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Review Article

Gene aberrations for precision medicine against lung adenocarcinoma

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Lung adenocarcinoma (LADC), the most frequent histological type of lung cancer, is often triggered by an aberration in a driver oncogene in tumor cells. Examples of such aberrations are *EGFR* mutation and *ALK* fusion. Lung adenocarcinoma harboring such mutations can be treated with anticancer drugs that target the aberrant gene products. Additional oncogene aberrations, including *RET*, *ROS1*, and *NRG1* fusions, skipping of exon 14 of *MET*, and mutations in *BRAF*, *HER2*, *NF1*, and *MEK1*, were recently added to the list of such "druggable" driver oncogene aberrations, and their responses to targeted therapies are currently being evaluated in clinical trials. However, approximately 30% and 50% of LADCs in patients in Japan and Europe/USA, respectively, lack the driver oncogene aberrations listed above. Therefore, novel therapeutic strategies, such as those that exploit the vulnerabilities of cancer cells with non-oncogene aberrations, are urgently required. This review summarizes the current status of research on precision medicine against LADC and enumerates the research priorities for the near future.

Lung Adenocarcinoma and Oncogene Addiction

Lung adenocarcinoma is the most common histological subtype of non-small-cell lung cancer. Cigarette smoking is a major cause of lung cancer; however, among the major histological types of lung cancer, LADC is the most weakly associated with smoking, and often occurs in females and never-smokers.[1,2] Lung adenocarcinoma is also the type of lung cancer in which somatic gene aberrations have been most extensively studied (Table S1).[3,4] Lung adenocarcinoma can be classified according to the presence of specific mutually exclusive oncogene aberrations that drive carcinogenesis.

Although many gene aberrations accumulate during the development of each individual case of LADC, these cancers are primarily driven by single oncogene aberrations that play major roles in oncogenesis and tumor progression. These aberrations are thus referred to as "driver oncogenes". In precision medicine, tumors with driver oncogene aberrations can be treated using "molecular targeted" drugs. For example, tumors that develop due to *EGFR* gene mutations or *ALK* gene fusions respond to therapy with TKIs that suppress the kinase activities of the aberrant EGFR and ALK proteins, respectively.[4] These therapeutic strategies are based on the concept of "oncogene addiction", that is, the dependence of a cancer cell on a single aberrant driver oncogene for survival and growth.[5]

Driver Oncogene Aberrations Occur in a Mutually Exclusive Manner

The contribution of driver gene aberrations to development of LADC differs by smoking status, sex, and ethnicity. To illustrate this phenomenon, we provide pie charts in Figure 1 and Table S2 showing the distributions of driver oncogene aberrations in two cohorts: National Cancer Center Hospital, Japan (NCC_Japan cohort, consisting of 319 Japanese patients), representing Asian cases,[6] and a TCGA (The Cancer Genome Atlas) study (TCGA_USA cohort, consisting of 230 US patients), representing European/US cases.[7] Known driver oncogene aberrations, such as mutations of the *EGFR*, *KRAS*, *BRAF*, and *HER2* genes, and fusions of the *ALK*, *RET*, and *ROS1* genes, occur mutually exclusively in both cohorts. Also, in both populations, skipping of exon 14 of the *MET* gene, which occurs as a result of a variety of splice site and intronic mutations,[7,8] is observed in cases that lack the aforementioned driver aberrations. Thus, irrespective of ethnicity, a common set of oncogenes drives lung adenocarcinogenesis.

