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CURRENT TOPICS REVIEW ARTICLE

Molecular oncology of lung cancer

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Abstract Progress in genetic engineering has made it possible to elucidate the molecular biological abnormalities in lung cancer. Mutations in *KRAS* and *P53* genes, loss of specific alleles, and DNA methylation of the tumor suppressor genes were the major abnormalities investigated between 1980 and the 2000s. In 2004, mutations in the epidermal growth factor receptor (*EGFR*) gene that cause oncogene addiction were discovered in non-small-cell lung cancers (NSCLCs), especially in adenocarcinomas. Because they are strongly associated with sensitivity to EGFR-tyrosine kinase inhibitors (EGFR-TKIs), a great deal of knowledge has been acquired in regard to both *EGFR* and other genes in the *EGFR* family and their downstream genes. Moreover, in 2007 the existence of the echinoderm microtubule-associated protein-like 4 (*EML4*)–anaplastic lymphoma kinase (*ALK*) fusion gene was discovered in NSCLC; and the same as EGFR-TKIs, ALK inhibitors are being found to be highly effective in lung cancers that have this translocation. These discoveries graphically illustrate that molecular biological findings are directly linked to the development of clinical oncology and to improving the survival rates of lung cancer patients. Here, we review the remarkable progress in molecular biological knowledge acquired thus far in regard to lung cancer, especially NSCLC, and the future possibilities.

Key words Lung cancer · Molecular oncology · Biology

Introduction

Lung cancer ranks first as the cause of cancer deaths both in Japan and worldwide[1,2]; and many studies, from basic to clinical, have been conducted with the aim of improving the results of lung cancer treatments. In particular, it is possible that the results of basic research will lead to both a deepened understanding of the molecular biology of lung cancer and to a dramatic improvement in the results of treatment. As an example, it became possible to expect a median survival time of more than 24 months in patients with advanced non-small-cell lung cancer (NSCLCs) with an *EGFR* mutation when they were treated with an epidermal growth factor–tyrosine kinase inhibitor (EGFR-TKI).[3] Furthermore, the availability of the vascular endothelial growth factor (VEGF) antibody bevacizumab made it possible that the median survival time can exceeded 12 months in advanced NSCLC.[4] It appears that such treatment strategies based on the molecular biological characteristics of the cancer will play a major role in the treatment of lung cancer in the future.

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Table 1 Genetic alteration and its frequency (%) in lung cancer

Gene	Chromosome	Function	Mechanism	NSCLC	SCLC of alteration
Oncogene					
MYCL	1p34.2	Transcriptional factor	exp, amp	<5	30
MYCN	2p24.1	Transcriptional factor	exp, amp	<5	10
ALK	2p23	Receptor tyrosine kinase	trans		
PIK3CA	3q26.3	PI3 kinase subunit	mut	<5	
Δ*NP63*	3q27-29	p53 homologue	amp	≤50 (squamous)	
c-*kit*	4q11-12	Receptor tyrosine kinase	exp	<5	50
FGFR4	5q35.3	Receptor tyrosine kinase	mut	<5 (adeno)	
EGFR/*ERBB11*	7p12	Receptor tyrosine kinase	mut, amp, exp	50 (adeno)	<5
BRAF	7q34	Ser/Thr kinase	mut		
MYCC	8q24	Transcriptional factor	exp, amp	30	30
CCND1	11q13	Cell cycle modulator	exp	50	
KRAS	12p12	GTP-binding protein	mut, amp	20 (adeno)	<5
HER2/*ERBB2*	17q11	Receptor tyrosine kinase	exp, amp, mut	25–60 (adeno)	<5
MET	7q31	Receptor tyrosine kinase	exp, amp, mut	2–21	
BCL–2	18q21	Anti-apoptosis	exp	20	60
EML4–ALK	2p	Fusion tyrosine kinase	trans	5 (adeno)	
Tumor suppressor gene					
LRP–DIT	2q21	Lipoprotein receptor	del	40	<5
FHIT	3p14.2	Dinucleotide triphosphatase	del, me	40–70	50–80
RASSF1A	3p21.3	Signal transduction?	del, me	30–40	70–100
NPRL2, *BLU*	3p21.3		del, mut	10	
FUS1, *HYAL1*	3p21.3		del, mut	10	
FUS2, *SEMA3B*	3p21.3		del, mut	10	
P16 (*INK4a*)	9p21	Cyclin-dependent kinase inhibitor	del, mut, me	60	<10
P14 (*ARF*)	9p21	Cyclin-dependent kinase inhibitor	me	8	
PPP1R3	7q31	Ser/Thr phosphatase	mut	15	
PTEN	10q23	Tyrosine phosphatase	del, mut	<10	10
PPP2R1B	11q23	Ser/Thr phosphatase	mut	15	
TSLC1	11q23	Adhesion molecule	me	85	
p27KIP1	12p13	Cycle regulator	exp	70	
RB	13q14	Cell cycle regulator	del, mut	20–30	80–100
P53	17q13	Cell cycle regulator	del, mut	60	80–100
LKB1/*STK11*	19p13	Ser/Thr phosphatase	del, mut	10	

