


REVIEW ARTICLE

The nonsmokers' and smokers' pathways in lung adenocarcinoma: Histological progression and molecular bases

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Abstract

There could be two carcinogenetic pathways for lung adenocarcinoma (LADC): the nonsmokers' pathway and the smokers' pathway. This review article describes the two pathways with special reference to potential relationships between histological subtypes, malignant grades, and driver mutations. The lung is composed of two different tissue units, the terminal respiratory unit (TRU) and the central airway compartment (CAC). In the nonsmokers' pathway, LADCs develop from the TRU, and their histological appearances change from lepidic to micropapillary during the progression process. In the smokers' pathway, LADCs develop from either the TRU or the CAC, and their histological appearances vary among cases in the middle of the progression process, but they are likely converged to acinar/solid at the end. On a molecular genetic level, the nonsmokers' pathway is mostly driven by *EGFR* mutations, whereas in the smokers' pathway, approximately one-quarter of LADCs have *KRAS* mutations, but the other three-quarters have no known driver mutations. p53 mutations are an important factor triggering the progression of both pathways, with unique molecular alterations associated with each, such as MUC21 expression and chromosome 12p13-21 amplification in the nonsmokers' pathway, and HNF4 α expression and TTF1 mutations in the smokers' pathway. However, investigation into the relationship between histological progression and genetic alterations is in its infancy. Tight cooperation between traditional histopathological examinations and recent molecular genetics can provide valuable insight to better understand the nature of LADCs.

KEYWORDS

lung adenocarcinoma, micropapillary, solid/acinar, progression, smoking

1 | INTRODUCTION

Lung adenocarcinoma (LADC) shows considerable heterogeneity in patients' characteristics, clinical courses, histological appearances, and molecular alternations. It is needed to clearly describe their biological nature for precision medicine.

Recent efforts in the field of molecular genetics have uncovered essential driver oncogenes, including *EGFR*, *KRAS*, *BRAF*, *ALK*, *ROS1*, *RET*, and *NRG1*, that can be targets for newly developed therapeutic agents.¹⁻⁷ Subtyping of LADC based on the driver mutations is beneficial in a clinical setting and is becoming increasingly common. However, the driver mutations themselves do not seem to be direct

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determinants for malignant grades,^{7,8} as subtyping solely based on the driver mutations may not be enough to support a prognosis. On the other hand, traditional histological subtyping is informative in terms of identifying histogenesis and malignant grades.⁷

It has been supposed there could be two carcinogenetic pathways for LADC: the nonsmokers' pathway and the smokers' pathway. This review article describes the two pathways with special reference to potential relationships between histological subtypes, malignant grades, and driver mutations.

2 | THE TWO PUTATIVE CARCINOGENETIC PATHWAYS

Current research suggests that there are two distinct pathways involved in the development of LADC in smokers and nonsmokers.⁷ Recently, Yatabe et al proposed a theory that the lung is composed of two different tissue units, the terminal respiratory unit (TRU) and the central airway compartment (CAC).^{7,9,10} The TRU includes the distal/terminal bronchiole to the alveoli and mainly participates in gas exchange, whereas non-TRU/CAC includes the trachea, bronchus, and the proximal/lobular bronchioles, which are responsible for directing gas into the alveoli. Most LADCs are developed from the TRU, which constantly expresses thyroid transcription factor 1 (TTF1).⁷ TRU-type LADCs predominantly occur in nonsmokers. The predisposition to nonsmokers is particularly interesting, as it is quite different from the other histological types, such as squamous cell, small cell, and large cell carcinomas.⁷ In contrast, TTF1-negative, non-TRU/CAC-type LADCs preferentially occur in smokers.⁷ Thus, this TRU/non-TRU concept is a concise theory to better understand the histogenesis of the nonsmokers' and smokers' pathways.

3 | A PROPOSAL OF FIVE ESSENTIAL GROUPS FOR LADCS

The TRU/non-TRU concept is a theory based on histogenesis. On the other hand, the nonsmokers'/smokers' concept is a theory to describe the potential effects of carcinogenetic stimuli on the development/progression of cancers. Actually, TRU-type LADCs can develop in both smokers and nonsmokers and can differentially progress each other. Thus, we have been considering that the TRU/non-TRU classification is not enough to better understand the tumor progression. To improve this, we here propose five groups based on histological appearances, which are modified from our previous publications,^{11,12} and describe them while linking together the nonsmokers'/smokers' pathways, the TRU/non-TRU concept, patients' baseline characteristics, clinical courses, and driver mutations (Table 1).