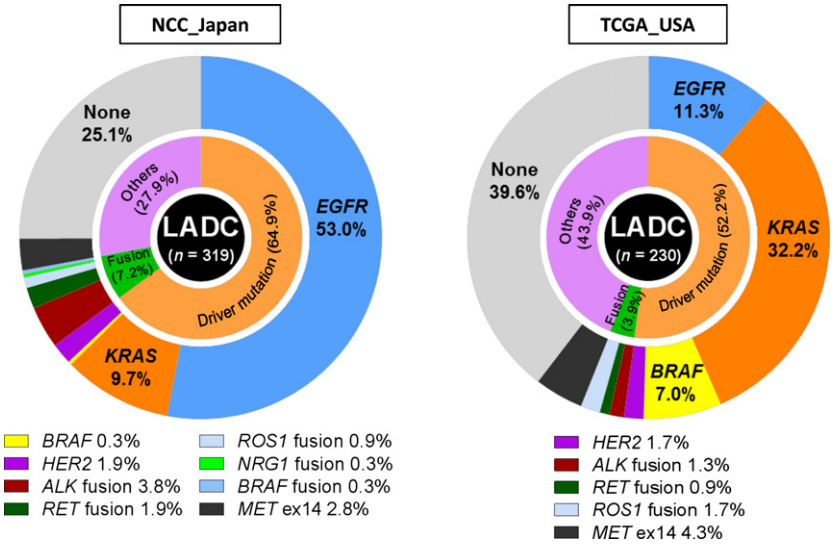

Fig. 1. Frequencies of driver oncogene aberrations in lung adenocarcinoma (LADC), shown as pie charts. Frequencies are shown for mutations in *EGFR*, *KRAS*, *BRAF*, and *HER2* (driver mutations), fusions involving *ALK*, *RET*, *ROS1*, *NRG1*, and *BRAF* (driver fusions), and skipping of *MET* exon (ex) 14 (others). Data were obtained from a Japanese cohort (n = 319) from the National Cancer Center Hospital, Tokyo (NCC_Japan) and a US cohort (n = 230) from The Cancer Genome Atlas study (TCGA_USA).

EGFR, a Major Driver Oncogene in Asian LADC

Despite the common features described above, the frequencies of some oncogene aberrations differ significantly between Asian and US/European populations, as is apparent in the Japanese and US cohorts (Fig. 1): *EGFR* mutations are more prevalent in Japanese patients, whereas *KRAS* and *BRAF* mutations are more prevalent in the US.[9] *KRAS* and *BRAF* mutations occur preferentially in LADC of ever-smokers and males.[10,11]

