD. Molecular biology of lung cancer: Clinical implications. Clin Chest Med 2011;32:703-40.
7. Cooper WA, Lam DC, O'Toole SA, Minna JD. Molecular biology of lung cancer. J Thorac Dis 2013;5 Suppl 5:S479-90.
8. Ji H, Li D, Chen L, Shimamura T, Kobayashi S, McNamara K, *et al*. The impact of human EGFR kinase domain mutations on lung tumorigenesis and *in vivo* sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-95.
9. Roh MS. Molecular pathology of lung cancer: Current status and future directions. Tuberc Respir Dis (Seoul) 2014;77:49-54.
10. Boolell V, Alamgeer M, Watkins DN, Ganju V. The evolution of therapies in non-small cell lung cancer. Cancers (Basel) 2015;7:1815-46.
11. Pirker R, Herth FJ, Kerr KM, Filipits M, Taron M, Gandara D, *et al*. Consensus for EGFR mutation testing in non-small cell lung cancer: Results from a European workshop. J Thorac Oncol 2010;5:1706-13.
12. Santarpia M, Liguori A, Karachaliou N, Gonzalez-Cao M, Daffinà MG, D'Aveni A, *et al*. Osimertinib in the treatment of non-small-cell lung cancer: Design, development and place in therapy. Lung Cancer (Auckl) 2017;8:109-25.
13. Minari R, Bordi P, Tiseo M. Third-generation epidermal growth factor receptor-tyrosine kinase inhibitors in T790M-positive non-small cell lung cancer: Review on emerged mechanisms of resistance. Transl Lung Cancer Res 2016;5:695-708.
14. Karachaliou N, Pilotto S, Lazzari C, Bria E, de Marinis F, Rosell R, *et al*. Cellular and molecular biology of small cell lung cancer: An overview. Transl Lung Cancer Res 2016;5:2-15.
15. Russell PA, Yu Y, Young RJ, Conron M, Wainer Z, Alam N, *et al*. Prevalence, morphology, and natural history of FGFR1-amplified lung cancer, including squamous cell carcinoma, detected by FISH and SISH. Mod Pathol 2014;27:1621-31.
16. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. J Clin Oncol 2013;31:1089-96.
17. Nursal AF. Importance of anaplastic lymphoma kinase gene re-arrangements on non-small cell lung cancer. Kafkas J Med Sci 2017;7:166-8.
18. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, *et al*. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561-6.
19. Reungwetwattana T, Dy GK. Targeted therapies in development for non-small cell lung cancer. J Carcinog 2013;12:22.
20. Kohno T, Nakaoku T, Tsuta K, Tsuchihara K, Matsumoto S, Yoh K, *et al*. Beyond ALK-RET, ROS1 and other oncogene fusions in lung cancer. Transl Lung Cancer Res 2015;4:156-64.
21. Wells SA Jr., Santoro M. Targeting the RET pathway in thyroid cancer. Clin Cancer Res 2009;15:7119-23.
22. Karnoub AE, Weinberg RA. Ras oncogenes: Split personalities. Nat Rev Mol Cell Biol 2008;9:517-31.
23. Kempf E, Rousseau B, Besse B, Paz-Ares L. KRAS oncogene in lung cancer: Focus on molecularly driven clinical trials. Eur Respir Rev 2016;25:71-6.
24. Riely GJ, Kris MG, Rosenbaum D, Marks J, Li A, Chitale DA, *et al*. Frequency and distinctive spectrum of KRAS mutations in never smokers with lung adenocarcinoma. Clin Cancer Res 2008;14:5731-4.
25. Nguyen-Ngoc T, Bouchaab H, Adjei AA, Peters S. BRAF alterations as therapeutic targets in non-small-cell lung cancer. J Thorac Oncol 2015;10:1396-403.
26. Payne LS, Huang PH. Discoidin domain receptor 2 signaling networks and therapy in lung cancer. J Thorac Oncol 2014;9:900-4.
27. Hammerman PS, Sos ML, Ramos AH, Xu C, Dutt A, Zhou W, *et al*. Mutations in the DDR2 kinase gene identify a novel

therapeutic target in squamous cell lung cancer. Cancer Discov 2011;1:78-89.
28. Perez-Moreno P, Brambilla E, Thomas R, Soria JC. Squamous cell carcinoma of the lung: Molecular subtypes and therapeutic opportunities. Clin Cancer Res 2012;18:2443-51.
29. Shames DS, Wistuba II. The evolving genomic classification of lung cancer. J Pathol 2014;232:121-33.
30. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. J Biomed Biotechnol 2011;2011:583929.
31. Husgafvel-Pursiainen K, Boffetta P, Kannio A, Nyberg F, Pershagen G, Mukeria A, *et al.* P53 mutations and exposure to environmental tobacco smoke in a multicenter study on lung cancer. Cancer Res 2000;60:2906-11.
32. Dong LX, Sun LL, Zhang X, Pan L, Lian LJ, Chen Z, *et al.* Negative regulation of mTOR activity by LKB1-AMPK signaling in non-small cell lung cancer cells. Acta Pharmacol Sin 2013;34:314-8.
33. Wang L, Li H, Ren Y, Zou S, Fang W, Jiang X, *et al.* Targeting HDAC with a novel inhibitor effectively reverses paclitaxel resistance in non-small cell lung cancer via multiple mechanisms. Cell Death Dis 2016;7:e2063.
34. Özbayer C, Üstüner D, Ak G, Saydam F, Metintaş M, Değirmenci İ. Evaluation of Plasma DNA Methyltransferases and Methy-CpG Binding Protein Levels in Patients with Lung Cancer. Dicle Tıp Derg 2017;44:57-64.
35. Langevin SM, Kratzke RA, Kelsey KT. Epigenetics of lung cancer. Transl Res 2015;165:74-90.
36. Kim H, Kwon YM, Kim JS, Han J, Shim YM, Park J, *et al.* Elevated mRNA levels of DNA methyltransferase-1 as an independent prognostic factor in primary non-small cell lung cancer. Cancer 2006;107:1042-9.
37. Shen H, Wang L, Spitz MR, Hong WK, Mao L, Wei Q, *et al.* A novel polymorphism in human cytosine DNA-methyltransferase-3B promoter is associated with an increased risk of lung cancer. Cancer Res 2002;62:4992-5.
38. Suzuki H, Ouchida M, Yamamoto H, Yano M, Toyooka S, Aoe M, *et al.* Decreased expression of the SIN3A gene, a candidate tumor suppressor located at the prevalent allelic loss region 15q23 in non-small cell lung cancer. Lung Cancer 2008;59:24-31.
39. Juergens RA, Wrangle J, Vendetti FP, Murphy SC, Zhao M, Coleman B, *et al.* Combination epigenetic therapy has efficacy in patients with refractory advanced non-small cell lung cancer. Cancer Discov 2011;1:598-607.
40. Yang M, Shen H, Qiu C, Ni Y, Wang L, Dong W, *et al.* High expression of miR-21 and miR-155 predicts recurrence and unfavourable survival in non-small cell lung cancer. Eur J Cancer 2013;49:604-15.
41. Bishop JA, Benjamin H, Cholakh H, Chajut A, Clark DP, Westra WH, *et al.* Accurate classification of non-small cell lung carcinoma using a novel microRNA-based approach. Clin Cancer Res 2010;16:610-9.
42. Lujambio A, Ropero S, Ballestar E, Fraga MF, Cerrato C, Setién F, *et al.* Genetic unmasking of an epigenetically silenced microRNA in human cancer cells. Cancer Res 2007;67:1424-9.