NSCLC, non-small-cell lung cancer; SCLC, small-cell lung cancer; del, deletion; me, methylation; mut, mutation; exp, alteration of expression; amp, gene amplification; trans, translocation; adeno, adenocarcinoma

Various alterations have been uncovered in the carcinogenesis of lung cancers. Genetic information flows from DNA to protein via RNA. Protein is finally modified to acquire the functional activity in cells. Not only DNA itself but also these processes can be a subject to oncogenic alteration, including DNA mutation, DNA methylation, splicing alteration, and posttranscriptional or posttranslational alterations (Table 1) These alterations result in the specific biological features that are described as the "hallmarks of cancer": (1) self-sufficiency in growth signals; (2) insensitivity to antigrowth signals; (3) evading apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis; (6) tissue invasion and metastasis. These hallmarks are also seen in lung cancers with alterations of relating pathways (Fig. 1). In this article we summarize the oncology of lung cancer, especially NSCLC, from a molecular biological standpoint.

Alteration of representative oncogenic factors

EGFR

Since 2004, attention has been focused on molecularly targeted drugs and on both *EGFR* family genes, which encode receptor-type tyrosine kinases, and their downstream signaling mechanism. The *EGFR* genes encode cell-membrane penetrating-type tyrosine kinases. When ligands bind to them, they form homo- or hetero-dimers with EGFR itself or EGFR family receptors, such as HER2; and they are involved in cell growth or cell survival signaling, among other activities.[5] It is thought that when a mutation occurs in exons that encode the EGFR tyrosine kinase protein (i.e., exons 18–21) EGFR is activated ligand-independently, leading to carcinogenesis.[6,7] It is especially noteworthy that EGFR-TKIs, such as gefitinib and erlotinib, are effective in approximately