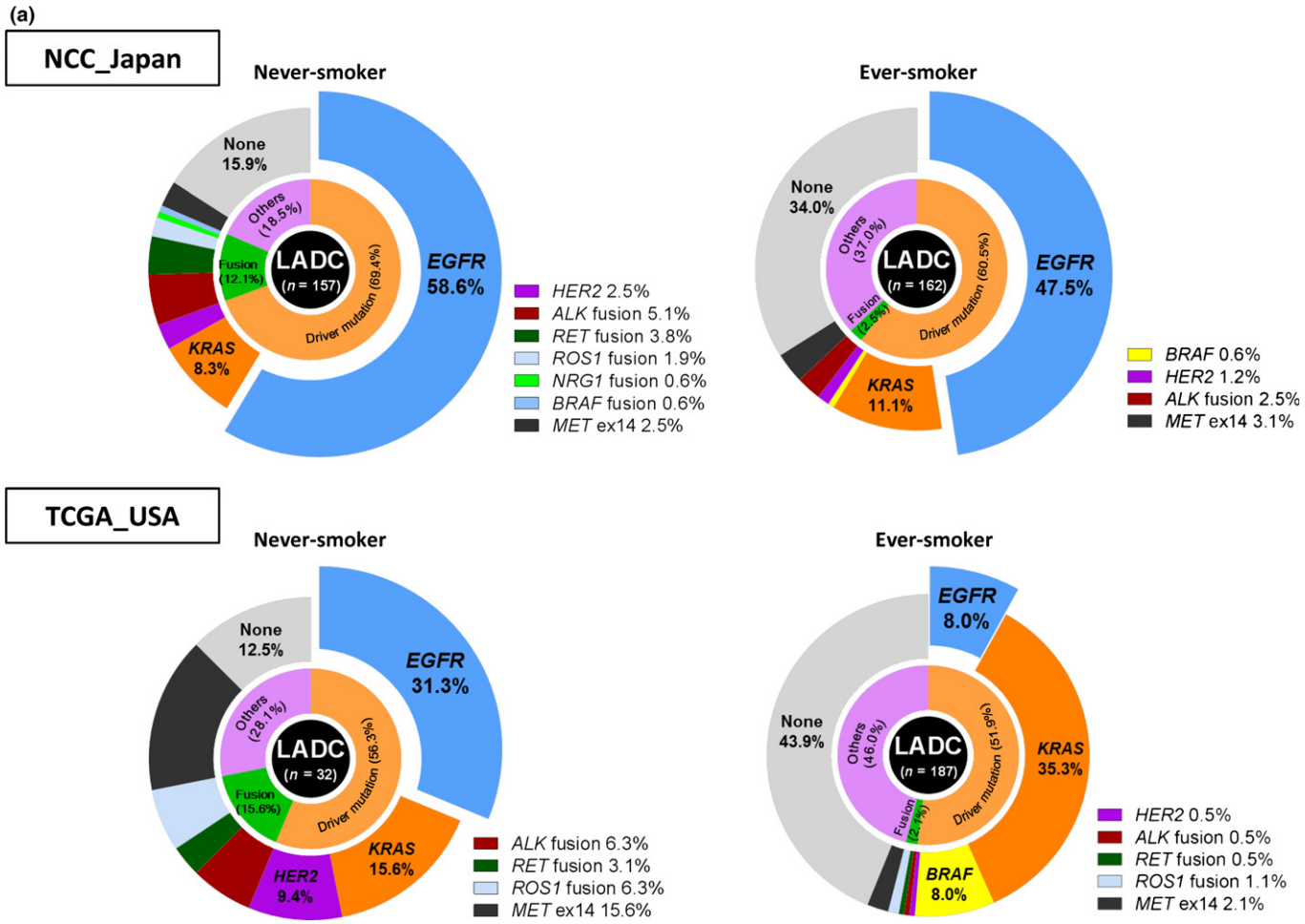

Fig. 2. Frequency of driver oncogene aberrations in lung adenocarcinoma (LADC) according to smoking status (a) and sex (b). Aberrations are shown for all Japanese and US cases for which information on sex and smoking was available. The oncogene aberrations referred to in the text are emphasized by exploding pie charts. ex, exon.