Briefly, **group A** is defined as lepidic or papillary dominant LADC without any mucin-producing element or micropapillary element (according to the WHO classification system,⁷ histological elements less than 5% were ignored [judged as none]); **group B** as LADC with acinar element of mucinous cribriform pattern; **group C** as LADC

with micropapillary elements; **group D** as mucinous adenocarcinoma (both invasive and in situ) and/or enteric adenocarcinoma; and **group E** as conventional acinar (not mucinous cribriform pattern) and/or solid dominant LADC. Representative histological appearances are shown with references to the nonsmokers'/smokers' pathways, essential molecular alterations, and the potential between-group crosstalk in Figure 1. Specific features in detail for each of the five groups are as follows:

3.1 | Group A

Group A includes TRU-type LADCs that typically affect female nonsmokers (Table 1), mostly show lepidic-dominant histology including adenocarcinoma in situ and minimally invasive adenocarcinomas, and occasionally show papillary-dominant histology. LADCs of this group are generally slow growing (Table 1) and not aggressive; hence, they are surgically operable in most cases. Thus, pathologists see this type of LADCs in surgical specimens frequently, where they comprise 42% (Table 1). Surgical removal is enough to completely control this group in most cases, and it ultimately results in favorable outcomes (Figure 2). Although majority of this group of LADCs have *EGFR* mutations (Table 2 and Figure 3), *EGFR* tyrosine kinase inhibitors (TKIs) are usually not needed because of the favorable postoperative outcomes.¹³

3.2 | Group B

This group includes TRU-type LADCs that entirely or partially show cribriform and solid elements with mucin production. This group affects relatively young nonsmokers (Table 1) and shows relatively favorable prognosis (Figure 2). Gender predisposition seems relatively weak (Table 1). This group is rare and comprises 2.5% of all surgically removed LADCs (Table 1). A particular feature is frequent fusion gene mutations, such as *ALK* and *ROS1* (Table 2 and Figure 3). This type can be described as "solid LADC with mucin production," "acinar LADC with cribriform structure with mucin production," or sometimes as "signet ring cell carcinoma," in pathological diagnosis reports.

3.3 | Group C

As group A, group C includes TRU-type LADCs that predominantly affect female nonsmokers. This type has a micropapillary element in lepidic or papillary backgrounds, where proportions of the micropapillary element vary among cases, but generally are not so large (typically 5 to 25%) in surgically removed LADCs.^{13,14} LADCs of this group are usually described as "lepidic or papillary-dominant LADC with micropapillary element" or simply as "lepidic or papillary-dominant LADC" or "minimally invasive adenocarcinoma" in pathological diagnosis reports, and they comprise 13.8% of surgically removed LADCs (Table 1). Proliferating activities are generally not

TABLE 1 Essential clinicopathological features in the five groups (A-E) proposed

	Group A (296)	Group B (18)	Group C (97)	Group D (65)	Group E (230)
Histological	Lepidic/papillary	With mucinous cribriform	With micropapillary	Mucinous/enteric	Acinar/solid
Cytological	TRU	TRU	TRU	Non-TRU	TRU/non-TRU
Immunohistochemical	TTF1+/HNF4 α -	TTF1+/HNF4 α -	TTF1+/HNF4 α -	TTF1-/HNF4 α +	TTF1+/-HNF4 α +
Cell growth (Ki-67 LI, mean \pm SD)	Weak (0.08 \pm 0.11)	Moderate (0.14 \pm 0.09)	Moderate (0.15 \pm 0.12)	Moderate (0.23 \pm 0.22)	Strong (0.35 \pm 0.18)
Frequency sW (s \leq I/s \geq II)	42.0% (54.3%/8.9%)	2.5% (2.1%/3.6%)	13.8% (11.5%/20.1%)	9.3% (9.5%/8.3%)	32.4% (22.5%/59.5%)
Age median (range)	68 (28-86)	61 (29-79)	73 (31-82)	68 (43-84)	69 (36-87)
Gender M/F	0.7	1.3	0.42	1.8	3.5
Smoking S/NS	0.6	0.3	0.3	1.5	7.3
Prognosis (5 y-DFS sW/s \leq I)	Favorable (92.6%/94.3%)	Worse (79.8%/100%)	Worst (49.0%/61.3%)	Worse (54.5%/70.0%)	Worst (46.6%/63.2%)
Main drivers	EGFR	ALK/ROS1	EGFR	KRAS/NRG1	KRAS
Potential progressors			p53 loss ²⁷ ; CXCL14 gain; ³² E-cadherin loss, axin1 gain, wnt signal gain; ³⁴ MUC21 gain; ¹⁶ DYRK2 gain; ³¹ c- met gain ³³	TTF1 loss; ^{46,47} pulmonary surfactant system loss ⁴⁶	p53 loss; ^{12,41} DUSP6 loss; ⁴³ S100A11 gain; ³⁷ FXYP3 loss; ⁴² HDAC9 loss; ³⁹ miR31 loss; ⁴⁰ CTSL1 loss; ⁴⁴ TPM1 loss; ⁴⁵ CLIC4 loss ³⁸