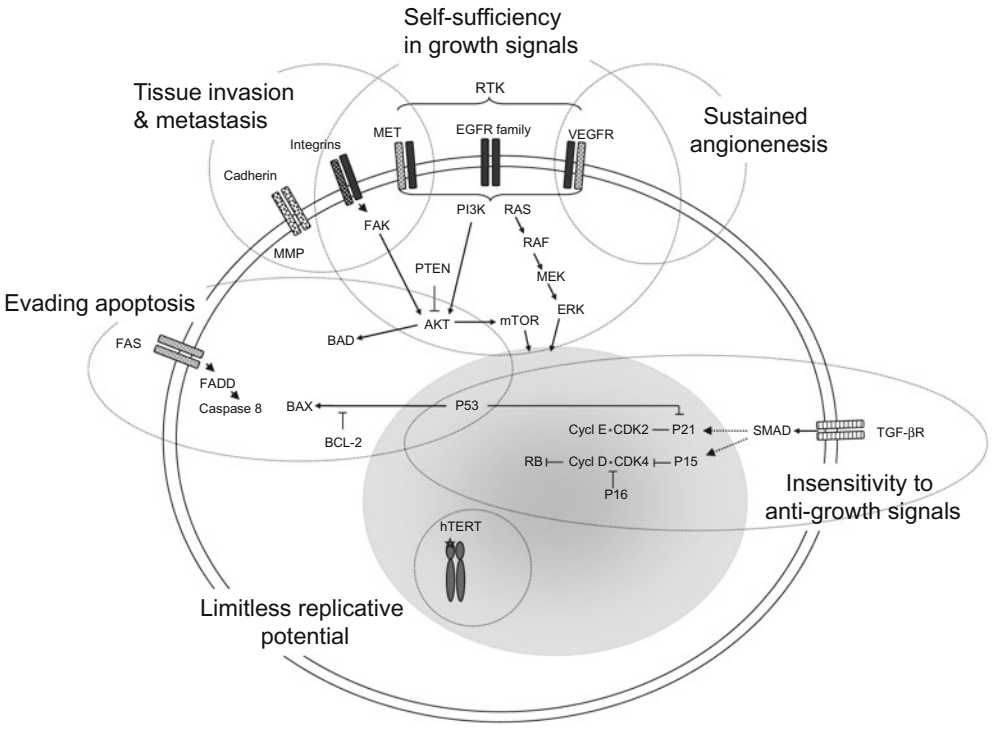

Fig. 1 Molecular alterations of lung cancer based on hallmarks of cancer. This schema shows six hallmarks of cancer and relating molecular alterations in lung cancer

80% of the lung cancer patients who have a deletion mutation of exon 19 and an L858R mutation of exon 21. EGFR mutations have been found to be extremely frequent in adenocarcinoma of the lung, nonsmokers, women, and Asians; approximately 40% of lung adenocarcinoma patients in Japan have a mutation.[8] On the other hand, two *EGFR* mutations—an insertion mutation in exon 20 and a threonine-to-methionine point mutation in codon 790 (T790M)—cause resistance to EGFR-TKIs. The T790M mutation has been found in about 50% of cases in which resistance to EGFR-TKIs has developed despite having the drug-sensitive mutation such as exon 19 deletion mutation and L858R mutation; and it appears to be a secondary mutation or a mutation derived from a minor clone before treatment.[9–11] The increased *EGFR* copy number, which is one of the mechanisms of *EGFR* activation, has been found in about 30% of NSCLC cases, and was significantly frequent in *EGFR* mutant cases.[12–14] In addition, EGFR-TKIs might be effective in some of the *EGFR*-increased tumors.[13,15]

HER2 somatic abnormalities are present in approximately 2% of adenocarcinomas of the lung.[16] Similar to *EGFR* mutations, they are more common in nonsmokers, adenocarcinoma, and Asians; and almost all of them are insertion mutations in exon 20. The increased *HER2* copy number is present in 25%–40% of NSCLCs.[17,18]

MET

MET is a tyrosine kinase receptor whose ligand is hepatocyte growth factor (HGF), and it is related to cell proliferation and to invasion and metastasis. Secondary gene amplification of the *MET* gene has been observed in approximately 20% of cases in which lung cancers have acquired resistance to EGFR-TKIs, being thought to be one of the factors in acquired resistance.[19] Amplification is observed in approximately 2% of untreated lung cancers.[20] Moreover, expression abnormalities as a result of gene mutations and splicing mutations have also been reported.[21] MET inhibitors have recently been developed, and combined treatment with an EGFR-TKI and MET inhibitor has been reported to have an antitumor effect in cases of EGFR-TKI resistance due to *MET* amplification.[19] A recent study reported that an association with HGF has been strongly suggested as a novel mechanism of EGFR-TKI resistance.[22] It has more recently been shown that even with acquisition of resistance to EGFR-TKI due to *MET* amplification, a very small *MET* amplification clone that is originally present before treatment is selected during EGFR-TKI therapy,

and the tumor becomes resistant.[23] Transient processing of HGF in this process is thought to promote amplification of the *MET* gene.

PI3K-AKT-mTOR

The PI3K-AKT-mTOR pathway is the EGFR signaling pathway that is mainly related to anti-apoptosis. PI3Ks exist in the form of heterodimers composed of a catalytic subunit and a regulator subunit, and they are important modulators of cell proliferation and apoptosis.[24,25] PI3Ks are divided into three classes. Class I PI3Ks are enzymes that phosphorylate the D-3 position of the inositol ring of phosphatidylinositol, and they ultimately activate the downstream signal that includes the AKT described below. Class I PI3Ks have been subclassified into IA and IB; class IA PI3Ks have been studied in the greatest detail. *PIK3CA* is the gene that encodes the p110α catalytic subunit of class IA PI3Ks. There is a high frequency of *PIK3CA* mutations in colorectal cancer and breast cancer, but their frequency in NSCLCs is only about 1%–2%.[26] By contrast, gene amplification is observed in approximately 30% of squamous cell carcinomas and 6% of adenocarcinomas.[26]

