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REVIEW PAPER

Early diagnostic biomarkers of Lung cancer; a review study

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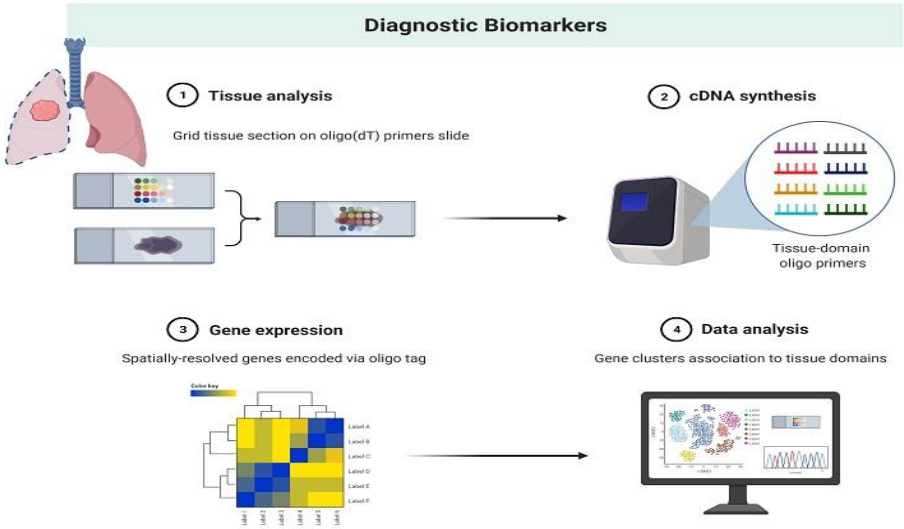
Highlights

- Lung cancer is the main national cause of cancer-related death.
- ALK gene rearrangement research is required to predict crizotinib reaction.
- PD-L1 should be tested with an approved assay to model reactions in patients with advanced adenocarcinoma.
- miRNAs could be used as a dynamic tumor predictor before and during therapy.
- lncRNA sheds fresh insight on our tumor pathway perception.

Graphical Abstract



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Abstract

Lung cancer is the main cause of cancer-related death. Typically, lung cancer has been classified in two histologic types; small and non-small cell (NSC), with adenocarcinoma, squamous cell form and large cell type. The availability of predictive biomarkers for the treatment of NSC lung cancer (NSCLC) has been changed in recent decades, especially in the form of adenocarcinoma. Controlling for sensitizing mutations inside the epidermal growth factor receptor (EGFR) for patients with advanced adenocarcinomas is currently needed before the achievement of anti-EGFR inhibitors (such as erlotinib, gefitinib, afatinib or osimertinib). In a patient with no signs of tumor tissue, the EGFR mutational plasma and urine examination may be performed. ALK gene rearrangement research is required to predict crizotinib reaction. Treatment with ceritinib, alectinib or brigatinib also relies on ALK rearrangements. PD-L1 should be tested with an approved assay to model reactions in patients with advanced adenocarcinoma or squamous cell NSCLCs to the single pembrolizumab agent in their first-line therapy. As miRNAs are a vital biomarker (diagnostic biomarkers), miRNAs also could be used as a dynamic tumor predictor before and during therapy because of their function in carcinogenesis at all stages. Nevertheless, lncRNA sheds fresh insight into our tumor pathway perception. In biomedicine, lncRNA is intensely involved, which can be used for a wide variety of cancers as a clinical diagnostic and prediction predictor.

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Introduction

Given the wide range of clinical responses in cancer patients and narrow therapeutic indices of anticancer drugs, new approaches are critical in improving patient`s health for individual cancer care. Our molecular cancer awareness has driven us to move away from tumors primarily because of their anatomical location and molecular profile (1). The majority of study into genomic cancer has been centered on discovery and clarification until recently, but with our knowledge of tumor molecular profiling, the clinic is getting more accessible with genomic cancer medicines (2). If there is more clinically available research trials in which tumor biomarkers are detected, the therapeutic results of mutations in these molecular pathways must be recognized by doctors. The study could be directed with detail clinical cancer biomarkers, potential connection to lung cancer and the clinical trials to approve these biomarkers.

Biomarker Review

For pharmacogenomics analysis, the DNA of somatic or germ-lines can be used. Somatic mutations of tumors are particularly useful in definition of pharmacodynamics consequences of a drug, such as a tumor reaction that involves tumor biopsy. A peripheral blood sample can identify variations in the germ-line or the inherited blood, which can help assess medication activity and drug reactions (3). Cancer biomarkers may be divided into two categories; prognostic and predictive. A prognostic biomarker (i.e. anaplastic lymphoma kinase (ALK), epidermal growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene homolog (KRAS)) is useful in the definition of a drug reaction associated with the results of disease and therapy (4). Examples of biomarkers, both prognostic and predictive, are human epidermal growth factor receptor-2 (HER1), proto-oncogene BRAF, serine/threonine kinase (BRAF). A subset of predictive biomarkers are pharmacodynamic biomarkers and can guide dose selection by treating tests on the tumor or the host. ThiopurineS-methyltransferase (TPMT) is used to guide 6-mercaptopurine dosing and glucuronosyl uridine-diphosphate transferase 1A1 (UGT1A1) to monitor irinotecan dosage (5). Molecular-based therapies have greatly improved their ability to extend longevity in patients with lung cancer with EGFR mutations and/or ALK translocations. The Cancer Genome Atlas Network used messenger sequences RNA, microRNA and DNA to molecularly profile 230 resected lung adenocarcinomas, as well as copy numbers, methylation and proteomic tests. Statistically important mutations were reported in RIT1, EGFR, NF1, MET, ERBB2, RBM10 and other genes in the mitogen-activated protein kinase (MAPK) pathway, with frequencies of mutations exceeding 9 per megabase (6). While some known genes are not currently druggable, and their prognostic importance is uncertain, it is essential to create personalized lung cancer treatment with knowledge of these molecular mechanisms and their predictive capabilities. The final part of the paper addresses the cancer biomarkers eligible for targeted therapies, their impact on lung cancer patients and potential new drug goals.

BRAF gene

B-RAF proto-oncogene, also known as serine/threonine kinase (BRAF), is located on the long arm of the chromosome at position 34. A serine/threonine kinase participates in the signalling cascade RAS/RAF/MEK/ERK (7). BRAF phosphorylates MEK and promotes cell growth, spreading and survival through oncogenic mutations (8). The highest incidence of BRAF (27 to 70%) is malignant melanoma caused by papillary thyroid cancer, colorectal cancer, and serious ovarian cancer (9). In 1 to 3% of NSCLC patients, BRAF variants were also reported (10). In contrast with melanoma, only half of the BRAF mutations in NSCLC are V600E mutations. G469A (35%) and D594G (10%) are two other NSCLC nonV600E mutations. For all BRAF mutations, those driver mutations such as EGFR, KRAS and ALK are mutually exclusive (11, 12). BRAF-mutated NSCLC has been recorded to be exclusively adenocarcinoma compared to EGFR patients or ALK rearrangements.

Patients suffering from BRAF deficiencies are primarily former or past users, unlike patients with virtually no smokers with other genetic mutations (12). In contrast, patients with NSCLC and BRAF V600E mutations

have a lower prognosis and less tolerance to chemotherapy dependent on platinum than patients with wild-type BRAF. Treatment with inhibitors of BRAF and MEK also benefited the patients (13). BRAF inhibitors, such as vemurafenib and dabrafenib, are highly potent and selective to the BRAF kinase V600E mutant with estimated 80 to 90% reaction rates. Around 33 and 42% (13, 14). BRAF and MEK antagonists are being screened for BRAF mutation-positive NSCLC in clinical tests, such as trametinib, selumetinib and dasatinib.

C-KIT gene

The C-KIT gene is a kinase that is a proto-oncogene that codes for the tyrosine kinase of a receptor, which links to the ligand of the stem cell factor. As a result of this interaction, melanocytes, erythrocytes, germ cells, and mast cells all grow and lead to dimerization, auto-phosphorization and signal transduction (15). Although C-KIT gain-of-function mutations are present in approximately 85 per cent of GIST (gastrointestinal stromal tumors) and predict imatinib therapy, research shows that some 40% of small cell lung cancer (SCLC) overexpresses C-KIT (16). However, C-KIT expression in SCL C showed no significant impact as a biomarker for survival, probably due to the tumor microenvironment (17). The analysis also reveals that C-KIT mutations are a contributing factor for a bad prognosis (18). The current knowledge package on C-KIT inhibition in SCLC is limited and more research is required. It must be of prognostic and predictive importance.