Note: Lung adenocarcinoma patients who underwent surgical operation in Kanagawa prefectural cardiovascular center hospital from 1994 to 2013 (706 cases in total, 514 pathological stage 0/I and 192 II/III) were subjected. Number of cases examined in each of the groups is shown parentheses after the alphabets. Pathological stages were determined according to the AJCC Cancer Staging Manual (8th edition).⁵⁰ Superscript numbers indicate the reference numbers.

Abbreviations: 5y-DFS, 5-y disease-free survival; F, female; LI, labeling index; M, male; NS, nonsmoker; S, smoker; sW, whole pathological stage; \leq I, pathological stage 0 and I; \geq II, pathological stage II and III; TRU, terminal respiratory unit.

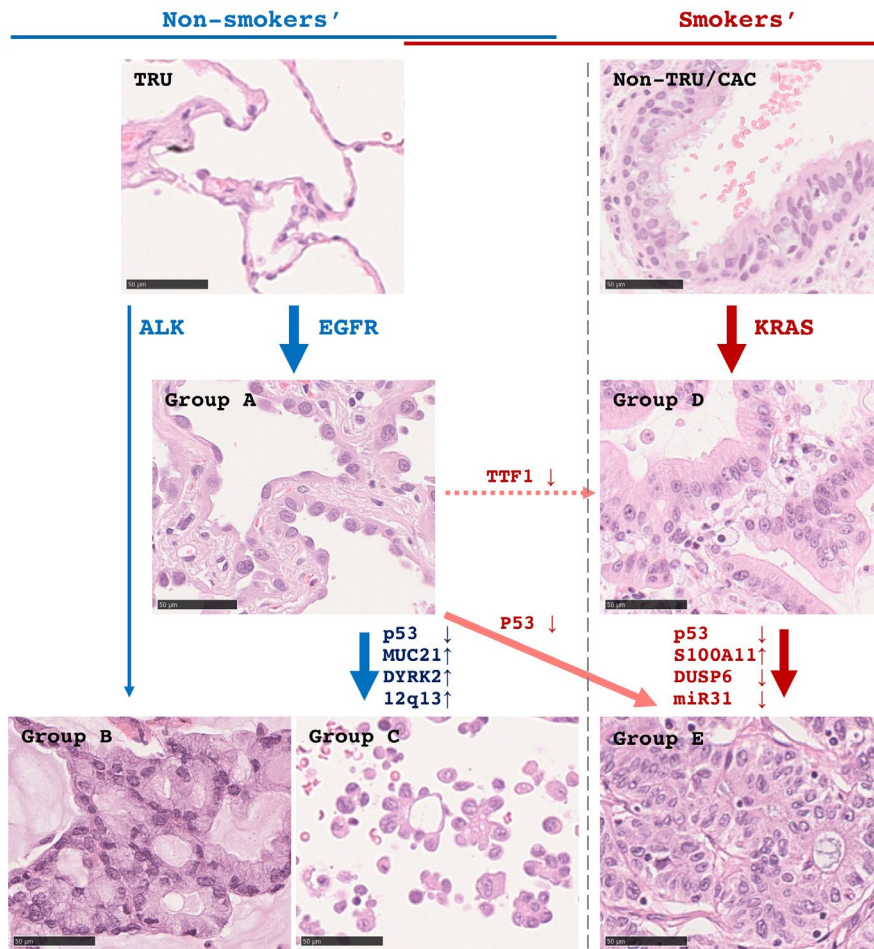


FIGURE 1 A scheme of histological progression of lung adenocarcinomas (LADCs) in the nonsmokers' (left panels, blue arrows) and smokers' (right panels, red arrows) pathway is shown. In the smokers' pathway, group A (lepidic histology) develops from the terminal respiratory unit (TRU) with *EGFR* mutations, and some of them can progress to group C (micropapillary) through accumulations of second molecular alterations. Group B (acinar/cribriform with mucin) may