AKT is a serine/threonine kinase located downstream of PI3K.[24] Mutations of the *AKT* gene are rare,[27] but it is an important gene that is related to anti-apoptosis.[28] Increased phosphorylation of AKT was reported in cases that responded to EGFR-TKIs,[29] and it was later learned that AKT tends to be activated by EGFR mutations.[6]

mTOR is another serine/threonine kinase and has been identified as an intracellular target of rapamycin.[30] mTOR is a protein that is activated as a result of phosphorylation by AKT, leading to cell proliferation. It has been attracting interest from the standpoint of treatment as well as cancer mechanisms. Several inhibitors have been developed, and their clinical application is anticipated.[31]

RAS-RAF-MEK

KRAS is a GTP binding protein.[32] In contrast to EGFR mutations, active mutations of the *KRAS* gene are present in many pulmonary adenocarcinomas in patients with a history of smoking.[16] Mutation sites are seen in codons 12, 13, and 61; although more than 90% of the mutations occur in codon 12.[33] Moreover, the frequency of *KRAS* mutations in Japan is slightly more than 10%, whereas they are observed at a frequency of 20%–30% in the United States.[16] Recent research has shown that the presence of *KRAS* mutations is sometimes associated with amplification of the *KRAS* gene, and they have also been found to be a predictor of a poor outcome in those with lung cancer.[12] Lung cancers in which a *KRAS* mutation is present are reported to be resistant to EGFR-TKI therapy. However, whether a *KRAS* gene mutation is present in lung cancers that do not have an *EGFR* mutation is not associated with survival time,[34] and the lack of an association appears simply to reflect the fact that an EGFR mutation is not present more than the significance of *KRAS* mutations.[10]

BRAF is a serine/threonine kinase located downstream of KRAS, and the frequency of gene mutations in lung cancer is about 1%.[16] The *MEK1* gene lies downstream of BRAF, and mutations are present in about 1%.[35] *EGFR*, *KRAS*, *BRAF*, and *MEK1* mutations are in mutually exclusive relations.[35] Transcription factors for *MYC*, *FOS*, and others lie downstream of phosphorylated ERK, and they are involved in cell proliferation.[36] Gene alterations, especially amplification, have been found in members of the *MYC* gene family (including *MYCC*, *MYCL*, and *MYNC*) in lung cancer (Table 1).

TITF1

Expression of TITF1 is observed in approximately 90% of lung cancers, especially in highly differentiated adenocarcinoma associated with a bronchoalveolar carcinoma (BAC) component.[37] *TITF1* gene amplification has recently been discovered in approximately 30% of pulmonary adenocarcinomas, and attention has been focused on its significance as a lineage survival oncogene. It has been reported that lung cancers in which *TITF1* amplification is observed may have a poor prognosis.[38]

Mutant allele-specific imbalance

Oncogenes are activated by gene mutations and aneuploidy, especially by increases in the number of gene copies. It has been found that functional loss of both of the alleles inherited from the two parents are required to inactivate tumor suppressor genes (homozygous alteration) but that activation of just one of the alleles is sufficient to activate oncogenes (one-hit theory, heterozygous alteration). However, approximately 20% of the oncogene mutations are homozygous mutations, and imbalances in which the mutant allele is dominant to the wild allele arise in cases associated with both an oncogene mutation and an increase in copy number.