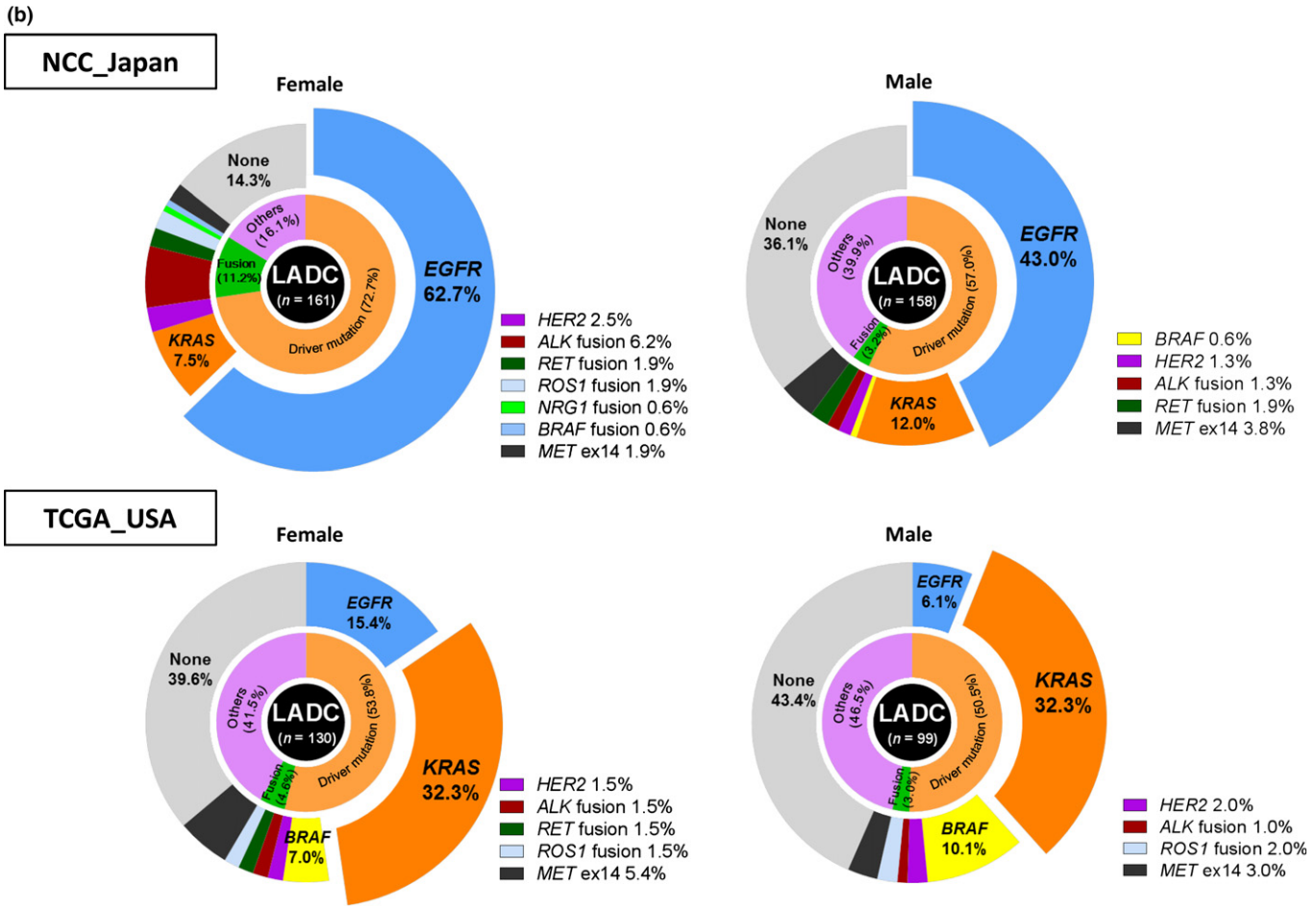

Fig. 2. Continued

Notably, Asian LADC cohorts more frequently include females and never-smokers than those of European descent.[12] Consistent with this, *EGFR* mutation, which preferentially occurs in LADCs in females and never-smokers, is more frequent in Asians than in US/European individuals.[9,13] Oncogene distributions are illustrated in patient populations stratified by smoking status (Fig. 2a) and sex (Fig. 2b). Frequencies of *EGFR* mutation were higher among never-smokers and females in both populations, but Japanese patients were more likely to have *EGFR* mutations than US patients in all groups stratified by smoking and/or sex (Figs 2,S1). Thus, frequent *EGFR* mutation is likely to be a robust feature of Japanese LADCs.

Asians, including Japanese people, might carry endogenous and/or exogenous risk factors responsible for the development of LADC with *EGFR* mutation. This idea is consistent with the fact that never-smoking Asians have higher lung cancer risk than never-smoking non-Asians.[14] Notably, genome-wide association studies have shown that odds ratios for genetic polymorphisms at LADC susceptibility loci, such as those at *TERT* and *TP63*, are higher in Asians than in individuals of European descent (Table S3).[15–17] In China, *TERT* polymorphisms are more strongly associated with risk of LADC with *EGFR* mutation than for LADC without such mutation.[18] In addition, Asian-specific LADC risk loci have been discovered.[19] Thus, genetic background (i.e., the overall complement of genetic polymorphisms) represents a potential endogenous risk factor that makes Asians more susceptible to LADC with *EGFR* mutation.

Oncogene Fusions Driving Lung Carcinogenesis

Like *EGFR* mutations, *ALK*, *RET*, and *ROS1* oncogene fusions arise preferentially in LADCs of never-smokers.[20,21] In fact, LADCs with these aberrations were more frequent in never-smokers than in ever-smokers in both the Japanese and US cohorts (Fig. 2a; 12.1% *vs* 2.5% in Japan, and 15.6% *vs* 2.1% in the US). Therefore, oncogene fusions are another important driver of lung adenocarcinogenesis in never-smokers.

To determine the risk factors for development of LADCs with oncogene fusions, genomic breakpoints for chromosome translocations causing *ALK*, *RET*, and *ROS1* fusion were characterized by cloning and sequencing of genomic fragments containing the fusion breakpoint junctions.[22,23] The breakpoints were clustered in regions of a few kilobases within the oncogenes (Fig. 3). Interestingly, the cluster region of *RET* included most *RET* fusion breakpoints observed in papillary thyroid cancers induced by the Chernobyl accident.[22] The structures of the breakpoint junctions indicated that two DNA double-strand break repair mechanisms, non-homologous end joining (active both in replicating and non-replicating cells) and synthesis-dependent end joining (active only in replicating cells), contribute to illegitimate joining of DNA ends of oncogenes and their fusion

