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ORIGINAL ARTICLE

Constitutional abnormality of nuclear membrane proteins in small cell lung carcinoma

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Abstract

Nuclear membrane proteins reportedly play important roles in maintaining nuclear structures and coordinating cell activities. Studying profiles of nuclear membrane proteins may help us evaluate the biological and/or clinical nature of malignant tumors. Using immunohistochemistry with antibodies for emerin, lamin A/C, lamin B, and LAP2, we examined 105 lung cancer tissues from 33 small cell lung carcinomas (SCLCs) and 72 non-SCLCs (34 adenocarcinomas, 30 squamous cell carcinomas, and 8 large cell carcinomas). Emerin had negative or local/weak positivity in 79% of SCLCs and 1% of non-SCLCs, and lamin A/C had similar positivity in 91% of SCLCs and 3% of non-SCLCs. LAP2's expression was similar between SCLCs and non-SCLCs. RT-PCR analyses for these four nuclear membrane proteins over 7 cell lines showed that mRNA of emerin and lamin A/C were distinctly downregulated in the SCLC cell lines, supporting the immunohistochemical results. In conclusion, we suggest that downregulation of the nuclear membrane proteins emerin and lamin A/C is characteristic of SCLC cells, and this constitutional abnormality of the nuclear membrane may be related to the biological and/or clinical nature of SCLC. In addition, knowing the nuclear protein profile in SCLC cells may contribute to our understanding of nuclear fragility known as the crush artifact in pulmonary biopsy specimens.

Keywords Nuclear membrane proteins · Lung carcinoma · Immunohistochemistry · Polymerase chain reaction (PCR)

Introduction

The nuclear membrane is comprised of two layers: the outer nuclear membrane (ONM) and the inner nuclear membrane (INM). The ONM is continuous with the endoplasmic reticulum while the INM is associated with the nuclear lamina, and these two membranes interact through the nuclear pores [1–3].

Emerin, MANl, and lamin-associated polypeptide (LAP2) are located in the INM. They are part of the LEM-domain family which shares a folded structure, the "LEM-domain," that binds a conserved chromatin protein named BAF [4–7]. The nuclear lamina, an additional feature of the metazoan nuclear envelope, is composed of the A-type and B-type lamins (lamin A/C, lamin B) that underlie the INM [8]. The influence of the lamins extends beyond the immediate vicinity of the nuclear envelope, encompassing chromatin organization and other aspects of nuclear metabolism, including transcription and replication [9]. LEM-domain proteins and lamins likely influence each other's localization and dynamics, mediate chromatin organization and tethering at the nuclear envelope, and play other important roles in cell activities [7, 10–14].

Lung carcinoma is the leading cause of cancer-related death worldwide [15–17], and it encompasses 2 main subtypes: non-small cell lung carcinoma (non-SCLC) and small cell lung carcinoma (SCLC) [18]. SCLC has a behavior distinct from the more common non-SCLC [19, 20]. SCLC has an aggressive clinical course and a short disease-free duration after initial therapy [21]. Unfortunately, diagnosing SCLC is difficult when biopsies are small and crushed, and this often occurs with this type of tumor because of the fragile nature of the tumor cells.

Several studies have examined the nuclear membrane proteins in various human cancers including ovarian cancer, basal cell carcinoma, lung carcinoma, thyroid carcinoma, colorectal

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carcinoma, hepatocellular carcinoma, and prostate carcinoma [22–32]. We found only three studies on nuclear membrane proteins published in English scientific literature, and these studies focused on only lamin A/C or lamin B; little is known about other nuclear membrane proteins [31–33]. Therefore, examining different types of nuclear membrane proteins within different tissues and cell lines would increase our knowledge of the precise biological significance of nuclear membrane proteins in lung carcinomas. In this study, we examined the immunohistochemical expression of emerin, lamin A/C, lamin B, and LAP2 in 105 lung carcinoma tissues from 33 SCLCs and 72 non-SCLCs. In addition, we analyzed the mRNA of these nuclear membrane proteins in seven cell lines (Lu-134, Lu-139, Lu-140, A549, II-18, EBC-1, and Lu-99B).