The concept of mutant allele-specific imbalance (MASI) has been attracting interest as a novel mechanism of oncogene activation. There are two mechanisms of MASI: one associated with a copy number gain and the other not associated with a copy number gain

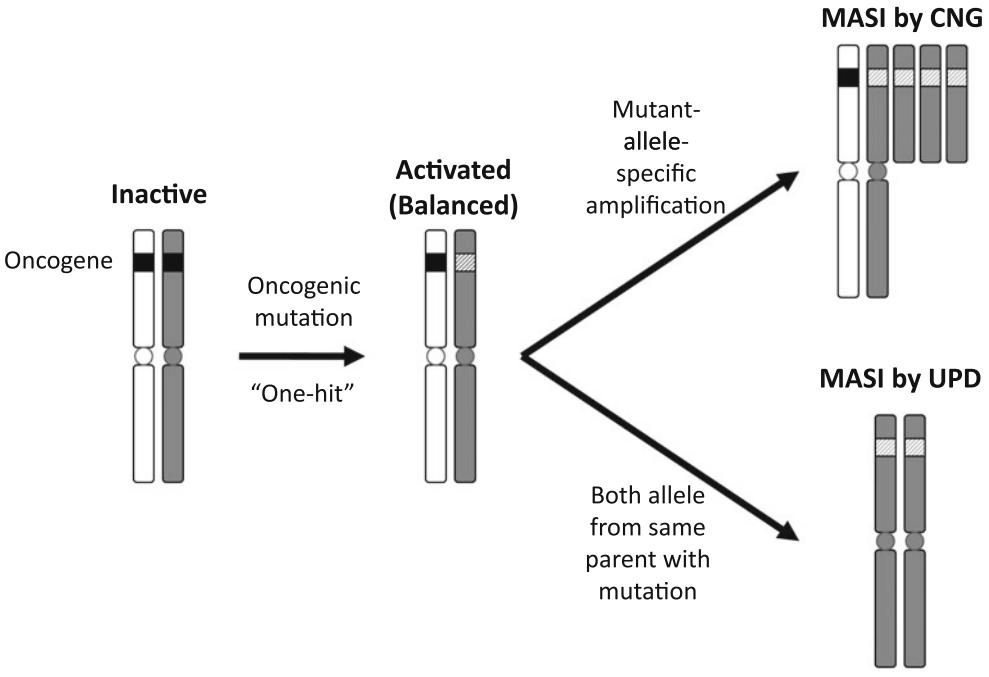

Fig. 2 Mutant allele specific imbalance (*MASI*). Three major patterns are observed: (1) balanced, having a mutant allele (mA): wild-type allele (wA) ratio (mA/wA) of about 1 without copy number gain (*CNG*) (i.e., MASI not present); (2) MASI by CNG, either complete (wA lost) or partial (wA present); and (3) uniparental disomy (*UPD*) (MASI without CNG), due to complete loss of wA and selective retention/duplication of mA, respectively. A fourth, rare pattern, reverse MASI, is defined as wild-type allele-specific imbalance

(Fig. 2). When associated with a copy number gain, MASI occurs as a result of specific amplification of the mutant allele alone; and when unassociated with a gene copy number gain, MASI occurs as a result of an increase in ploidy of the mutant allele and loss of the wild allele. The latter is called uniparental disomy (UPD). Interestingly, a high frequency of MASI is observed in both *EGFR* and *KRAS* mutations, but MASI as a result of mutant-allele-specific gene copy number gain is the main mechanism in *EGFR* mutations. By contrast, MASI as a result of UPD is the main mechanism in *KRAS* mutations.[12]

Echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase

The echinoderm microtubule-associated protein-like 4–anaplastic lymphoma kinase (*EML4-ALK*) fusion gene was discovered as an oncogene that is activated by a gene translocation.[39] Many fusion genes that arise as a result of translocation are observed in hematological malignancies, and they are also present in some solid cancers, including prostate and thyroid cancers; however, they are generally rare.[40] The *EML4-ALK* gene is located on chromosome 2p. *ALK* is a transmembrane type protein that possesses a tyrosine kinase domain, and translocations with the *NPM* gene have been reported to occur in non-Hodgkin's lymphoma. The occurrence of translocations with more than 10 different genes, including the gene coding tropomyosin 3 and the *TRK*-fused gene, have subsequently been reported in hematological malignancies.[41] The existence of a novel *KIF5B-ALK* fusion gene has been reported in lung cancer.[42] Regardless of the translocation partner gene, all of the *ALK* gene translocations have arisen in the intracellular tyrosine kinase domain portion. It is activated by constantly being dimerized by the gene translocation and is thought to be involved in carcinogenesis.[41] Constant activation of the ALK tyrosine kinase also occurs in the *EML4-ALK* fusion gene in lung cancer,[39] and at least six variants according to the translocation site in the *EML4* gene have been reported.[43]