EGFR

The epidermal growth factor (EGFR) receptor for tyrosine kinase receptor belongs to the ERBB class. The EGFR gene is situated at 12 on the short arm of chromosome 7 (19). When an extracellular ligand binds EGFR, it leads to homo- or heterodimerization of the receptor, leading to phosphatidylinositol 3-kinase phosphatic cytoplasmic tyrosine sites and various intracellular pathways. Rapamycin (mTOR) and RAS/RAF/mitogen-activated protein kinase (MAPK) aim pathways (PI3K). These pathways are involved in cell proliferation, metastasis and apoptosis prevention (20). EGFR is excessively expressed in 62% of NSCLCs, and its existence is related to poor prediction (21). Lung tumors associated with EGFR mutations impact about 10% of U.S. lung adenocarcinoma patients and between 30 and 50% of East Asian Lung adenocarcinoma patients (22). Exons 18-21 code for a certain portion of the EGFR kinase domain (23). Exon 19 in-frame deletions make up about 90% of EGFR mutations, while exon 21 mutations make up 44 and 41%, respectively, of all mutations (24). Activating mutations in the kinase domain of EGFR contributes to the activation of ligand-independent tyrosine kinase, resulting in receptor hyperactivation.

Downstream anti-apoptotic signaling pathways (25). Women never smokers with lepidic adenocarcinomas are more prone to have EGFR mutations (26). Treatment with tyrosine kinase inhibitors (TCIs), including gefitinib, has a considerable reaction time (55-78%). Due to the significantly improved progression-free survival (PFS) of erlotinib and afatinib treated EGFR-mutant tumors patients, EGFR TKI was the recommended treatment for such mutations (27). Due to the occurrence of a new chromosome, however, most of these patients develop tolerance and recurrence in a short time (T790M) Exon 20 of the EGFR (50%) kinase domain, reach oncogene amplification (21%), or PI3KCA mutations (28).

The most common methods for detecting EGFR mutations are gene sequence and reaction-based polymerase chain reactions (PCR). Both approaches have been established for productivity and specificity in identifying these mutations in formalin and paraffin-integrated tissues (29). EGFR mutants were tested using an IHC-based technique with novel antibodies against mutant proteins, but the results were deceptive. Sensitivity is diverse, and the measurements vary widely (30).

HER2

Preclinical evidence suggests that deregulation of HER2 may change tumor sensitivity to anti-EGFR medications. HER2, in fact, the primary EGFR partner and the activated heterodimeric complexes with HER2 are more stable on the cell surface than the EGFR family's other complexes that show in Figure 1 (31).

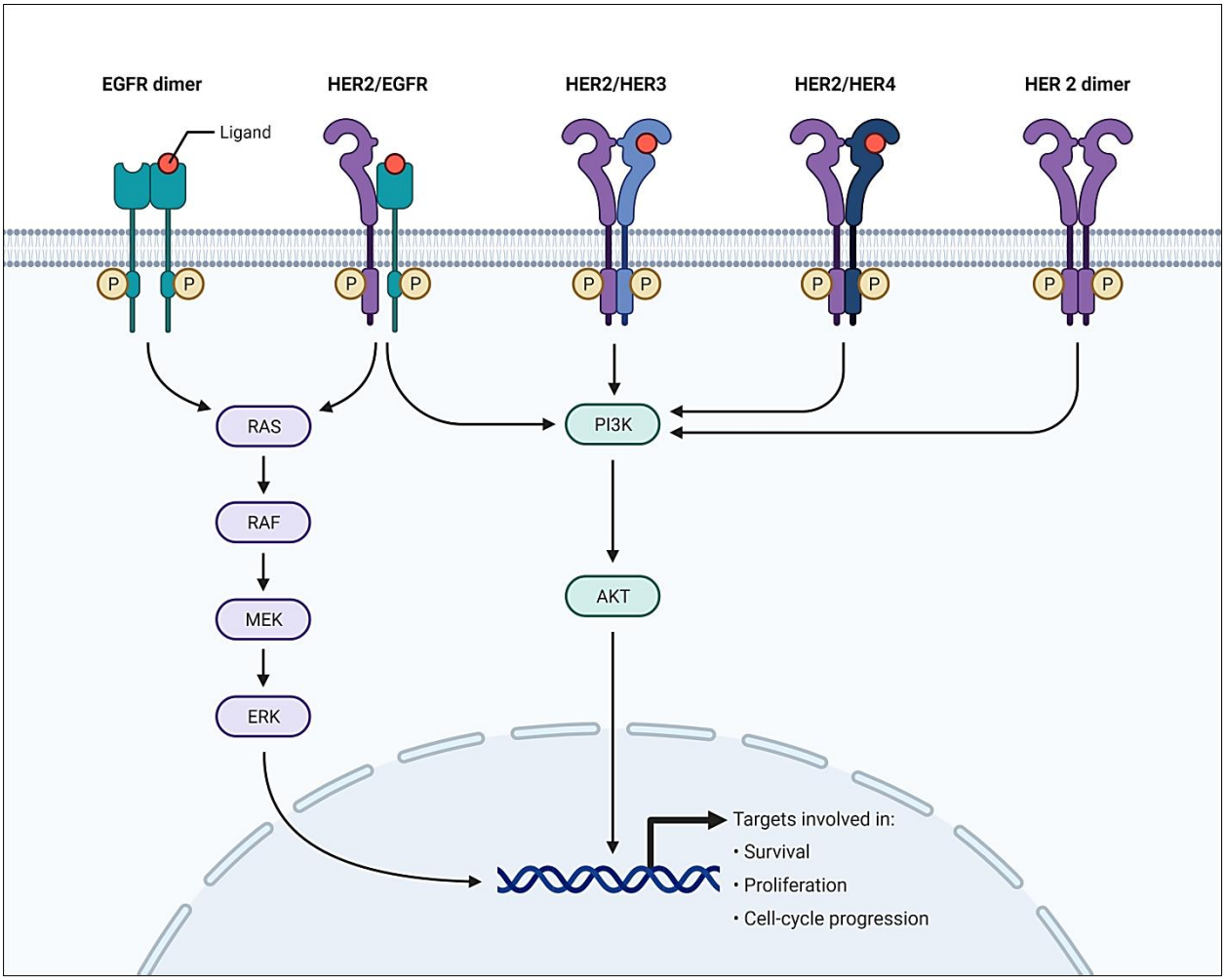

Figure 1. HER2 is the primary EGFR partner and the activated heterodimeric complexes on the cell surface.

The EGFR (32) dissociation of ligands from their cognate receptor may also slow down with HER2. Finally, EGFR-TK is small molecules that can block EGFR signals through phosphorylation of the intracellular domain of the protein TK (33, 34, 35). At the start of our EGFR study, a group of 63 NSCLC pretreated patients were examined 10 years ago in order to investigate the connection between HER2 expression and anti-EGFR care effectiveness concerning reaction rate (RR), development period (TTP) and overall survival (OS) (36). HER2 values scored on the scale of 0 to 3+ were calculated using IHC, with a staining force of 2+ or 3+ for more than 10 percent of the cells considered positive. IHC was used to evaluate EGFR amounts. Of the 43 HER2/EGFR patients analyzed, 15 (34,8%) were categorized as HER2 2+/3+, whereas 28 (65,2%) were classified as unfavourable. There was no significant difference between HER2 over-expressing and HER2 negative patients in terms of disease control severity (DCR: 40-64.3%), TT PTP (3.5-3.7 months), and SO (5.7-6.8 months), meaning that HER2 over-expression was not helpful to predict gefitinib susceptibility in unselected NSCLC patients (37, 38). In a detailed study, Looyenga et al., examined whether FISH-measured genomic gains of HER2 were associated with fitinib sensitivity in 102 pretreated advanced NSCLC patients to assess further the role of HER2 dysregulation in modular EGFR-TKI sensitivity (38). In 9% of cases, HER2 amplification has been detected, and all patients with high polysomy or gene amplification have been considered positive using the same EGFR criterion (39). Patients with HER2 FISH were higher than those with HER2 FISH negative, most certainly because HER2 GCN was compared to the key FITINIB predictors that are EGFR mutations. Takezawa et al., recently found that high HER2 amplification levels play a role in acquired EGFR-TKI resistance in around 12% of cases (26). Overall, these observations show the value of HER2 GCN with a strong predictive feature. EGFR and HER2 work together to make tumor cells highly dependent on the HER axis and more likely to be anti-EGFR therapy in the presence of an increased HER2 copy number. However, HER2 makes it an important

promoter of tumor growth and metastatic expansion without an EGFR inhibition. Related results have been published for metastatic colorectal cancer (mCRC) treated with monoclonal anti-EGFR antibody (40). In preclinical trials, the amplification of the HER2 gene was associated with cetuximab resistance since EGFR downstream paths were continued to activate when cetuximab binds to EGFR (41, 42). In 170 KRAS patients receiving cetuximab or panitumumab alone or in combination with chemotherapy (43), 4% had HER2 gene enhancement, 61% had HER2 enhancement due to polysomy and/or gene amplification in limited clones, and 35% had no or minor HER2 enhancement in conjunction with GCN HER2. HER2 amplified patients had poorer results in RR ($p = 0.0006$), progression-free survival (PFS; $p = 0.0001$), and total survival (OS, $p = 0.0001$). On the other hand, patients with HER2 polysomy have the highest chance of survival (44). Although HER2 mutations were reported in 2004, translational research in this specific molecular environment has only been widespread in the last few years. The presence of a mutation produces a conformational variation in the kinase domain of the receptor, resulting in greater kinase activity than the wild-type variety. In the absence of a ligand, HERYVMA may activate EGFR irrespective of the presence of triggering EGFR mutation (44, 45).