Materials and methods

Tissue preparation

We examined a series of tissue specimens from patients with lung carcinomas selected from the surgical files of Yamanashi University Hospital. The specimens comprised a wide range of lung carcinomas including 33 cases of SCLC (11 from surgical tissue cases and 22 from biopsy tissue cases), 34 adenocarcinomas, 30 squamous cell carcinomas, and 8 large cell carcinomas.

The histologic types and subtypes of the tumor specimens fit the criteria of the World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart published in 2004. All specimens were processed after removal according to routine procedures, then embedded in paraffin and stained with hematoxylin-eosin (HE).

Cell lines and cell culture

Human lung carcinoma–derived cell lines include Lu-134, Lu-139, and Lu-140 (the originally established cell lines derived from human SCLC); A-549 and II-8 (derived from human adenocarcinoma), EBC-1 (derived from human squamous carcinoma), and Lu-99B (derived from human large cell carcinoma). Cells were maintained in RPMI 1640 (GIBCO, Grand Island, NY, USA) supplemented with 10% fetal bovine serum (FBS) and penicillin G sodium (100 mg/l). Cells were cultured in a standard, humidified incubator at 37 °C in a 5% carbon dioxide atmosphere. To prepare the cell pellets, semiconfluent plates were washed, trypsinized (excluding Lu-134, Lu-139), and centrifuged into pellets.

Immunohistochemical analysis

Table 1 characterizes the antibodies used in this study. Formalin-fixed and paraffin-embedded tissues were cut into 3-μm-thick serial sections, mounted on silanized slides, and deparaffinized. For immunohistochemical analysis, we carried out the heat-induced epitope retrieval in citrate buffer in an autoclave, and endogenous peroxidase activity was blocked for 10 min with 3% (vol/vol) hydrogen peroxide. Sections were incubated in the primary antibody overnight at 4 °C or 1 h at room temperature. Subsequently, we carried out a labeled polymer method (EnVision Detection System; Dako, Glostrup, Denmark) according to the manufacturer's instructions. A positive reaction was visualized with 3,3V-diaminobenzidine tetrahydrochloride solution (Dako, Glostrup, Denmark) followed by counterstaining with hematoxylin. We evaluated the immunoreactivity using a scale from negative to 3 (negative; 1 = positive in less than 10% of cancer cells; 2 = positive in 10–50% of cancer cells; 3 = positive in more than 50% of cancer cells).

RNA extraction and reverse transcription PCR

We used TRIzol (Invitrogen, Carlsbad, CA, USA) to isolate total RNA from cultured cells and the TaqMan reverse transcription (RT) reagent kit (Applied Biosystems, Foster City, CA, USA) to generate cDNA. Table 2 lists the specific PCR primers targeting emerin, lamin A/C, lamin B, LAP2, and glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*, as an internal control). We amplified with the HotStarTaq DNA polymerase kit (Qiagen, Tokyo, Japan). PCR conditions were as follows: (1) 95 °C for 15 min; (2) 30 cycles of 94 °C for 30 s, 58 °C for 30 s, and 72 °C for 1 min; (3) 72 °C for 10 min; and (4) 4 °C hold. Negative controls omitting RT or without cDNA and appropriate positive controls were included in each PCR reaction.

Statistical analysis

SPSS software was used for statistical analyses. We compared the SCLC group to the non-SCLC group using the Mann-

Table 1 Antibodies used in this study

Antibody	Dilution	Clone	Vendor
Emerin	1:50	Monoclonal, 4G5, mouse	Novocastra
Lamin A/C	1:50	Polyclonal, rabbit	Cell Signaling Technology
Lamin B	1:100	Polyclonal, c-20, goat	Santa Cruz Biotechnology
LAP2	1:100	Monoclonal, 27/LAP2, mouse	BD Biosciences