Clinically, cancers with an *EML4-ALK* fusion gene have been attracting interest as a novel subgroup of pulmonary adenocarcinomas because the *EML4-ALK* fusion gene (1) is an NSCLC-specific gene abnormality; (2) is observed in approximately 4% of pulmonary adenocarcinomas and in approximately 30% of pulmonary adenocarcinomas in persons <50 years of age, and has a mutually exclusive relation with *EGFR* and *KRAS* mutations, mentioned above[43,44]; (3) histologically, is common in the acinar type, cribriform type, and signet ring cell; and (4) ALK-TKIs are highly effective against lung cancers that have the *EML4-ALK* fusion gene.[39,45]

Alteration of representative tumor suppressive factors

P16-RB

The pathway from p16 via cyclin D1 to RB suppresses the cell cycle.[46] An abnormality of any one of these families of molecules is present in as many as more than 80%

of cancers, and a high frequency of abnormalities is also observed in lung cancer. RB is a nucleoprotein that suppresses the G_0/G_1 phase and inhibits proliferation; and abnormalities are seen in 20%–30% of NSCLCs and in more than 90% of small-cell lung cancers (SCLCs).[47,48] P16 binds to CDK and is one of the CDK inhibitors that negatively modulates the cell cycle.[46] Gene deletions, mutations, and methylation have been found to be mechanisms of *P16* inactivation.[49] Methylation of *P16* is common in squamous cell carcinoma and is related to smoking in adenocarcinoma, but it is rarely observed in SCLCs.[50]

P14-MDM-2-P53

The *P53* gene is a tumor suppressor gene, and abnormalities of the *P53* gene are seen in the largest number of cancers. P53 expression increases in response to external stress (e.g., DNA damage); and as a transcription factor, p53 induces gene expression of *AIP1*, among others, resulting in cell cycle arrest and apoptosis. There is a high frequency of *P53* gene abnormalities in smokers, and transversion mutations in which there is a change in the base sequence from a purine base (A, G) to a pyrimidine base (T, C) or vice versa are observed.[51,52] *P53* abnormalities are seen in approximately 50% of NSCLCs and approximately 80% of SCLCs.[53,54] MDM2 binds to p53 and suppresses the function of p53. MDM2 is highly expressed in approximately 30% of lung cancers.[55] MDM2 antagonists have recently been developed, and an antitumor effect is anticipated.[56] P14 is a CDK inhibitor, the same as p16. It is expressed by alternative splicing from the same gene region as p16. P14 stabilizes p53 by suppressing MDM2.[57]

Chromosome deletions

The tumor suppressor gene-inactivating mechanism requires that the function of the two genes is eliminated by some mechanism.[58] Because a specific region of one of the two chromosomes is often deleted in cancer, deletion of one of the genes and loss of function of the remaining gene as a result of a mutation (e.g., methylation) is thought to be one of the common events in cancer. A tumor suppressor gene is assumed to exist in regions where a high frequency of deletions is observed. Deletions are observed in many regions in lung cancer as well.[59] In particular, 3p21.3 is a site where a highly frequent allele deletion is observed in lung cancer, strongly suggesting the presence of a tumor suppressor gene.[60,61] The *RASSF1* gene, which is located at the same site, has a RAS-associated region, and it has a variety of splicing variants.[62] One of them, *RASSF1A*, is suppressed by methylation of the promoter region in 30%–40% of NSCLCs and 70%–100% of SCLCs.[63] The *FHIT* gene is also the tumor suppressor gene candidate located on 3p14. Gene expression abnormalities are observed in 40%–70% of NSCLCs and 50%–80% of SCLCs.[64,65] Methylation has also been reported to be a mechanism of inactivation.[66]

Other abnormalities

Immortalization

Immortalization is a characteristic of cancer cells. Telomeres are composed of DNA containing a characteristic repeated sequence (TTAGGG) and various proteins at the end of the chromosome, and they are required for chromosome distribution during cell division, but become shorter with each cell division.[67] Telomerase is related to cell immortalization by maintaining telomere length, and a relationship between telomerase and cancer has been suggested. Telomerase activity is seen in approximately 80% of NSCLCs and 100% of SCLCs, and it has been linked to the cell growth and progression stage.[68,69]