JAK2

Janus kinase 2 is a protein that controls Janus kina activity (JAK2) JAKs is non-receptor TKs that transmit intracellular signals from cytokines and factors of development. The mutation is a single nucleotide change at codon 617, contributing to a valine substitution for phenylalanine and affecting about 55% of patients with the condition. Myeloproliferative cell disorders (46). The transcript of many pro-proliferative and anti-apoptotic genes is increased as the JAK-STAT pathway is triggered. Ruxolitinib is the first FDA certified JAK inhibitor for myelofibrosis and myeloproliferative disorders.

In Week 48 in the COMFORT-II trial, the proportion of patients who received a 35% reduction in spleen volume was 28.5 percent in ruxolitinib and 0 percent in better possible treatments (P0.0001) (47). While NSCLC mutations of JAK are rare, evidence suggests that activation of JAK2 contributes to the acquired erlotinib resistance. The combination of JAK2 inhibition and erlotinib has retained the erlotinib sensitivity and decreased tumour size in erlotinib-resistant lung cancer cell lines in a murine xenograft model (48). Another research indicates that JAK2 stimulates STAT3, a commonly mutated pathway in NSCLC solid tumors, independently of other critical oncogenic motors. Ruxolitinib therapy has nevertheless been seen to work with NSCLC triggered with STAT3. Inhibition of growth was not observed in cell lines (49). Ruxolitinib inhibition JAK2 is currently being investigated in NSCLC chemotherapy/erlotinib patients in clinical trials (ClinicalTrials.gov).

KRAS gene

The carcinogenic Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation is the most common gain-of-function alteration, accounting for 30% of lung adenocarcinomas in Western countries and around 10% lung adenocarcinomas in Asian countries (50). KRAS is a membrane-bound small GTPase that switches between active GTP-bound and inactive GDP-bound states controlled by guanine nucleo (51). RAS's intrinsic GTPase activity is insufficient; however, in the presence of GAPs like neurofibromin 1 (NF1), it can raise its hydrolytic activity by many orders of magnitude. GEFs, such as the son of sevenless homolog 1 (SOS1), mediate the reactivation of GDP-bound RAS by promoting the release of bound GDP, which cellular GTP then replaces to bind to RAS. Mutations that hinder KRAS' capacity to hydrolyze GTP are assumed to trap the oncoprotein in a constitutively active state through triggering downstream signalling cascades, resulting in unregulated cell proliferation and survival. The majority of KRAS mutations occur in codon 12, although mutations in codons 13 and 61 are less common (52). In lung cancer, significant progress has been made in developing molecularly-driven therapeutics, primarily including targeted therapies against oncogenic drivers such as EGFR, HER2, EML4-ALK, MET, ROS1, and BRAF mutations, as well as immunotherapy (53, 54). However, therapeutic choices for KRAS-mutant lung cancer are also restricted, and chemotherapies are still the first-line recommendation.

Update the most current scientifically essential aspects of the pathobiology of KRAS-mutant non-small cell lung cancer (NSCLC) in this study, emphasising tumor heterogeneity, therapeutic effects, and novel treatment options. The presence of a KRAS amino acid substitute in lung cancer patients impacts their prognosis and is related to a weak reaction to targeted therapy (55, 56) and chemotherapy (57, 58, 59). According to molecular modelling studies, different conformations placed by different KRAS oncogene substitutions could lead to altered interaction with downstream signalling transducers (60). In particular, the mutant KRASG12C or KRASG12V is less reliant on AKT than wild-type KRAS, but other mutant KRAS proteins are more intimately involved.

Different amino acid substitutions in mutant KRAS have been linked to different biological behaviors (61) and clinical effects (62, 63, 64). KRASG12C-positive tumors had more significant phosphorylation of ERK1/2 than KRASG12D-positive tumors in KRAS-mutant lung cancer (65). Studies using a genetically modified mouse model found that KrasG12C tumors were substantially more susceptible to MEK inhibitor than KrasG12D tumors, and that MEK inhibition enhanced chemotherapeutic efficacy and progression-free survival (PFS) in KRASG12C mice. As various amino acid substitutions in oncogenic KRAS are combined, they result in variation in the mutant protein's biological activities, suggesting the need for genotype-specific research to classify clinically significant subgroups of patients that can eventually affect care decisions. It can also be considered when inhibiting various downstream signalling mechanisms for patients with KRAS amino acid substitutions in their tumors.

miRNA

miRNA expression profiles are highly specific to individual types of cells, tissues, and organs (66), and unique miRNA sequences have been discovered in corresponding healthy and malignant tissues (67). More than half of all miRNAs in humans are found in sensitive chromosome regions that undergo amplification, deletion, and translocation during carcinogenesis (68, 69). Mutations in essential oncogenes (e.g., KRAS and HER2/neu) are found at the pre-invasive carcinoma level (carcinoma in situ). The involvement of several genetic and epigenetic changes in tumor cells characterizes invasive lung carcinoma (70). This results in deregulated expression of some miRNAs (71), resulting in dramatic improvements in their concentrations and formulations, as well as their movements (referred to as miRNA under- or overexpression), and these miRNAs are possible clinical biomarkers (72, 73). Previous research has verified the utility of miRNAs as NSCLC biomarkers (74, 75).

He et al., (63) (510 patients and 465 safe volunteers) and Wang et al., (31) (2121 patients and 1582 volunteers) conducted meta-analyses that looked at the overall diagnostic success of miRNA and the variables that may influence its diagnostic accuracy in NSCLC. In both studies, panels with multiple miRNAs had a much higher diagnostic utility than single miRNAs and had a much greater use potential as possible NSCLC biomarkers. A single miRNA biomarker had a sensitivity of 78.3 percent in detecting early-stage NSCLC in a meta-analysis performed by He et al., (63), while a miRNA panel had a sensitivity of 83 percent. Wang et al., (31) obtained similar findings, with 77% sensitivity and 71% specificity for a single miRNA and 83% sensitivity and 82% specificity for several miRNAs. However, it is important to note that the approximately 80% sensitivity recorded in those studies is minimal diagnostic value without more risk group stratification (76, 77, 78, 79).

Importantly, numerous studies have shown the effectiveness of utilizing several miRNA signatures as biomarkers for cancer screening or assessment of high-risk populations. Investigators in the Moderate screening study measured the diagnostic efficiency of plasma microRNAs as complementary biomarkers for LDCT screening in a population of active or former smokers aged 50 and up (80). They looked at plasma miRNA signatures in samples from 939 people, including 69 lung cancer patients and 870 disease-free people. The sensitivity and specificity of miRNAs for lung cancer diagnosis were 87 percent and 81%, respectively; the negative predictive value (NPV) was 99%. The use of both miRNA and LDCT resulted in a fivefold reduction in the LDCT false-positive incidence. In the COSMOS lung cancer screening study, another group of researchers used a 13 miRNA signature on 1115 participants (heavy smokers over 50 years old) and recorded sensitivity

and precision of 79.2 and 75.9%, respectively, with an NPV of 99% (81). The investigators proposed that the miRNA test should be used as a first-line diagnostic technique in high-risk individuals after observing an adverse outcome in 810 of the 1067 (76%) individuals without lung cancer and 10 of the 48 (21%) individuals with lung cancer.

However, miRNAs are useful for more than just early detection of NSCLC (82, 83). With sensitivities and specificities in the range of 60-100%, miRNA panels will distinguish NSCLC from benign lesions and assess the histological tumor form from a tissue sample (84, 85, 86). According to Boeri et al., (65), unique miRNAs detected in plasma samples obtained from stable smokers with an average exposure of 40 pack-years enabled for the detection of those with NSCLC 1-2 years before the first signs of lung cancer appeared, as well as the determination of their prognoses. Cazzoli et al., tested 742 miRNAs derived from circulating exosomes and found four miRNAs (miR-378a, miR-379, miR-139-5p, and miR-200b-5p) to be screening markers for distinguishing lung adenocarcinoma and granuloma patients from stable former smokers (AUC = 0.908; P 0.001) (68). The researchers then discovered six miRNAs (miR-151a-5p, miR-30a-3p, miR-200b-5p, miR-629, miR-100, and miR-154-3p) that distinguished between lung adenocarcinoma and lung granuloma patients (AUC = 0.760; P 0.001). Early identification of lung cancer using specific miRNAs, which is usually not feasible with traditional imaging techniques, opens the door to creating more accurate diagnostic algorithms. In comparison to research examining the utility of miRNAs as diagnostic and prognostic indicators, verification of miRNAs' predictive importance in the treatment of NSCLC has received comparatively little study (87).

LncRNA

There is much evidence that human genome lncRNA transcripts include biological processes related to lung cancer.