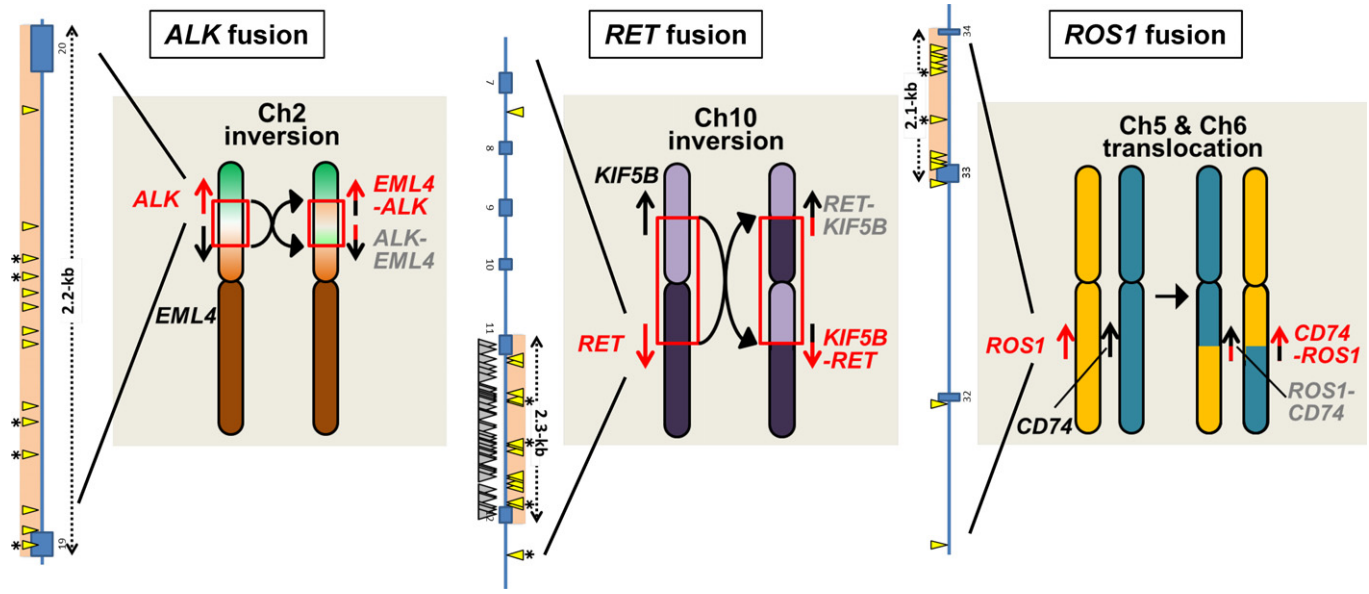

Fig. 3. Molecular process of oncogene fusion. *ALK*, *RET*, and *ROS1* oncogene fusions are the results of illegitimate DNA end-joining repair of DNA strand breaks at defined genomic regions. Locations of breakpoints are indicated by yellow (lung adenocarcinoma) and gray (Chernobyl accident-induced papillary thyroid cancers) arrowheads.[22,23] Breakpoints in lung adenocarcinomas of ever-smokers are indicated by asterisks. Ch, chromosome.

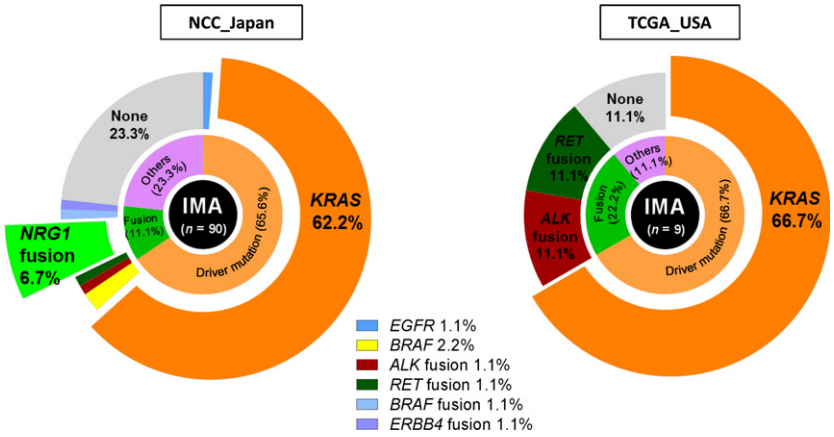

Fig. 4. Frequency of driver oncogene aberrations in invasive mucinous lung adenocarcinoma (IMA). Data were obtained from a Japanese cohort (n = 90) from the National Cancer Center Hospital, Tokyo (NCC_Japan)[46] and a US cohort (n = 9) from The Cancer Genome Atlas study (TCGA_USA).[7] The oncogene aberrations referred to in the text are emphasized by exploding pie charts.

partners.[22,23] Thus, DNA strand breaks at specified regions of oncogenes in replicating and non-replicating lung epithelial cells are likely to be responsible for the development of LADCs with oncogene fusions, although the endogenous and exogenous factors that cause these strand breaks are unknown.