Table 2 PCR primers

Gene symbol	Gene accession	AT (°C)	Product size (bp)	Primer sequence (5′-3′)
Emerin	NM-000117	58	130	F: 5′-GGCCTGTAGTAGGATCAACT CG-3′
		58		R: 5′-GTCGAATTCAAGTCAGAGAA GC-3′
Lamin A	NM-170707	58	150	F: 5′-AGGCTCTGCTGAACTCCAAG-3′
		58		R: 5′-GCATCTCATCCTGAAGTTGCTT-3′
Lamin B	NM-005573	58	148	F: 5′-AGTTTCGCAAAAGCATGTAT GA-3′
		58		R: 5′-CGCCAGCTTGTACTCATACTCA-3′
LAP 2	NM-003276	58	144	F: 5′-TTGGATCAGCTTGTGAAATACG-3′
		58		R: 5′-TGAAGAAGAAATTGTTGGCA GA-3′
GAPDH	NM-002046	58	186	F: 5′-GATGACATCAAGAAGGTGGT GA-3′
		58		R: 5′-TTCGTTGTCATACCAGGAAA TG-3′

AT, annealing temperature; *F*, forward primer; *R*, reverse primer; *bp*, base pairs

Whitney rank sum test to analyze categorical variables. Statistical significance was considered as $P < 0.05$.

Results

Non-neoplastic tissue

Immunohistochemical examination with antibodies for the nuclear membrane proteins (emerin, lamin A/C, lamin B, and LAP2) showed the nuclei of all pulmonary cells, including alveolar, bronchial, and bronchiole cells, and alveolar macrophages were clearly positive appearing in a ring-like fashion (Fig. 1). Staining pattern and intensity were similar among these four antibodies.

Neoplastic tissue

We examined immune-expression of emerin, lamin A/C, lamin B, and LAP2 in 33 SCLC tissues and 72 non-SCLC tissues including adenocarcinoma ($n = 34$), squamous cell carcinoma ($n = 30$), and large cell carcinoma ($n = 8$). Nuclear membrane proteins were immunohistochemically identified in neoplastic cell nuclei in a ring-like pattern. However, the positive cell rates for each of the four different nuclear membrane proteins varied between the histological types of lung carcinoma (Fig. 2).

Emerin

Table 3 presents representative findings for emerin immunohistochemistry. Immunoreactivity of emerin was lower in SCLCs compared with that in the non-SCLCs. There were negative and focally positive (grade 1) staining in 79% of SCLCs and only one (1%) of the non-SCLCs. In contrast, there was a strong and diffuse staining in 6% of SCLCs and 76% of non-SCLCs. The positive cell rate for emerin was significantly different between SCLCs and non-SCLCs or other histological types of lung carcinomas ($P < 0.001$).

Lamin A/C

Representative findings for lamin A/C immunohistochemistry appear in Table 4. We observed a negative and grade 1 staining of lamin A/C in 91% of SCLCs and grade 1 in 3% of non-

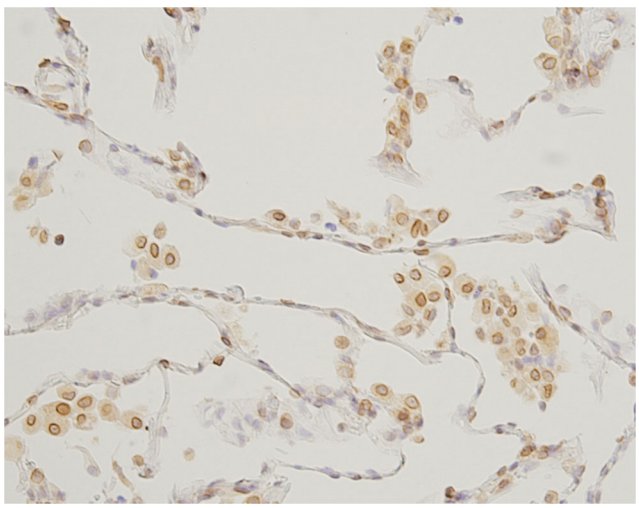

Fig. 1 Non-neoplastic lung tissue. Specific immunoreactivity of emerin in the nuclei of the type II alveolar cells and macrophages displaying a ring-like configuration. Original magnification: × 20, immunoperoxidase method