MALAT1

MALAT1a is also known as nuclear-enriched abundant transcript 2 (NEAT2). MALAT1 is often distributed in human tissues regularly and is found in nuclear spikes (88). It is one of the first lncRNAs associated with lung cancer and demonstrates the diffusion of Adenoma carcinoma. Metastasis-related genes are mainly expressed in histological cases and the development of diseases (89). MALAT1 has two possible action modes. MALAT1 can regulate alternate pre-mRNAs splicing by modulating serine/arginine splicing phosphorylation factors in the first model (90). In order to regulate genes which control growth between polycomb bodies and inter-chromatinous granules, MALAT1 can interact with the demethylated chromo box homolog 4 (CBX4), also known as polycomb 2 (Pc2) (91). The exact findings of MALAT1 are, however, still uncertain. In most tumors, MALAT1 is increased and has metastases, cell proliferation, apoptosis, migration and clinically poor prognosis (92, 93, 94). MALAT1 was also the first lncRNA used for selective treatment of lung cancer using lncRNA molecules. Antisense oligonucleotides (ASOs) suppress MALAT1, significantly reducing lung cancer metastasis in a mouse model (95).

HOTAIR

Hox transcript antisense RNA is one of the few well-studied lncRNAs (HOTAIR). It can be found in chromosome 12. It is present in the nucleus and contributes to trans-silencing (96). HOTAIR was first identified to be one of 231 lncRNAs associated with HOX loci in foreskin fibroblasts, where the HOXD locus could serve 40 kb of transcription in transcription (97). HOTAIR overexpression activates PRC2, containing EZH2 and SUZ12 and EED protein polycomb. As a consequence of this pan-genomic impact, H3K27 methylation and gene expression patterns are changed, enhancing cancer invasiveness and metastase (98, 99). Metastasis can include lymph nodes with far higher precision in later cancer and tumor levels (100). Cell invasion, proliferation and activation of the cell cycle were all impeded by removing the HOTAIR gene.

Apoptosis induced by HOTAIR is a direct inhibitor of the growth of cancer (101, 102). Its NSCLC role has not yet been fully known. Knocking the HOTAIR gene in vitro and in vivo will avoid NSCLC invasion and metastasis. The invasion of NSCLC cells may be affected in part by the regulation of HOXA5 expression. Compared to patients with higher HOTAIR expression, the overall survival time of cancer patients is marginally longer (103). HOTAIR seems to be directly involved in modulating and controlling cancer development; as the above data indicate, HOTAIR may be used to track the growth of NSCLC as a possible prognostic biomarker.

CDKN2B

CDKN2B-AS1 is a protein produced by the CDKN2B gene , CDKN2B antisense RNA 1 (CDKN2B-AS1), also classified as antisense non-coding RNA in the INK4 locus (ANRIL), which is distributed in the opposite direction of the INK4A-ARF-INK4B gene cluster and plays an anti-tumorigenesis role (104). The majority of ANRIL is in the nucleus. ANRIL activates repressive complexes Polycomb, PRC1 and PRC2, injecting chromatin and gene cluster silence that code for tumor suppressor types p16INK4A, p14ARF and p15INK4B. ANRIL inhibits cell replication, ageing and apoptosis triggered by tension. Phospholipase D (PLD) dysregulation inhibition contributed to improved ANRIL expression (105). ANRIL promotes apoptosis and autophagy, which inhibits cancer development. Using small interfering RNA to knock ANRIL significantly decreased PLD inhibition, leading to apoptosis. Using an inhibition of ANRIL and PLD may be a novel and effective approach to treat lung cancer (105). According to Nie et al., NSCLC cell proliferation and apoptosis may be regulated by ANRIL (85, 94). It has been found that ANRIL can bind to PRC2 and repress Kruppel-like transcription of factor 2 (KLF2) and P21. The designers proposed that silencing KLF2 may affect the oncogenic properties of ANRIL (106).

CCAT2

Ling et al., found colon cancer-associated lncRNA molecule transcript 2 (CCAT2) (86). The polymorphism of SNP rs6983267 is located in this locus and is transcribed by chromosome 8. Components of the DNA enhancers are located in the SNP genomic region. Both transcription factor versions 7-like 2 [T-cell unique, HMG-Box] were found to have different binding affinities (TCF7L2). CCAT2 can affect the transcription of the TCF7L2 gene and regulate the target genes of the WNT gene by binding and modulating the transcription factor. This would probably be done in two ways: by modulating the connection between TCF7L2 and negative Groucho/TLE and CTBP 1 and CTNNB1 and the CTNNB1 or by changing TCF7L2 activities by forming a bridge in transcriptional complexes between TCF7L2 and other proteins (107). This polymorphism has been associated with a higher prevalence of lung cancer and a worse prognosis in Han Chinese citizens (108). In GG polymorphism patients, the expression of CCAT2 transcripts is increased and may suggest that CCAT2 is a potential biomarker for metastatic cancer (109, 110). CCAT2 overexpression is a natural occurrence leading to the development of AC. This enzyme has now acquired a new name: lung adenocarcinoma-specific lncRNAs and may play a part in developing these lncRNAs. CCAT2 is a molecule whose overexpression is only seen in AC, but a recent study shows that lncRNA may be used in NSCLC as a diagnostic marker. CCAT2 was known to play a role in cancerogenesis and metastases as an oncogenic lncRNA (111, 112, 113).

PVT1

Pvt1 oncogene is a nuclear-positioned lincRNA on chromosome 15 (114). The gene for translocation of the mouse plasmacytoma variant is homologous. In several human tumors, PVT1 is found to be overexpressed (115). Wang et al., observed that PVT1 behavior stimulates the cell proliferation and cell cycle by offering them characteristics similar to stem cells by stabilizing nucleic protein (NOP2) in hepatocellular carcinoma (HCC) cells (NOP2) (91, 95). Takahashi et al., showed that higher PVT1 expression is correlated with poor prognosis in patients with colon cancer (92). Cui et al., found that increased PVT1 expression in the tissues of NSCLC was

related to advanced tumor phase (T characteristic), advanced tumour-node-metastasis (TNM) and regional lymph nodes (93). According to the results, PVT1 continues to function in tumorigenesis and NSCLC progression. According to Cui et al., knockdown of PVT1 greatly inhibits cell proliferation and over-expression. In comparison, the knockdown of PVT1 raises the number of cells at level G0/G1, reducing the number of cells at stage S (93). CDKN1A/P21 and CDKN2B/P15 are inhibitors of cell cycle control that inhibit cell development. In cells transfected with PVT1 siRNA, the P15 and P21 proteins were substantially up-regulated and down-regulated in cells transfected with pcDNA3.1- PVT1 has also been shown that PVT1 facilitates the growth of NSCLC cancer cell by modulating expression of P15 and P21 (115).

Concluion

In addition to the EGFR as mentioned earlier, ALK, and C-KIT, JAK2, and KRAS mutations, some other potentially operable mutations may be identified in NSCLC. Among these are MET mutations/amplifications, BRAF mutations, and HER2 mutations/amplification. Instead of evaluating these improvements one by one, scientists are increasingly interested in using NGS to research multiple genes (16, 17, 18) concurrently. It has been almost twenty years since miRNAs were detected, and many studies subsequently based on the ability to use these small regulatory molecules as biomarkers for multiple types of cancer, like NSCLC. MiRNAs can be used not only as of essential biomarkers (diagnostic biomarkers) but also as a dynamic tumor predictor before and during therapy due to their involvement in carcinogenesis at all stages (prognostic biomarkers) (predictive biomarkers). In the early stages of lung cancer development, extracellular miRNAs secreted into the blood and other body fluids in a healthy form by tumor cells seem to be particularly helpful in clinical practice. Their key advantage is the flexibility of their quantitative and qualitative changes to be monitored in real-time and in every stage of the disease without causing patients anxiety by invasive testing specimen collection. Significant technological progress has been made in detecting and identifying miRNA in the last decade, especially in high-performance techniques such as NGS.