Therapy Targeting Driver Oncogene Aberrations

Targeted therapies using TKIs against tumors with *EGFR* mutations and *ALK* fusions have yielded dramatic success in precision LADC medicine.[24–26] Therefore, additional driver oncogenes are being translated into molecular targeted therapies.

One representative example of a TKI target is *RET* oncogene fusion, discovered by our group and others.[6,27,28] Oncogene addiction of tumors harboring this fusion and the therapeutic utility of TKIs against RET kinase activity have been demonstrated by *in vitro* studies[6,27,28] and in a transgenic mouse model.[29] In addition, several LADC cases with *RET* fusions responded to RET TKIs approved by the FDA for the treatment of tumors other than lung cancers.[30–34] Consequently, the utility of repositioning existing RET TKIs to LADC therapy is being evaluated in clinical trials,[35] e.g., LURET (lung cancer with *RET* rearrangement study; clinical trial registration no. UMIN000010095) in Japan, a phase II clinical trial investigating the therapeutic effects of vandetanib.[36] Similarly, LADC cases with *ROS1* fusions have been subjected to clinical trials of ROS1 TKIs, such as crizotinib, yielding promising results.[37] Clinical trials targeting other driver oncogene aberrations, such as *BRAF* and *HER2* mutations, are also underway. Lung adenocarcinomas with the *BRAF* V600E mutation or an in-frame insertion in *HER2* exon 20 respond to treatment with the BRAF inhibitor vemurafenib[38,39] and anti-HER2 drugs such as trastuzumab or afatinib,[40] respectively.

Other Infrequent Driver Oncogene Aberrations

Additional driver oncogenes have been identified that occur in a subset of LADCs lacking the oncogene aberrations described above. *NF1*, a tumor-suppressor gene in which mutations cause the hereditary cancer-prone disease neurofibromatosis type 1, encodes a negative regulator of RAS proteins. Recent

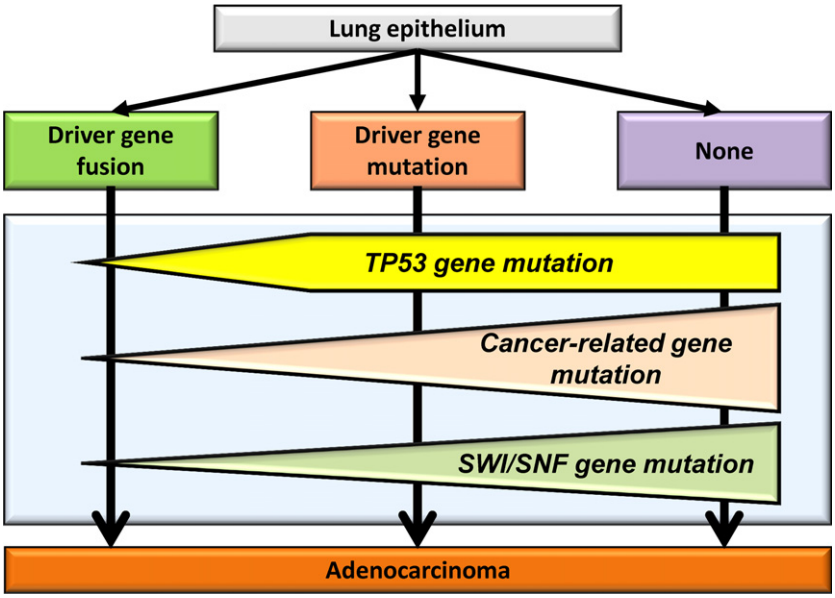

Fig. 5. Deduced molecular pathway of carcinogenesis and progression of lung adenocarcinoma, according to driver oncogene aberration. The relative timing of mutations in *TP53*, switch/sucrose non-fermenting (SWI/SNF) chromatin remodeling, and other cancer-related genes is unknown.

genome-wide studies revealed that inactivating/deleterious *NF1* mutations are present in 8.3% of US LADCs.[7] In addition, gain-of-function mutations in *MEK1*, also called *MAP2K1*, which activate the MAPK/ERK pathway, were also detected in oncogene-negative LADCs in a US patient group (0.9%).[41] Tumors harboring *NF1* inactivation or *MAP2K1* activation could be targeted by MEK inhibitors.[7,41] Such mutations have been observed in a few cases of driver oncogene-negative LADCs in the Japanese cohort (Table S4),[42] supporting the idea that these two genes also function as drivers.