Angiogenesis

One of the angiogenesis factors, vascular endothelial growth factor (VEGF), plays an important role as a factor involved in endothelial cell proliferation.[70] Overexpression of VEGF in lung cancer is associated with tumor angiogenesis and metastasis, being correlated with tumor progression and a poor prognosis.[71] Results of application to treatment have been reported showing a median survival time of over 12 months when the VEGF monoclonal antibody bevacizumab was used for combined therapy with a platinum doublet to treat advanced NSCLC.[4]

Invasion and metastasis

For cancer cells to acquire motility and the ability to invade, they must lose many epithelial phenotypes and undergo a morphological transformation into mesenchymal cells, a process referred to as "epithelial-mesenchymal transition (EMT)."[72] Repressed expression of cytokeratin and E-cadherin and induction of expression of N-cadherin and vimentin have been reported as changes in the gene expression profile related to EMT. Secretion of metalloproteinases (MMPs) by cancer cells is a sign of EMT, and MMP2 and MMP9, in particular, have been investigated in detail (Fig. 3). The extra-

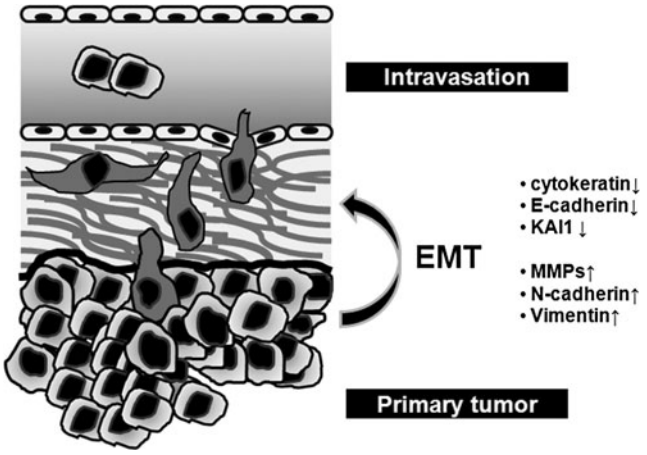

Fig. 3 Epithelial-mesenchymal transition (*EMT*). Repression and induction of various genes—cytokeratin, cadherins, matrix metalloproteinases (*MMPs*), vimentin, and KAI1—are associated with EMT, resulting in the invasion and metastasis features of lung cancers

cellular matrix, including fibronectin and collagen, is degraded by MMPs, creating gaps into which cancer cells are able to migrate. There is a report that serum MMP2 levels are associated with spreading, metastasis, and survival in lung cancer.[73] MMPs and vimentin are molecules that promote invasion and metastasis, whereas *KAI1*/*CD82* should be called "metastasis suppressor genes," the same as E-cadherin; and KAI1 suppresses cell movement and invasion in cell cultures and simultaneously promotes cell aggregation. KAI1 expression has been reported to be repressed in many advanced cancers, including lung cancers.

Development and progression of lung cancer

Multistep carcinogenesis-type lung cancer

Various abnormalities are observed in lung cancer. A multistep carcinogenesis model called the "adenoma–carcinoma sequence" has been advocated in colorectal cancer,[74] and there may also be a group of lung cancers that become clinical cancers as a result of the accumulation of various abnormalities. They could be described as a "cumulative-abnormality-type" of lung cancer. It has been reported that nonmalignant cells located adjacent to the tumor pathologically already have the same abnormalities—such as *KRAS* mutations, *P53* mutations, *EGFR* mutations, *P16* methylation, various losses of heterozygosity (LOHs)—as the tumor.[75,76] This suggests that a precancerous-state region exists as a result of the abnormalities on the molecular level. Also, when some sort of additional abnormalities that cause "cancer characteristics" accumulate in these cells, they progress into a tumor that is clinically recognized.[77]