directly develop from the TRU with *ALK* mutations. In the smokers' pathway, group D (mucinous subtype) develops from the non-TRU/central airway compartment (CAC), where one major driver in the smoker's pathway is *KRAS*. Some can progress to group E (conventional acinar/solid) through second alterations. Alternatively, there are putative extra-bypassing pathways. Under exposing to smoking stimuli, group A can progress to group E (orange arrow). Also, through acquired thyroid transcription factor 1 (TTF1) inactivation, group A can progress to group D (dashed orange arrow). Scale bars, 50 μm

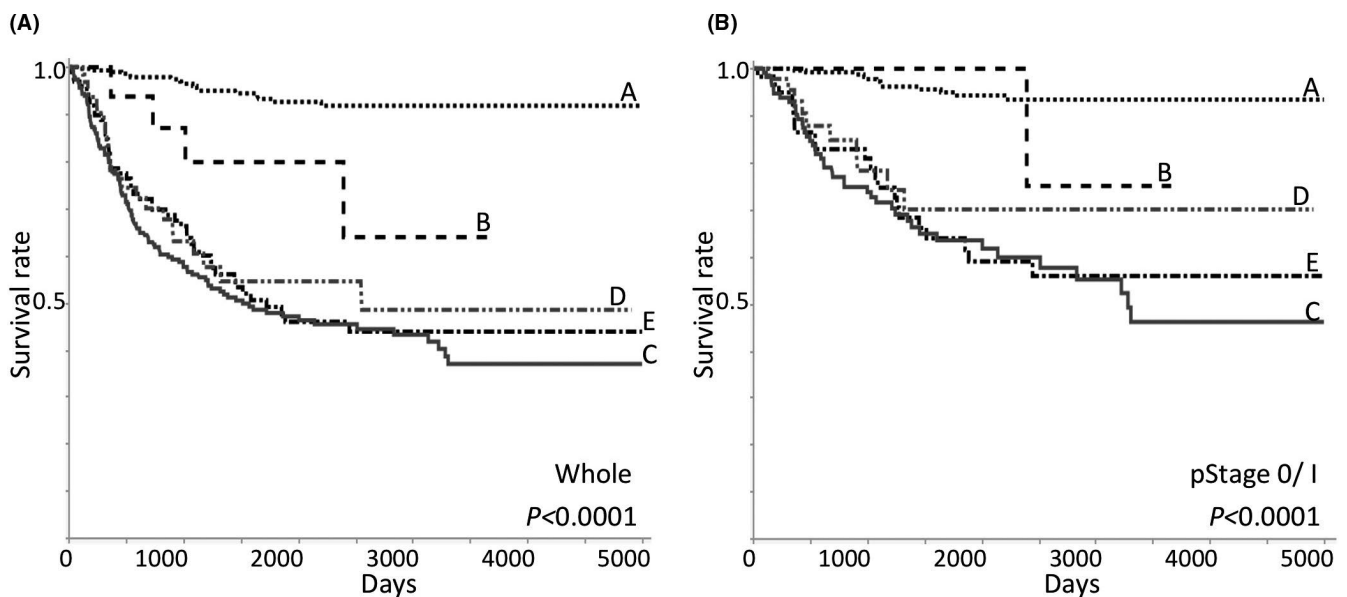


FIGURE 2 Kaplan-Meier's disease-free survival curves from whole (A) and pathological stage 0/I (pStage 0/I) lung adenocarcinomas (LADCs) (B) are shown. A total of 706 cases who underwent surgical resection in Kanagawa Prefectural Cardiovascular and Respiratory Center Hospital from 1994 to 2013 were examined: 514 stage 0/I (279 group A, 11 group B, 59 group C, 49 group D, and 116 group E), 192 stage II/III (17 group A, 7 group B, 38 group C, 16 group D, and 114 group E). Pathological stages were determined according to the AJCC Cancer Staging Manual 8th edition⁵⁰