The *NTRK1* gene encodes the tropomyosin receptor kinase A (TRKA) protein, which activates the MAPK, phospholipase C-γ (PLC-γ), and phosphatidylinositol 3-kinase (PI3K) pathways. Fusions of *NTRK1* have been detected in oncogene-negative LADCs,[43] although their incidence is likely to be less than 1% in the USA.[44] Notably, the tropomyosin receptor kinase A inhibitor, entrectinib, has yielded promising results against such tumors.[44] In addition, activating mutation of *ARAF* was detected in a case of LADC that was an exceptional responder to sorafenib, a multiple kinase inhibitor.[45] Therefore, *NTRK* fusion and *ARAF* mutation represent druggable oncogene aberrations. However, no *NTRK* fusions or *ARAF* mutations have been observed in our Japanese LADC cohort, indicating that these aberrations make little or no contribution to the development of LADC in people of Japanese descent.

Distinct Driver Oncogene of Lung Tumors with Specific Subtypes

Invasive mucinous lung adenocarcinoma, a histological subtype of LADC composed predominantly of goblet cells, constitutes 5–10% of all LADC cases. Invasive mucinous lung adenocarcinoma tumors frequently harbor activating *KRAS* mutations. Recently, our group and others identified *CD74–NRG1* fusion as another driver oncogene aberration in IMA of Japanese patients, particularly in females and never-smokers (Figs 4,S2).[46,47] The *NRG1* gene encodes a ligand of ERBB receptor tyrosine kinases, neuregulin/heregulin, and its fusion to *CD74* leads to extracellular expression of the epidermal growth factor-like domain of neuregulin, providing a ligand for the HER2–HER3 complex. Activated HER2–HER3 signaling increases cancer stem cell properties through an autocrine loop mediated by IGF2.[48] Thus, IMA with *CD74–NRG1* fusion can be treated using TKIs that target HER and /or IGFR kinases. Ciliated muconodular papillary tumor, a rare peripheral non-endobronchial lung nodule, frequently harbors *BRAF* mutation (50%).[49] Together, these observations indicate that the relative significance of specific driver oncogene aberrations is likely to differ between common LADCs and lung tumors with distinct histologies.

Precision LADC Medicine Based on Multistep Molecular Carcinogenesis

Both *EGFR* and *KRAS* mutations are detected in invasive and non-invasive tumors (adenocarcinomas *in situ*). By contrast, mutations in the *TP53* tumor-suppressor gene are detected exclusively in invasive tumors with *EGFR* and *KRAS* mutations, but never in non-invasive tumors.[50–52] Therefore, it is likely that *EGFR* and *KRAS* mutations contribute to the genesis of non-invasive tumor cells, and that *TP53* aberration facilitates progression of non-invasive tumor cells to the invasive state (Fig. 5). Consistent with this, several studies reported that loss of *TP53* function promotes the development of an invasive /metastatic tumor phenotype.[53,54] These observations suggest that targeting cells with aberrant *TP53* function, for example, by attacking vulnerabilities cause by *TP53* dysfunction[55,56] or restoring the function of abnormal TP53 protein,[57] might be an effective strategy against tumors harboring such mutations.

By contrast, the majority of LADCs with *ALK*, *RET*, and *ROS1* fusions are negative for *TP53* aberrations as well as other cancer-related gene aberrations.[42] At present, it not clear whether these fusions occur in pre-invasive lung tumors; however, the fusion gene products may be able to generate LADC and promote tumor progression by themselves. Thus, these results support the current therapeutic strategy of using TKIs to suppress the activity of gene fusion products in fusion-positive LADCs.

Approximately 30% and 50% of Japanese and US LADCs, respectively, lack targetable oncogene aberrations (Fig. 1). Patients with these tumors were previously thought not to benefit from molecular targeted therapy; several therapeutic means of circumventing this situation are currently being investigated.

First, patients with driver oncogene-negative LADCs are often males and ever-smokers, and their tumors have larger numbers of mutations, especially tobacco-associated transversions, than those in never-smokers.[42] Therefore, such cases should respond well to immune checkpoint blockade therapy, whose effectiveness depends on the mutation burden of tumor cells.[58] Second, oncogene-negative LADCs frequently harbor deleterious aberrations in genes encoding subunits of the SWI/SNF chromatin remodeling complexes, such as *SMARCA4/BRG1* and *ARID1A/BAF250A* (Fig. S3).[42,59] Such SWI/SNF gene defects are thought to contribute to carcinogenesis through dysregulation of gene expression and cell differentiation, in cooperation with other cancer-related gene aberrations. However, these mutations also create a vulnerability in cancer cells: specifically, tumor cells with SWI/SNF defects are more dependent on functions of other chromatin remodeling genes than those without such defects. For example, *SMARCA4*-deficient cancer cells depend on *SMARCA2/BRM*, and growth of *ARID1A*-deficient cancer cells is dependent on *EZH2*.[59–62] Several inhibitors for *EZH2* histone H3K27 methyltransferase have been developed for the treatment of blood tumors with activating *EZH2* mutations, and repositioning of these drugs represents a promising approach to treating oncogene-negative LADC.