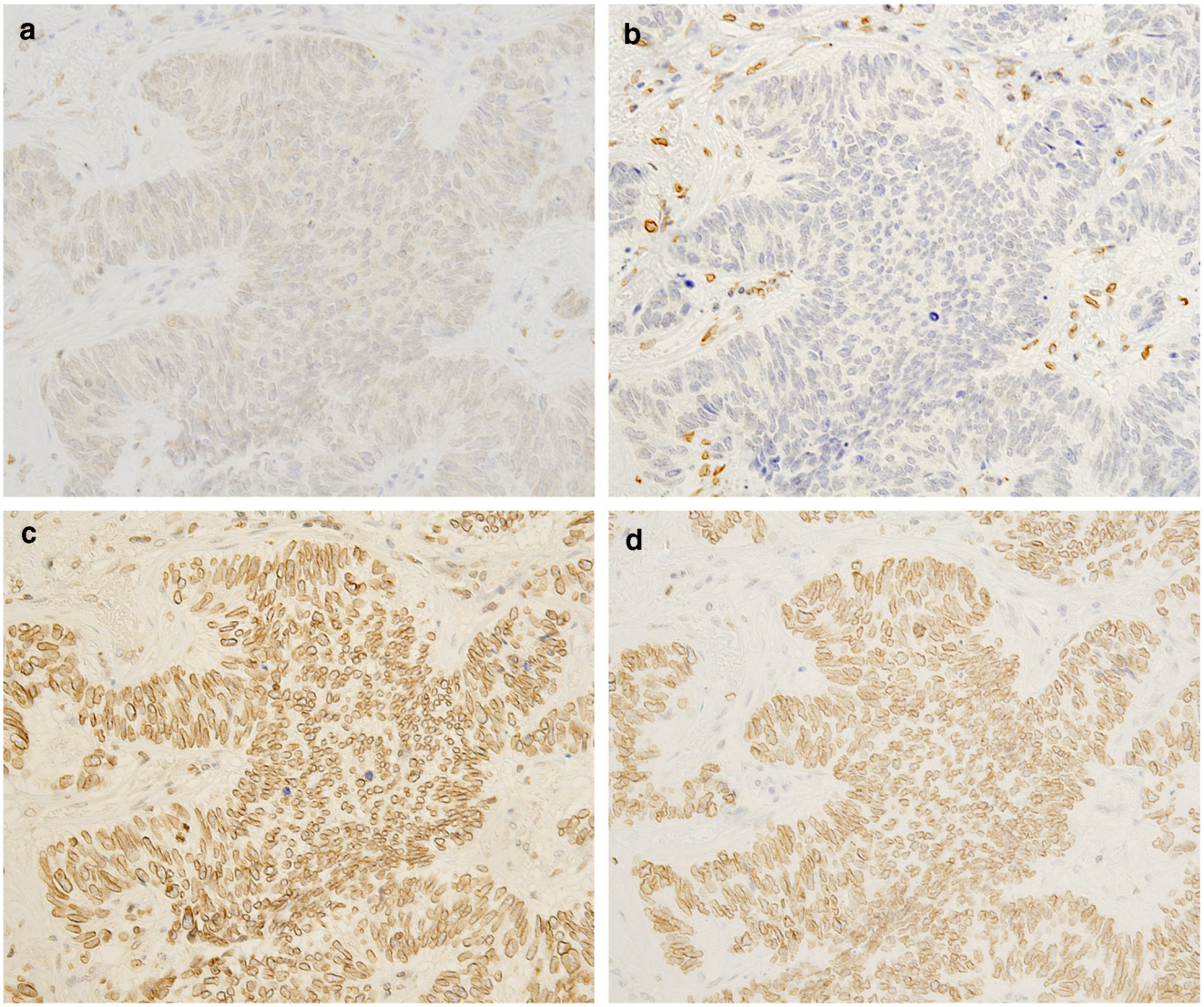

Fig. 2 Small cell lung carcinoma tissues. Immunoexpression of emerin (**a**) and lamin A/C (**b**) was negative in tumor cell nuclei, while lamin B (**c**) and LAP2 (**d**) were moderately or strongly positive. Original magnification: × 20, immunoperoxidase method