TABLE 2 Frequencies (%) of driver mutations in the five groups (A-E) proposed

	A (184)	B (15)	C (79)	D (46)	E (166)
<i>EGFR</i>	72.3	0.0	74.7	0.0	11.5
<i>ERBB2</i>	4.9	0.0	1.3	0.0	1.8
<i>MET</i>	2.7	0.0	5.1	0.0	1.2
<i>ALK</i>	1.1	60.0	2.5	0.0	1.2
<i>ROS1</i>	1.1	20.0	0.0	0.0	0.0
<i>RET</i>	0.0	6.7	0.0	0.0	0.0
<i>BRAF</i>	0.5	0.0	1.3	0.0	3.6
<i>KRAS</i>	2.2	0.0	0.0	55.4	18.1
<i>NRG1</i>	0.0	0.0	0.0	10.9	0.0
NONE	13.6	13.3	16.5	34.8	63.3

Note: Lung adenocarcinomas surgically resected in Kanagawa prefectural cardiovascular center hospital were examined. Number in each of the groups is shown in parentheses after the alphabets.

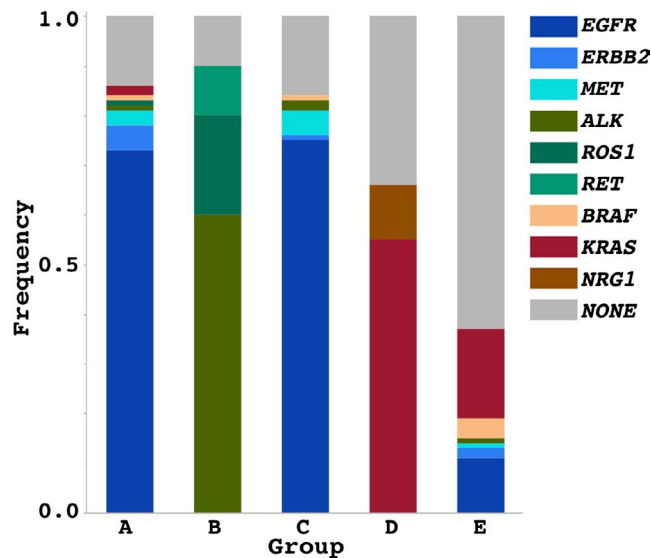


FIGURE 3 Frequencies of driver mutations are shown in each of the groups. A difference in the driver mutations is remarkable between the groups. *EGFR* mutations are mostly seen in groups A and C, *ALK* and *ROS1* mutations are seen in group B, and *KRAS* mutations are more commonly seen in group D, followed by group E

as strong (Table 1), but they often show strong lymphatic canal and vascular involvements and aggressive clinical courses^{13,15} (Figure 2). Most inoperable cases from nonsmokers belong to this group.^{13,16} Fortunately, this group generally has *EGFR* mutations (Table 2 and Figure 3) and can respond well to *EGFR*-TKI treatments.^{13,15,17,18}

3.4 | Group D

This group exclusively comprises specific histological subtypes of mucinous LADC (invasive or in situ) and enteric LADC. They consist

of tall columnar neoplastic cells that are usually mucin producing. This group is negative for TTF1 and positive for hepatocyte nuclear factor 4 α (HNF4 α), an important transcription factor in the upper digestive tract epithelia, implying their gastric/intestinal differentiation; hence they are categorized as non-TRU-type.¹⁹ This group is infrequent and comprises 9.3% of surgically removed LADCs (Table 1). LADCs of this group preferentially develop in male smokers, but gender difference and smoker predisposition seems to be not so significant. This group shows relatively poor clinical courses (Figure 2). LADCs of this group are frequently affected by *KRAS* mutations but almost never by *EGFR* mutations (Table 2 and Figure 3).^{7,10,19,20} Interestingly, *NRG1* mutations are specific to group D.²¹ Another particular feature is a strong relationship to pulmonary fibrosis.²⁰ Most of pulmonary fibrosis patients are smokers.²⁰ Smoking-related carcinogens, chronic cellular damage, and tissue remodeling might promote this group of LADC in cooperation. LADCs of this group can be described as “mucinous LADC,” “enteric LADC,” or maybe sometimes “acinar LADCs” in pathological diagnosis reports.