Finally, with the number and functions of known lncRNAs expanded, researchers proposed various therapeutic applications for these molecules. While several critical questions remain unresolved, lncRNA sheds fresh insight into our perception of the mechanisms of the tumor. In bio-medicine, lncRNA has several promises and can be used for a wide variety of cancers as a scientific diagnostic and forecast predictor. They can also have medical effects that include several years of research before they can be utilized entirely.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: Cancer J Clinic 2015; 65(1): 5-29. https://doi.org/10.3322/caac.21254
2. Cagle PT, Allen TC, Olsen RJ. Lung cancer biomarkers: present status and future developments. Arch Pathol Lab Med 2013; 137(9): 1191-8119. https://doi.org/10.5858/arpa.2013-0319-CR
3. Fujimoto J, Wistuba II. Current concepts on the molecular pathology of non-small cell lung carcinoma. Semin Diagn Pathol 2014; 31(4): 306-313. https://doi.org/10.1053/j.semdp.2014.06.008
4. Kerr KM, Bubendorf L, Edelman MJ, Marchetti A, Mok T, Novello S, O'Byrne K, Stahel R, Peters S, Felip E, Stahel R. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. Ann Oncol 2014; 25(9): 1681-1690. https://doi.org/10.1093/annonc/mdu145
5. Mok TS. Personalized medicine in lung cancer: what we need to know. Nat Rev Clin Oncol 2011; 8(11): 661-668. https://doi.org/10.1038/nrclinonc.2011.126
6. Cardarella S, Ogino A, Nishino M, Butaney M, Shen J, Lydon C, Yeap BY, Sholl LM, Johnson BE, Jänne PA. Clinical, pathologic, and biologic features associated with BRAF mutations in non–small cell lung cancer. Clin Cancer Res 2013; 19(16): 4532-4540. https://doi.org/10.1158/1078-0432.CCR-13-0657
7. Garnett MJ, Marais R. Guilty as charged: B-RAF is a human oncogene. Cancer Cell 2004; 6(4): 313-319. https://doi.org/10.1016/j.ccr.2004.09.022

8. Paik PK, Arcila ME, Fara M, Sima CS, Miller VA, Kris MG, Ladanyi M, Riely GJ. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clinical Oncol 2011; 29(15): 2046.
9. Planchard D, Kim TM, Mazieres J, Quoix E, Riely G, Barlesi F, Souquet PJ, Smit EF, Groen HJ, Kelly RJ, Cho BC. Dabrafenib in patients with BRAFV600E-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. Lancet Oncol 2016; 17(5): 642-650. https://doi.org/10.1016/S1470-2045(16)00077-2
10. Hyman DM, Puzanov I, Subbiah V, Faris JE, Chau I, Blay JY, Wolf J, Raje NS, Diamond EL, Hollebecque A, Gervais R. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. New Engl J Med 2015; 373(8): 726-736. https://doi.org/10.1056/nejmoa1502309
11. Yasuda A, Sawai H, Takahashi H, Ochi N, Matsuo Y, Funahashi H, Sato M, Okada Y, Takeyama H, Manabe T. Stem cell factor/c-kit receptor signaling enhances the proliferation and invasion of colorectal cancer cells through the PI3K/Akt pathway. Dig Dis Sci 2007; 52(9): 2292-2300. https://doi.org/10.1007/s10620-007-9759-7
12. Heinrich MC, Corless CL, Demetri GD, Blanke CD, Von Mehren M, Joensuu H, McGreevey LS, Chen CJ, Van den Abbeele AD, Druker BJ, Kiese B. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003; 21(23): 4342-4349. https://doi.org/10.1200/JCO.2003.04.190
13. Boldrini L, Ursino S, Gisfredi S, Faviana P, Donati V, Camacci T, Lucchi M, Mussi A, Basolo F, Pingitore R, Fontanini G. Expression and mutational status of c-kit in small-cell lung cancer: prognostic relevance. Clin Cancer Res 2004; 10(12): 4101-4108. https://doi.org/10.1158/1078-0432.CCR-03-0664
14. Barlesi F, Blons H, Beau-Faller M, Rouquette I, Ouafik LH, Mosser J, Merlio JP, Bringuier PP, Jonveaux P, Le Marechal C, Denis MG. Biomarkers (BM) France: results of routine EGFR, HER2, KRAS, BRAF, PI3KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 non-small cell lung cancer (NSCLC) patients (pts). https://doi.org/10.1200/jco.2013.31.15_suppl.8000
15. Rekhtman N, Paik PK, Arcila ME, Tafe LJ, Oxnard GR, Moreira AL, Travis WD, Zakowski MF, Kris MG, Ladanyi M. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res 2012; 18(4): 1167-1176. https://doi.org/10.1158/1078-0432.CCR-11-2109
16. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004; 304(5676): 1497-1500. https://doi.org/10.1126/science.1099314
17. Pao W, Miller V, Zakowski M, Doherty J, Politi K, Sarkaria I, Singh B, Heelan R, Rusch V, Fulton L, Mardis E. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Nat Acad Sci 2004; 101(36): 13306-13311. https://doi.org/10.1073/pnas.0405220101
18. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, Fujiwara SI, Watanabe H, Kurashina K, Hatanaka H, Bando M. Identification of the transforming EML4–ALK fusion gene in non-small-cell lung cancer. Nature 2007; 448(7153): 561-566. https://doi.org/10.1038/nature05945
19. Lenferink AE, Pinkas-Kramarski R, van de Poll ML, van Vugt MJ, Klapper LN, Tzahar E, Waterman H, Sela M, van Zoelen EJ, Yarden Y. Differential endocytic routing of homo-and hetero-dimeric ErbB tyrosine kinases confers signaling superiority to receptor heterodimers. EMBO J 1998; 17(12): 3385-3397. https://doi.org/10.1093/emboj/17.12.3385
20. Karunagaran D, Tzahar E, Beerli RR, Chen X, Graus-Porta D, Ratzkin BJ, Seger R, Hynes NE, Yarden Y. ErbB-2 is a common auxiliary subunit of NDF and EGF receptors: implications for breast cancer. EMBO J 1996; 15(2): 254-264. http://doi.org/10.1002/j.1460-2075.1996.tb00356.x

21. Moasser MM, Basso A, Averbuch SD, Rosen N. The tyrosine kinase inhibitor ZD1839 ("Iressa") inhibits HER2-driven signaling and suppresses the growth of HER2-overexpressing tumor cells. Cancer Res 2001; 61(19): 7184-7188.
22. Moulder SL, Yakes FM, Muthuswamy SK, Bianco R, Simpson JF, Arteaga CL. Epidermal growth factor receptor (HER1) tyrosine kinase inhibitor ZD1839 (Iressa) inhibits HER2/neu (erbB2)-overexpressing breast cancer cells in vitro and in vivo. Cancer Res 2001; 61(24): 8887-8895.
23. Anido J, Matar P, Albanell J, Guzmán M, Rojo F, Arribas J, Averbuch S, Baselga J. ZD1839, a specific epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, induces the formation of inactive EGFR/HER2 and EGFR/HER3 heterodimers and prevents heregulin signaling in HER2-overexpressing breast cancer cells. Clin Cancer Res 2003; 9(4): 1274-1283.
24. Cappuzzo F, Gregorc V, Rossi E, Cancellieri A, Magrini E, Paties CT, Ceresoli G, Lombardo L, Bartolini S, Calandri C, De Rosa M. Gefitinib in pretreated non–small-cell lung cancer (NSCLC): Analysis of efficacy and correlation with HER2 and epidermal growth factor receptor expression in locally advanced or metastatic NSCLC. J Clin Oncol 2003; 21(14): 2658-2663. https://doi.org/10.1200/JCO.2003.01.039
25. Cappuzzo F, Hirsch FR, Rossi E, Bartolini S, Ceresoli GL, Bemis L, Haney J, Witta S, Danenberg K, Domenichini I, Ludovini V. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non–small-cell lung cancer. J Nat Cancer Inst 2005; 97(9): 643-655. https://doi.org/10.1093/jnci/dji112
26. Takezawa K, Pirazzoli V, Arcila ME, Nebhan CA, Song X, de Stanchina E, Ohashi K, Janjigian YY, Spitzler PJ, Melnick MA, Riely GJ. HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. Cancer Discov 2012; 2(10): 922-933. https://doi.org/10.1158/2159-8290.CD-12-0108
27. Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, Ercan D, Rogers A, Roncalli M, Takeda M, Fujisaka Y. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. Sci Translat Med 2011; 3(99): 99ra86-. https://doi.org/10.1126/scitranslmed.3002442
28. Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, Corà D, Di Nicolantonio F, Buscarino M, Petti C, Ribero D. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. Cancer Discov 2011; 1(6): 508-523. https://doi.org/10.1158/2159-8290.CD-11-0109
29. Martin V, Landi L, Molinari F, Fountzilas G, Geva R, Riva A, Saletti P, De Dosso S, Spitale A, Tejpar S, Kalogeras KT. HER2 gene copy number status may influence clinical efficacy to anti-EGFR monoclonal antibodies in metastatic colorectal cancer patients. Br J Cancer 2013; 108(3): 668-675. https://doi.org/10.1038/bjc.2013.4
30. Agus DB, Akita RW, Fox WD, Lewis GD, Higgins B, Pisacane PI, Lofgren JA, Tindell C, Evans DP, Maiese K, Scher HI. Targeting ligand-activated ErbB2 signaling inhibits breast and prostate tumor growth. Cancer Cell 2002; 2(2): 127-137. https://doi.org/10.1016/S1535-6108(02)00097-1
31. Wang SE, Narasanna A, Perez-Torres M, Xiang B, Wu FY, Yang S, Carpenter G, Gazdar AF, Muthuswamy SK, Arteaga CL. HER2 kinase domain mutation results in constitutive phosphorylation and activation of HER2 and EGFR and resistance to EGFR tyrosine kinase inhibitors. Cancer Cell 2006; 10(1): 25-38. https://doi.org/10.1016/j.ccr.2006.05.023
32. Kilpivaara O, Mukherjee S, Schram AM, Wadleigh M, Mullally A, Ebert BL, Bass A, Marubayashi S, Heguy A, Garcia-Manero G, Kantarjian H. A germline JAK2 SNP is associated with predisposition to the development of JAK2 V617F-positive myeloproliferative neoplasms. Nat Genet 2009; 41(4): 455-459. https://doi.org/10.1038/ng.342
33. Ostojic A, Vrhovac R, Verstovsek S. Ruxolitinib for the treatment of myelofibrosis: its clinical potential. Ther Clin Risk Manag 2012; 8: 95. https://doi.org/10.2147/TCRM.S23277
34. Harada D, Takigawa N, Ochi N, Ninomiya T, Yasugi M, Kubo T, Takeda H, Ichihara E, Ohashi K, Takata S, Tanimoto M. JAK 2-related pathway induces acquired erlotinib resistance in lung cancer cells harboring an

epidermal growth factor receptor-activating mutation. Cancer Sci 2012; 103(10): 1795-1802. https://doi.org/10.1111/j.1349-7006.2012.02363.x