Atypical adenomatous hyperplasia is regarded as the site of origin of this type of carcinogenesis in pulmonary adenocarcinoma, and dysplasia is regarded as the site of origin in squamous cell carcinoma.[78] Recently, cancer stem cells characterized by having the capacity for self-renewal and pluripotency have been attracting interest as the source of cancer cells. The aspects of cancer stem cells in lung cancer are unclear, including their very existence.[79] However, aldehyde dehydrogenase, which is known to exist in brain tumors and breast cancer, is strongly regarded as a surface marker of cancer stem cells in lung cancer.[80] In addition, activation and abnormalities of pathways involved in self-renewal (i.e., the Notch pathway, Hedgehog pathway, and Wnt pathway) have also been reported in lung cancer.[81–83]

Oncogene addiction and oncogene shock

Marked tumor regression in response to EGFR-TKIs is seen in lung cancers that have an *EGFR* mutation, suggesting that the survival of lung cancers with an *EGFR* mutation greatly depends on the mutant EGFR kinaes activity, regardless of whether other minor alterations are present.[6,7] This phenomenon, in which a cancer is dependent on a specific oncogene, is called "oncogene addiction."[84] The *EML4-ALK* fusion gene also appears to be an abnormality that causes oncogene addiction. Moreover, there are tumors that exhibit a marked antitumor effect with a single tumor suppressor gene, such as *P53*, and this is called "tumor suppressor gene hypersensitivity." These gene abnormalities have strong carcinogenicity and may cause carcinogenesis even when the gene abnormality is solitary or relatively limited. In our study, the frequency of methylation of tumor suppressor genes such as *P16* was lower in lung cancers that had an *EGFR* mutation than in lung cancers that had a *KRAS* mutation.[85]

It is also possible that because of genome or chromosome instability, abnormalities at the molecular level accumulate and/or a specific genetic abnormality occurs as a result of this process. As mentioned, in tumors addicted to a specific oncogene, drastic tumor shrinkage is induced by targeted therapy, which this is considered an apoptotic response. What is the mechanism for exhibiting the drastic response? It has been demonstrated that upon acute inactivation of the oncogenic kinases, pro-survival and pro-apoptotic signals decayed at different rates, with the survival signals decaying much more rapidly than the apoptotic signals.[86,87] Based on these studies, the concept "oncogenic shock" was proposed

that together with the oncogene addiction model provides a hypothesis to explain the response to targeted therapy. The success of EGFR-TKI treatment for *EGFR* mutant lung cancer strongly suggests that the strategy based on oncogene addiction and oncogene shock is a promising path that we direct.

Noncoding small RNA

Micro-RNAs (miRNA) are a group of noncoding small RNAs that regulate target mRNAs by posttranscriptional repression.[88] Some miRNAs have been classified as oncogenic or tumor-suppressive miRNAs according to their function in cellular transformation.[89] Alterations of several miRNAs have been reported in NSCLCs. Among them, down-regulation of Let-7 or up-regulation of miR-155 has been reported to be a poor prognostic factor for NSCLC.[90,91] More recently, miR-146b alone has been identified as a strong predictor for prognosis in squamous cell carcinoma of the lung.[92]

As a unique relation between miRNA and tumor suppressor gene, the miR-34 family members are identified as direct transcriptional targets of p53, constituting part of the p53 tumor suppressive network=inducing cell cycle arrest, apoptosis, and senescence, which are the major consequences of p53 activation. In lung cancer, miR34b/c was found to be down-regulated, and introduction of miR-34b/c suppresses the proliferation of some NSCLC cell lines. Another major miRNA alteration studied in lung cancer includes the miR-17-92 cluster located at 13q31.3 that is overexpressed and amplified in lung cancer, especially SCLCs.[93] The polycistronic miRNA cluster miR-17-92 is known to promote tumor angiogenesis in a paracrine fashion.

Conclusion

The pathogenesis of lung cancer is complicated, and many years of effort have not completely uncovered the mechanism of carcinogenesis. In addition, the molecular and clinical characteristics of individual NSCLCs are not identical, and it is not appropriate to regard them as a same disease. There has been a recent comprehensive analysis of the genome that included a genome-wide approach using the next generation sequencer. In addition, new challenges using OMICS analysis such as transcriptomics, proteomics, and metabolomics are being performed to understand the pathogenesis of lung cancer. Based on new findings, customized therapy based on the characteristics of the individual cancer is mandatory to improve therapeutic outcomes of NSCLC. Further understanding of the molecular pathogenesis of NSCLC and the development of new therapeutic strategies comprise a mission to be achieved.

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