3.5 | Group E

The fifth group is typically observed in male heavy smokers. This group comprises 32.4% of all surgically removed LADCs (Table 1). LADCs of this group histologically show acinar or solid architecture, where neoplastic cells tend to be larger and show more remarkable nuclear atypism and polymorphism than the other groups.¹² Noteworthy, 12.3% of LADCs in this group are negative for both TTF1 and HNF4 α (our original data), suggesting their poor degree of differentiation. Proliferating activity is generally high, with a Ki-67 labeling index of more than 0.3 (Table 1). This group shows significantly worse clinical courses (Figure 2). Genetically, 18.1% of LADCs have *KRAS* mutations, and also small proportions have *EGFR* or *ALK* mutations (Table 2, Figure 3). However, more than 60% of LADCs in this group have no known driver mutations (Table 2, Figure 3). Thus, due to its heterogeneity, group E might be the terminal of the different pathways. LADCs of this group can be described as “acinar dominant LADC,” “solid dominant LADC,” or “poorly differentiated LADC” in pathological diagnosis reports.

4 | TUMOR PROGRESSION IN THE NONSMOKERS' PATHWAY

A micropapillary element is an essential determinant for the malignant activity in TRU-type LADCs.^{16,17,22,23} As mentioned previously, group C has *EGFR* mutations as frequently as group A; both are TRU-type LADCs and commonly share a lepidic (or papillary) element. Thus, it is suggested that a micropapillary element could generate from lepidic (or papillary) elements. So far, pathologists have investigated morphological features of micropapillary elements and suggested that a micropapillary element is a structure

resulting from tumor cells' focal stacking to form pseudopapillary projections without fibrovascular stalks.^{17,24,25} To form such structures, neoplastic cells are inevitably anchorage independent, detach from basement membranes, can grow, and simultaneously have to retain epithelial polarity and an intercellular adhesion system partially.^{13,23-26} It is essential to question how lepidic (or papillary) elements acquire the micropapillary phenotype in terms of their molecular basis.^{14,23-25,27} p53 mutations can be an important factor to trigger this process,²⁸⁻³⁰ but there also seem to be additional unique events. Our recent study demonstrated differentially expressed genes in micropapillary elements compared with lepidic elements.³¹ The results showed some alterations in adhesion molecules, basement membrane materials, and kinases.³¹ In particular, overexpression of oligo-glycosylated MUC21 protein²² and amplification of chromosome 12q13-21 locus covering *CDK4*, *MDM2*, and *DYRK2* genes³¹ were suggested to participate in producing micropapillary elements. Although there are no other studies that comprehensively compare molecular profiles between micropapillary and background lepidic (or papillary) elements in individual tumors, several studies have shown differences in molecular alterations (genetic mutations) between high-grade and low-grade components of LADCs (that were not specified as micropapillary).²⁸ They also demonstrated molecular alterations likely to be involved in producing micropapillary morphology, such as gain of *CXCL14*, *MET*, *AXIN1*, and *WNT* family proteins^{18,26,32-34} (Table 1). The mechanisms behind the molecular alterations and how these alterations produce micropapillary elements are still largely unclear. Uncovering these, as well as carcinogens which promote this process, could lead to the establishment of novel therapeutic and prevention strategies.

5 | TUMOR PROGRESSION IN THE SMOKERS' PATHWAY

The smokers' pathway appears to be more complex. Poorly differentiated LADCs (group E) can arise from other groups mentioned, not only non-TRU/CAC-type LADCs (group D) but also TRU-type LADCs (group A), as group E includes both TTF1-negative (non-TRU) and positive (TRU) LADCs (Table 1). Interestingly, in group E, even in TTF1-positive LADCs, *EGFR* mutations are rather rare (Table 2 and Figure 3). The frequency of *KRAS* mutations, that are the most common driver mutations in the smokers' pathway, is also not high (Table 2 and Figure 3),^{12,35} suggesting that there could be another alternative tumor-driving system.^{7,28} We propose a hypothesis that there may be no single strong leading mutation in LADCs in the smoker's pathway. Several tiny mutations each could participate in small quantities, the sum of which could be equivalent to one driver mutation to promote tumor development. In fact, smokers' LADCs have been shown to accumulate more genetic mutations than nonsmokers'.^{28,36} It is of great interest to uncover how such small mutations collectively drive the driver mutation-negative smokers' LADCs. Concentrating efforts

in molecular genetics and bioinformatics will solve this molecular puzzle in the near future.