The *NKX2-1/TTF-1* gene was rediscovered as a target oncogene for focal amplification in LADC.[63] *NKX2-1* encodes a lineage-specific transcription factor that has an essential role in the formation of type II pneumocytes, which line the alveoli of the lung; therefore, it is a lineage survival oncogene. Recent studies revealed that the receptor tyrosine kinase *ROR1* is a transcriptional target of *NKX2-1* and is a promising target for LADC therapy, irrespective of *EGFR* mutation status.[64,65] Targeting of IGF1/2, IGF1R, and vascular endothelial growth factor receptor (VEGFR) for the therapy of LADC has also been reported.[66,67] Thus, drugs targeting several oncogene products are predicted to contribute further to precision LADC medicine in the near future.

Toward Further Improvements in Precision Medicine

In this review, we summarized the gene aberrations that underlie carcinogenesis and guide personalized therapy against LADC. To further understand the molecular characteristics of these aberrations and improve precision medicine for LADC, we believe that studies carried out in the near future should focus on the following priorities. First, we need to identify gene aberrations that drive the development of oncogene-negative LADCs and to which cancer cells become addicted. Genetic and epigenetic aberrations that have not been detected by whole-exome sequencing studies to date may be responsible for oncogene activation and/or tumor-suppressor gene inactivation. Strong candidates for such aberrations include oncogene activation by intra-gene rearrangements, such as exon duplication in *EGFR*,[68] or by super-enhancer formation/amplification.[69] Deficiency in chromatin remodeling genes might also activate oncogenes and/or inactivate tumor-suppressor genes. Second, we must identify genes that affect the efficacy of molecular targeted therapy. Tumor response to these therapies varies even among cases harboring the same driver oncogene aberration. Elucidation of the responsible factors will enable us to improve the efficacy of existing therapies. Finally, we must identify the genetic polymorphisms or germline mutations that underlie the development of LADC interacting with the occurrence of driver oncogene aberrations. This information will aid in prevention and early, accurate detection of LADC. Because most molecular targeted therapies are given to patients with advanced cases, and eventually fail due to drug resistance, efforts toward prevention and early diagnosis will ultimately make a significant contribution to curing these diseases.

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Disclosure Statement

The authors have no conflict of interest.

Abbreviations

ALK	anaplastic lymphoma kinase
BRAF	B-Raf proto-oncogene
EGFR	epidermal growth factor receptor
HER	human epidermal growth factor receptor
IGF	insulin-like growth factor
IGFR	insulin-like growth factor receptor
IMA	invasive mucinous lung adenocarcinoma
LADC	lung adenocarcinoma
RET	Ret proto-oncogene
ROS1	proto-oncogene 1
SWI/SNF	switch/sucrose non-fermenting
TKI	tyrosine kinase inhibitor

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Fig. S1. Frequency of driver oncogene aberrations in lung adenocarcinoma according to combined sex and smoking status.

Fig. S2. Frequency of driver oncogene aberrations in invasive mucinous lung adenocarcinoma according to sex and smoking status.

Fig. S3. Positions and types of *SMARCA4* and *ARID1A* mutations in Japanese and US patients with lung adenocarcinomas.

Table S1. Representative large-scale genomic sequencing studies in major histological types of lung cancer.

Table S2. Comparison of clinical and pathological characteristics in patients with lung adenocarcinomas between a Japanese cohort from the National Cancer Center Hospital, Tokyo (NCC_Japan) and a US cohort from The Cancer Genome Atlas study (TCGA_USA).

Table S3. Odds ratios for single nucleotide polymorphisms in two loci associated with lung adenocarcinoma risk.

Table S4. Other infrequent candidate driver gene aberrations in a lung adenocarcinoma patient cohort from the National Cancer Center Hospital, Tokyo (NCC) (Saito *et al.*, 2015).