35. Riely GJ, Marks J, Pao W. KRAS mutations in non–small cell lung cancer. Proc Am Thor Soc 2009; 6(2): 201-205. https://doi.org/10.1513/pats.200809-107LC
36. Dearden S, Stevens J, Wu YL, Blowers D. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol 2013; 24(9): 2371-2376. https://doi.org/10.1093/annonc/mdt205
37. Kranenburg O. The KRAS oncogene: past, present, and future. Biochim Biophys Acta 2005; 1756(2): 81-82. https://doi.org/10.1016/j.bbcan.2005.10.001
38. Looyenga BD, Hutchings D, Cherni I, Kingsley C, Weiss GJ, MacKeigan JP. STAT3 is activated by JAK2 independent of key oncogenic driver mutations in non-small cell lung carcinoma. PloS One 2012; 7(2): e30820. https://doi.org/10.1371/journal.pone.0030820
39. Cortinovis D, Abbate M, Bidoli P, Capici S, Canova S. Targeted therapies and immunotherapy in non-small-cell lung cancer. Cancer Med Sci 2016; 10. https://doi.org/10.3332/ecancer.2016.648
40. Nagano T, Tachihara M, Nishimura Y. Molecular mechanisms and targeted therapies including immunotherapy for non-small cell lung cancer. Curr Cancer Drug Targets 2019; 19(8): 595-630. https://doi.org/10.2174/1568009619666181210114559
41. Rulli E, Marabese M, Torri V, Farina G, Veronese S, Bettini A, Longo F, Moscetti L, Ganzinelli M, Lauricella C, Copreni E. Value of KRAS as prognostic or predictive marker in NSCLC: results from the TAILOR trial. Ann Oncol 2015; 26(10): 2079-2084. https://doi.org/10.1093/annonc/mdv318
42. Papadimitrakopoulou V, Lee JJ, Wistuba II, Tsao AS, Fossella FV, Kalhor N, Gupta S, Byers LA, Izzo JG, Gettinger SN, Goldberg SB. The BATTLE-2 study: a biomarker-integrated targeted therapy study in previously treated patients with advanced non–small-cell lung cancer. J Clin Oncol 2016; 34(30): 3638. https://doi.org/10.1200/JCO.2015.66.0084
43. Garassino MC, Marabese M, Rusconi P, Rulli E, Martelli O, Farina G, Scanni A, Broggini M. Different types of K-Ras mutations could affect drug sensitivity and tumour behaviour in non-small-cell lung cancer. Ann Oncol 2011; 22(1): 235-237. https://doi.org/10.1093/annonc/mdq680
44. Park S, Kim JY, Lee SH, Suh B, Keam B, Kim TM, Kim DW, Heo DS. KRAS G12C mutation as a poor prognostic marker of pemetrexed treatment in non-small cell lung cancer. Korean J Int Med 2017; 32(3): 514. https://doi.org/10.3904/kjim.2015.299
45. Renaud S, Guerrera F, Seitlinger J, Reeb J, Voegeli AC, Legrain M, Mennecier B, Santelmo N, Falcoz PE, Quoix E, Chenard MP. KRAS-specific amino acid substitutions are associated with different responses to chemotherapy in advanced non–small-cell lung cancer. Clin Lung Cancer 2018; 19(6): e919-e931. https://doi.org/10.1016/j.cllc.2018.08.005
46. Ihle NT, Byers LA, Kim ES, Saintigny P, Lee JJ, Blumenschein GR, Tsao A, Liu S, Larsen JE, Wang J, Diao L. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. J Nat Cancer Inst 2012; 104(3): 228-239. https://doi.org/10.1093/jnci/djr523
47. Renaud S, Seitlinger J, Falcoz PE, Schaeffer M, Voegeli AC, Legrain M, Beau-Faller M, Massard G. Specific KRAS amino acid substitutions and EGFR mutations predict site-specific recurrence and metastasis following non-small-cell lung cancer surgery. Br J Cancer 2016; 115(3): 346-353. https://doi.org/10.1038/bjc.2016.182
48. Helena AY, Sima CS, Shen R, Kass S, Gainor J, Shaw A, Hames M, Iams W, Aston J, Lovly CM, Horn L. Prognostic impact of KRAS mutation subtypes in 677 patients with metastatic lung adenocarcinomas. J Thor Oncol 2015; 10(3): 431-437. https://doi.org/10.1097/JTO.0000000000000432
49. Fu XH, Chen ZT, Wang WH, Fan XJ, Huang Y, Wu XB, Huang JL, Wang JX, Lin HJ, Tan XL, Wang L. KRAS G12V mutation is an adverse prognostic factor of Chinese gastric cancer patients. J Cancer 2019; 10(4): 821. https://doi.org/10.7150/jca.27899

50. Wiesweg M, Kasper S, Worm K, Herold T, Reis H, Sara L, Metzenmacher M, Abendroth A, Darwiche K, Aigner C, Wedemeyer HH. Impact of RAS mutation subtype on clinical outcome—a cross-entity comparison of patients with advanced non-small cell lung cancer and colorectal cancer. Oncogene 2019; 38(16): 2953-2966. https://doi.org/10.1038/s41388-018-0634-0
51. Li S, Liu S, Deng J, Akbay EA, Hai J, Ambrogio C, Zhang L, Zhou F, Jenkins RW, Adeegbe DO, Gao P. Assessing therapeutic efficacy of MEK inhibition in a KRASG12C-driven mouse model of lung cancer. Clin Cancer Res 2018; 24(19): 4854-4864. https://doi.org/10.1158/1078-0432.CCR-17-3438
52. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, Sweet-Cordero A, Ebert BL, Mak RH, Ferrando AA, Downing JR. MicroRNA expression profiles classify human cancers. Nature 2005; 435(7043): 834-838. https://doi.org/10.1038/nature03702
53. Ferdin J, Kunej T, Calin GA. Non-coding RNAs: identification of cancer-associated microRNAs by gene profiling. Technol Cancer Res Treat 2010; 9(2): 123-138. http://doi.org/10.1177/153303461000900202
54. Calin GA, Sevignani C, Dumitru CD, Hyslop T, Noch E, Yendamuri S, Shimizu M, Rattan S, Bullrich F, Negrini M, Croce CM. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Nat Acad Sci 2004; 101(9): 2999-3004. https://doi.org/10.1073/pnas.0307323101
55. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. Dev Biol 2007; 302(1): 1-2. https://doi.org/10.1016/j.ydbio.2006.08.028
56. Hirsch FR, Franklin WA, Gazdar AF, Bunn PA. Early detection of lung cancer: clinical perspectives of recent advances in biology and radiology. Clin Cancer Res 2001; 7(1): 5-22. ISSN: 10780432
57. Esquela-Kerscher A, Slack FJ. Oncomirs—microRNAs with a role in cancer. Nat Rev Cancer 2006; 6(4): 259-269. https://doi.org/10.1038/nrc1840
58. Yu SL, Chen HY, Chang GC, Chen CY, Chen HW, Singh S, Cheng CL, Yu CJ, Lee YC, Chen HS, Su TJ. MicroRNA signature predicts survival and relapse in lung cancer. Cancer Cell 2008; 13(1): 48-57. https://doi.org/10.1016/j.ccr.2007.12.008
59. Dvinge H, Git A, Gräf S, Salmon-Divon M, Curtis C, Sottoriva A, Zhao Y, Hirst M, Armisen J, Miska EA, Chin SF. The shaping and functional consequences of the microRNA landscape in breast cancer. Nature 2013; 497(7449): 378-382. https://doi.org/10.1038/nature12108
60. Nasser MW, Datta J, Nuovo G, Kutay H, Motiwala T, Majumder S, Wang B, Suster S, Jacob ST, Ghoshal K. Down-regulation of micro-RNA-1 (miR-1) in lung cancer: suppression of tumorigenic property of lung cancer cells and their sensitization to doxorubicin-induced apoptosis by miR-1. J Biol Chem 2008; 283(48): 33394–33405. https://doi.org/10.1074/jbc.M804788200
61. Garofalo M, Quintavalle C, Di Leva G, Zanca C, Romano G, Taccioli C, Liu CG, Croce CM, Condorelli G. MicroRNA signatures of TRAIL resistance in human non-small cell lung cancer. Oncogene 2008; 27(27): 3845-3855. https://doi.org/10.1038/onc.2008.6
62. Hayashita Y, Osada H, Tatematsu Y, Yamada H, Yanagisawa K, Tomida S, Yatabe Y, Kawahara K, Sekido Y, Takahashi T. A polycistronic microRNA cluster, miR-17-92, is overexpressed in human lung cancers and enhances cell proliferation. Cancer Res 2005; 65(21): 9628-9632.
63. He WJ, Li WH, Jiang B, Wang YF, Xia YX, Wang L. MicroRNAs level as an initial screening method for early-stage lung cancer: a bivariate diagnostic random-effects meta-analysis. Int J Clin Exp Med 2015; 8(8): 12317.
64. Wang H, Wu S, Zhao L, Zhao J, Liu J, Wang Z. Clinical use of micro RNA s as potential non-invasive biomarkers for detecting non-small cell lung cancer: A meta-analysis. Respirology 2015; 20(1): 56-65. https://doi.org/10.1111/resp.12444
65. Boeri M, Verri C, Conte D, Roz L, Modena P, Facchinetti F, Calabrò E, Croce CM, Pastorino U, Sozzi G. MicroRNA signatures in tissues and plasma predict development and prognosis of computed tomography detected lung cancer. Proc Nat Acad Sci 2011; 108(9): 3713-3718. https://doi.org/10.1073/pnas.1100048108