Apart from driver mutations, regarding tumor progression, p53 mutations are an important trigger factor,^{29,30} and disruptions of oncogenic *KRAS*-induced negative feedback systems, such as down-regulation of *DUSP6*, *miR-31*, and upregulation of *S100A11*, are common events in the smokers' pathway.³⁷⁻⁴⁵ Moreover, *TTF1* mutations and surfactant protein gene mutations are also reported to be unique to the smokers' pathway.^{46,47}

6 | EXTRA-BYPASSING PATHWAYS

Alternatively, there could be extra-bypassing pathways. Actually, LADCs having both TTF1-positive lepidic and HNF4 α -positive mucinous components are occasionally seen. Interestingly, Matsubara D et al demonstrated that mucinous LADCs with TTF1-positive lepidic component more often had TTF1 gene mutations and methylations than pure mucinous LADCs.⁴⁷ The findings suggest that there could be a bypass from A to D (Figure 1). Also, as mentioned afore, group E might be the terminal of the different pathways. Under exposing to smoking stimuli, different groups might progress to group E (Figure 1).

7 | ISSUES IN RECENT LUNG CANCER RESEARCH

Large-scale genetic analyses have provided us with a large volume of information and are helping to uncover a fuller picture of the molecular basis of LADC. However, more care should be taken regarding the processing of analytical results. For example, it is important to take into consideration if the tumor is definitely negative for driver mutations. Analytical results may be false negatives due to extremely small neoplastic cell contents. In general, LADCs, particularly, poorly differentiated ones, have many leukocytes and fibroblasts, and hence this "noise" can easily result in false negatives. Purification of neoplastic cells from tumor tissues is an important process to improve accuracy of mutational analyses. At present, histological (or cytological) appearance is the most reliable biological marker that detects neoplastic cells. However, using artificial intelligence to detect neoplastic cells and the automatic operation of microdissection systems can improve accuracy.

8 | FUTURE PERSPECTIVE

Again, the recent advance in molecular genetics has uncovered a lot of molecular targets for therapeutic agents. However, this progress seems to have been slowing down in recent years. Going forward, we should focus on molecular alterations responsible for tumor progression, which would be targets for next-generation therapies. For such alterations, we here suggest a term "progressor." We know

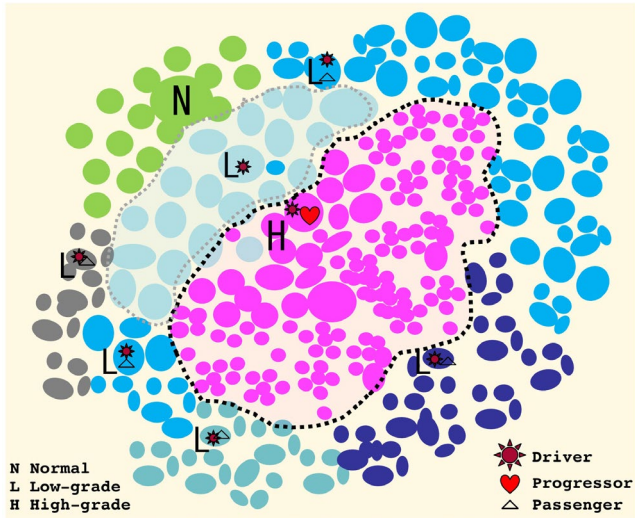


FIGURE 4 A scheme for progression of lung adenocarcinoma (LADC). During the progression process, one LADC can produce genetically heterogeneous subpopulations. At first, driver mutations transform normal counterpart cells (N) to low-grade neoplastic cells (L). While the neoplastic cells are proliferating, many additional mutations can occur, most of which might be nonfunctional passenger mutations, and some of which can be true progressors to produce high-grade elements (H)

intratumor subclonal heterogeneity and passenger mutations (non-functional noise) are critical obstacles against successful detection of essential molecular alterations to promote tumor progression.^{48,49} Thus, simple large-scale analyses on bulky tumor samples are not sufficient for the success. As is shown in Figure 4, if we comparatively analyze high-grade components and background low-grade components from identical tumors, it alleviates the issue of noise. Microdissection systems can be the most dependable way to reach such targets.

9 | SUMMARY AND CONCLUSION

There are the two major pathways in LADC carcinogenesis. In the nonsmokers' and smokers' pathways, the terminals are micropapillary and acinar/solid histology, respectively. LADCs are highly heterogeneous even in an identical tumor. Different genetic alterations can participate in each pathway, and identifying essential molecular alterations promoting tumor progression is a critical task. To meet the next goal, focusing on high-grade elements based on careful histological examinations is necessary.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest.

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