66. Hennessey PT, Sanford T, Choudhary A, Mydlarz WW, Brown D, Adai AT, Ochs MF, Ahrendt SA, Mambo E, Califano JA. Serum microRNA biomarkers for detection of non-small cell lung cancer. PloS One 2012; 7(2): e32307. https://doi.org/10.1371/journal.pone.0032307
67. Solomides CC, Evans BJ, Navenot JM, Vadigepalli R, Peiper SC, Wang ZX. MicroRNA profiling in lung cancer reveals new molecular markers for diagnosis. Acta Cytolog 2012; 56(6): 645-654. https://doi.org/10.1159/000343473
68. Cazzoli R, Buttitta F, Di Nicola M, Malatesta S, Marchetti A, Rom WN, Pass HI. microRNAs derived from circulating exosomes as noninvasive biomarkers for screening and diagnosing lung cancer. J Thor Oncol 2013; 8(9): 1156-1162. https://doi.org/10.1097/JTO.0b013e318299ac32
69. Hutchinson JN, Ensminger AW, Clemson CM, Lynch CR, Lawrence JB, Chess A. A screen for nuclear transcripts identifies two linked noncoding RNAs associated with SC35 splicing domains. BMC Genom 2007; 8(1): 1-6. https://doi.org/10.1186/1471-2164-8-39
70. Ji P, Diederichs S, Wang W, Böing S, Metzger R, Schneider PM, Tidow N, Brandt B, Buerger H, Bulk E, Thomas M. MALAT-1, a novel noncoding RNA, and thymosin β 4 predict metastasis and survival in early-stage non-small cell lung cancer. Oncogene 2003; 22(39): 8031-8041. https://doi.org/10.1038/sj.onc.1206928
71. Tripathi V, Ellis JD, Shen Z, Song DY, Pan Q, Watt AT, Freier SM, Bennett CF, Sharma A, Bubulya PA, Blencowe BJ. The nuclear-retained noncoding RNA MALAT1 regulates alternative splicing by modulating SR splicing factor phosphorylation. Mol Cell 2010; 39(6): 925-938. https://doi.org/10.1016/j.molcel.2010.08.011
72. Yang L, Lin C, Liu W, Zhang J, Ohgi KA, Grinstein JD, Dorrestein PC, Rosenfeld MG. ncRNA-and Pc2 methylation-dependent gene relocation between nuclear structures mediates gene activation programs. Cell 2011; 147(4): 773-788. https://doi.org/10.1016/j.cell.2011.08.054
73. Gutschner T, Hämmerle M, Eißmann M, Hsu J, Kim Y, Hung G, Revenko A, Arun G, Stentrup M, Groß M, Zörnig M. The noncoding RNA MALAT1 is a critical regulator of the metastasis phenotype of lung cancer cells. Cancer Re 2013; 73(3): 1180-1189. https://doi.org/10.1158/0008-5472.CAN-12-2850
74. Xu YJ, Du Y, Fan Y. Long noncoding RNAs in lung cancer: what we know in 2015. Clin Translat Oncol 2016; 18(7): 660-665. https://doi.org/10.1007/s12094-015-1448-y
75. Saxena A, Carninci P. Long non-coding RNA modifies chromatin: epigenetic silencing by long non-coding RNAs. Bioessays 2011; 33(11): 830-839. https://doi.org/10.1002/bies.201100084
76. Rinn JL, Kertesz M, Wang JK, Squazzo SL, Xu X, Brugmann SA, Goodnough LH, Helms JA, Farnham PJ, Segal E, Chang HY. Functional demarcation of active and silent chromatin domains in human HOX loci by noncoding RNAs. Cell 2007; 129(7): 1311-1323. https://doi.org/10.1016/j.cell.2007.05.022
77. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, Hung T, Argani P, Rinn JL, Wang Y. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 2010; 464(7291): 1071-1076. https://doi.org/10.1038/nature08975
78. Yang Z, Zhou L, Wu LM, Lai MC, Xie HY, Zhang F, Zheng SS. Overexpression of long non-coding RNA HOTAIR predicts tumor recurrence in hepatocellular carcinoma patients following liver transplantation. Ann Surg Oncol 2011; 18(5): 1243-1250. https://doi.org/10.1245/s10434-011-1581-y
79. Kim K, Jutooru I, Chadalapaka G, Johnson G, Frank J, Burghardt R, Kim S, Safe S. HOTAIR is a negative prognostic factor and exhibits pro-oncogenic activity in pancreatic cancer. Oncogene 2013; 32(13): 1616-1625. http://dx.doi.org/10.1038/onc.2012.193
80. Liu XH, Liu ZL, Sun M, Liu J, Wang ZX, De W. The long non-coding RNA HOTAIR indicates a poor prognosis and promotes metastasis in non-small cell lung cancer. BMC Cancer 2013; 13(1): 1-0. https://doi.org/10.1186/1471-2407-13-464
81. Kogo R, Shimamura T, Mimori K, Kawahara K, Imoto S, Sudo T, Tanaka F, Shibata K, Suzuki A, Komune S, Miyano S. Long noncoding RNA HOTAIR regulates polycomb-dependent chromatin modification and is

associated with poor prognosis in colorectal cancers. Cancer Res 2011; 71(20): 6320-6326. https://doi.org/10.1158/0008-5472.CAN-11-1021

82. Kotake Y, Nakagawa T, Kitagawa K, Suzuki S, Liu N, Kitagawa M, Xiong Y. Long non-coding RNA ANRIL is required for the PRC2 recruitment to and silencing of p15 INK4B tumor suppressor gene. Oncogene 2011; 30(16): 1956-1962. https://doi.org/10.1038/onc.2010.568
83. Lin L, Gu ZT, Chen WH, Cao KJ. Increased expression of the long non-coding RNA ANRIL promotes lung cancer cell metastasis and correlates with poor prognosis. Diagn Pathol 2015; 10(1): 1-7. https://doi.org/10.1186/s13000-015-0247-7
84. Kang YH, Kim D, Jin EJ. Down-regulation of phospholipase D stimulates death of lung cancer cells involving up-regulation of the long ncRNA ANRIL. Anticancer Res 2015; 35(5): 2795-2803.
85. Nie FQ, Sun M, Yang JS, Xie M, Xu TP, Xia R, Liu YW, Liu XH, Zhang EB, Lu KH, Shu YQ. Long noncoding RNA ANRIL promotes non–small cell lung cancer cell proliferation and inhibits apoptosis by silencing KLF2 and P21 expression. Mol Cancer Ther 2015; 14(1): 268-277. https://doi.org/10.1158/1535-7163.MCT-14-0492
86. Ling H, Spizzo R, Atlasi Y, Nicoloso M, Shimizu M, Redis RS, Nishida N, Gafà R, Song J, Guo Z, Ivan C. CCAT2, a novel noncoding RNA mapping to 8q24, underlies metastatic progression and chromosomal instability in colon cancer. Genome Res 2013; 23(9): 1446-1461. https://doi.org/10.1101/gr.152942.112
87. Zhang X, Chen Q, He C, Mao W, Zhang L, Xu X, Zhu J, Chen B. Polymorphisms on 8q24 are associated with lung cancer risk and survival in Han Chinese. PLoS One 2012; 7(7): e41930.
88. Qiu M, Xu Y, Yang X, Wang J, Hu J, Xu L, Yin R. CCAT2 is a lung adenocarcinoma-specific long non-coding RNA and promotes invasion of non-small cell lung cancer. Tumor Biol 2014; 35(6): 5375-5380. https://doi.org/10.1007/s13277-014-1700-z
89. Guan Y, Kuo WL, Stilwell JL, Takano H, Lapuk AV, Fridlyand J, Mao JH, Yu M, Miller MA, Santos JL, Kalloger SE. Amplification of PVT1 contributes to the pathophysiology of ovarian and breast cancer. Clin Cancer Res 2007; 13(19): 5745-5755. https://doi.org/10.1158/1078-0432.CCR-06-2882
90. Colombo T, Farina L, Macino G, Paci P. PVT1: a rising star among oncogenic long noncoding RNAs. Bio Med Res Int 2015; 2015. https://doi.org/10.1155/2015/304208
91. Wang F, Yuan JH, Wang SB, Yang F, Yuan SX, Ye C, Yang N, Zhou WP, Li WL, Li W, Sun SH. Oncofetal long noncoding RNA PVT1 promotes proliferation and stem cell-like property of hepatocellular carcinoma cells by stabilizing NOP2. Hepatology 2014; 60(4): 1278-1290. https://dx.doi.org/10.1002/hep.27239
92. Takahashi Y, Sawada G, Kurashige J, Uchi R, Matsumura T, Ueo H, Takano Y, Eguchi H, Sudo T, Sugimachi K, Yamamoto H. Amplification of PVT-1 is involved in poor prognosis via apoptosis inhibition in colorectal cancers. British journal of cancer. 2014; 110(1): 164-171. https://dx.doi.org/10.1038/bjc.2013.698
93. Cui D, Yu CH, Liu M, Xia QQ, Zhang YF, Jiang WL. Long non-coding RNA PVT1 as a novel biomarker for diagnosis and prognosis of non-small cell lung cancer. Tumor Biol 2016; 37(3): 4127-4134. https://dx.doi.org/10.1007/s13277-015-4261-x
94. Nie W, Ge HJ, Yang XQ, Sun X, Huang H, Tao X, Chen WS, Li B. LncRNA-UCA1 exerts oncogenic functions in non-small cell lung cancer by targeting miR-193a-3p. Cancer letters. 2016; 371(1): 99-106. https://dx.doi.org/10.1016/j.canlet.2015.11.024
95. Wang HM, Lu JH, Chen WY, Gu AQ. Upregulated lncRNA-UCA1 contributes to progression of lung cancer and is closely related to clinical diagnosis as a predictive biomarker in plasma. Int J Clin Exp Med 2015; 8(7): 11824.
96. Hung T, Wang Y, Lin MF, Koegel AK, Kotake Y, Grant GD, Horlings HM, Shah N, Umbricht C, Wang P, Wang Y. Extensive and coordinated transcription of noncoding RNAs within cell-cycle promoters. Nat Genet 2011; 43(7): 621-629. http://dx.doi.org/10.1038/ng.848

97. Sang Y, Tang J, Li S, Li L, Tang X, Cheng C, Luo Y, Qian X, Deng LM, Liu L, Lv XB. LncRNA PANDAR regulates the G1/S transition of breast cancer cells by suppressing p16 INK4A expression. Sci Rep 2016; 6(1): 1-0. http://dx.doi.org/10.1038/srep22366
98. Han L, Zhang EB, Yin DD, Kong R, Xu TP, Chen WM, Xia R, Shu YQ, De W. Low expression of long noncoding RNA PANDAR predicts a poor prognosis of non-small cell lung cancer and affects cell apoptosis by regulating Bcl-2. Cell Death Dis 2015; 6(2): e1665-. http://dx.doi.org/10.1038/cddis.2015.30
99. Peng W, Fan H. Long non-coding RNA PANDAR correlates with poor prognosis and promotes tumorigenesis in hepatocellular carcinoma. Biomed Pharmacother 2015; 72: 113-118. http://dx.doi.org/10.1016/j.biopha.2015.04.014.
100. Ma P, Xu T, Huang M, Shu Y. Increased expression of LncRNA PANDAR predicts a poor prognosis in gastric cancer. Biomed Pharmacother 2016; 78: 172-176. http://dx.doi.org/10.1016/j.biopha.2016.01.025
101. Shi Y, Li J, Liu Y, Ding J, Fan Y, Tian Y, Wang L, Lian Y, Wang K, Shu Y. The long noncoding RNA SPRY4-IT1 increases the proliferation of human breast cancer cells by upregulating ZNF703 expression. Mol Cancer 2015; 14(1): 1-3. http://dx.doi.org/10.1186/s12943-015-0318-0.
102. Khaitan D, Dinger ME, Mazar J, Crawford J, Smith MA, Mattick JS, Perera RJ. The melanoma-upregulated long noncoding RNA SPRY4-IT1 modulates apoptosis and invasion. Cancer Res 2011; 71(11): 3852-3862. http://dx.doi.org/10.1158/0008-5472.CAN-10-4460.
103. Feng J, Sun Y, Zhang EB, Lu XY, Jin SD, Guo RH. A novel long noncoding RNA IRAIN regulates cell proliferation in non small cell lung cancer. Int J Clin Exp Pathol 2015; 8(10): 12268.
104. Sun M, Liu XH, Lu KH, Nie FQ, Xia R, Kong R, Yang JS, Xu TP, Liu YW, Zou YF, Lu BB. EZH2-mediated epigenetic suppression of long noncoding RNA SPRY4-IT1 promote s NSCLC cell proliferation and metastasis by affecting the epithelial–mesenchymal transition. Cell Death Dis 2014; 5(6): e1298. http://dx.doi.org/10.1038/cddis.2014.256.
105. Sun J, Li W, Sun Y, Yu D, Wen X, Wang H, Cui J, Wang G, Hoffman AR, Hu JF. A novel antisense long noncoding RNA within the IGF1R gene locus is imprinted in hematopoietic malignancies. Nucleic Acids Res 2014; 42(15):9588-9601. http://dx.doi.org/10.1093/nar/gku549.
106. Kang L, Sun J, Wen X, Cui J, Wang G, Hoffman AR, Hu JF, Li W. Aberrant allele-switch imprinting of a novel IGF1R intragenic antisense non-coding RNA in breast cancers. Eur J Cancer 2015; 51(2): 260-270. http://dx.doi.org/10.1016/j.ejca.2014.10.031.
107. Reinmuth N, Liu W, Fan F, Jung YD, Ahmad SA, Stoeltzing O, Bucana CD, Radinsky R, Ellis LM. Blockade of insulin-like growth factor I receptor function inhibits growth and angiogenesis of colon cancer. Clin Cancer Res 2002; 8(10): 3259-3269. ISSN: 10780432
108. Winder T, Zhang W, Yang D, Ning Y, Bohanes P, Gerger A, Wilson PM, Pohl A, Mauro DJ, Langer C, Rowinsky EK. Germline polymorphisms in genes involved in the IGF1 pathway predict efficacy of cetuximab in wild-type KRAS mCRC patients. Clin Cancer Res 2010; 16(22): 5591-5602. http://dx.doi.org/10.1158/1078-0432.CCR-10-2092
109. Fürstenberger G, Senn HJ. Insulin-like growth factors and cancer. Lancet Oncol 2002; 3(5): 298-302. https://doi.org/10.1016/S1470-2045(02)00731-3
110. Liang W, Lv T, Shi X, Liu H, Zhu Q, Zeng J, Yang W, Yin J, Song Y. Circulating long noncoding RNA GAS5 is a novel biomarker for the diagnosis of nonsmall cell lung cancer. Medicine 2016; 95(37). http://dx.doi.org/10.1097/MD.0000000000004608
111. Yang M, Abdalrahman H, Sonia U, Mohammed AI, Vestine U, Wang M, Ebadi AG, Toughani M. The application of DNA molecular markers in the study of Codonopsis species genetic variation, a review. Cell Mol Biol 2020; 66(2): 23-30. https://doi.org/10.14715/cmb/2020.66.2.3
112. Yang M, Shi D, Wang Y, Ebadi AG, Toughani M. Study on Interaction of Coomassie Brilliant Blue G-250 with Bovine Serum Albumin by Multispectroscopic. Int J Pept Res Ther 2021; 27(1): 421-431. https://doi.org/10.1007/s10989-020-10096-6

113. Wen L, Zhang Y, Yang B, Han F, Ebadi AG, Toughani M. Knockdown of Angiopoietin-like protein 4 suppresses the development of colorectal cancer. Cell Mol Biol 2020; 66(5): 117-124. https://doi.org/10.14715/cmb/2020.66.5.21
114. Tan Q, Zuo J, Qiu S, Yu Y, Zhou H, Li N, Wang H, Liang C, Yu M, Tu J. Identification of circulating long non-coding RNA GAS5 as a potential biomarker for non-small cell lung cancer diagnosisnon-small cell lung cancer, long non-coding RNA, plasma, GAS5, biomarker. Int J Oncol 2017; 50(5): 1729-1738. https://doi.org/10.3892/ijo.2017.3925
115. Miao L, Huang Z, Zengli Z, Li H, Chen Q, Yao C, Cai H, Xiao Y, Xia H, Wang Y. Loss of long noncoding RNA FOXF1-AS1 regulates epithelial-mesenchymal transition, stemness and metastasis of non-small cell lung cancer cells. Oncotarget 2016; 7(42): 68339. http://dx.doi.org/10.18632/oncotarget.11630.

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