SCLCs. None of the non-SCLC tissues had negative expression. Neoplastic tissue with grade 3 staining of lamin A/C was identified in 82% of adenocarcinomas, 74% of squamous cell carcinoma, and 37% of large cell carcinoma, but there was no staining in the SCLCs. Positive cell rate for lamin A/C was significantly different between SCLCs and non-SCLCs or other histological types of lung carcinoma ($P < 0.001$).

Lamin B

Table 5 shows representative findings for lamin B immunohistochemistry. All cases of lung cancer were positive for lamin B. The prevalence rate of grade 3 expression (strong and diffusely positive) was lower in SCLC tissues compared with that in non-SCLC tissues: 31% of SCLCs and 60% of non-SCLCs. The prevalence rates of grades 2 and 3 did not vary among the histologic types of non-SCLC, but the positive cell rate for lamin B was significantly different between the SCLCs and non-SCLCs ($P < 0.001$).

LAP2

Immunoreactivity of LAP2 in lung carcinomas was the highest among the nuclear membrane proteins we examined in Table 6. No samples had negative immunoreactivity, and only one adenocarcinoma sample had a grade 1 immunoreactivity. Grade 3 immunoreactivity was identified in 85% of SCLCs and 97% of non-SCLCs. The positive cell rate for LAP2 was significantly different between SCLCs and non-SCLCs ($P < 0.05$). However, it was not significantly different between SCLCs and adenocarcinoma or large cell carcinoma.

Table 3 Immunohistochemical expression of emerin in lung carcinoma

Histological type	*n*	Immunohistochemical grade			
		Negative	1	2	3
SCLC	33	11 (34%)	15 (45%)	5 (15%)	2 (6%)
Non-SCLC					
AC	34	0	0	9 (26%)	25 (74%)
SCC	30	0	1 (3%)	4 (13%)	25 (84%)
LCC	8	0	0	3 (38%)	5 (62%)

Grade 1, focal (1 to 9% of cells positive); grade 2, intermediate (10 to 50% of cells positive); grade 3, diffuse (more than 51% of cells positive)

SCLC, small cell lung carcinoma; *AC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *LCC*, large cell carcinoma

Messenger RNA expression of nuclear membrane proteins

Using RT-PCR with oligonucleotide primers, mRNA expression levels of emerin, lamin A/C, lamin B, and LAP2 were examined in cell lines established from SCLC (Lu-134, Lu-139, and Lu-140), adenocarcinoma (A-549 and II-18), squamous cell carcinoma (EBC-1), and large cell carcinoma (Lu-99B) (Fig. 3). We saw reduced expression levels of emerin in two of three SCLC cell lines. Lamin A/C expression was lower in the three SCLC cell lines than in cell lines of other histologic types. There was a strong expression of lamin B in two of the three SCLC cell lines, and the expression of LAP2 was different among all cell lines.

Discussion

The SCLC cells appear rather small with scant cytoplasm, round to oval nuclei, and granular, dense chromatin [34]. The tumor samples often have significant necrosis and "crush" artifacts limiting the amount of intact tumor available for assessment [19]. This crush artifact suggests that nuclei of SCLC cells may be brittle or fragile due to some constitutional defect of the nuclei. Therefore, we used immunohistochemistry to study the expression of four nuclear membrane proteins, i.e., emerin, lamin A/C, lamin B, and LAP2, in samples of SCLC and non-SCLC.

In our current study, we found a negative or weak immunohistochemical expression (grade 1) of emerin in 26 out of 33 SCLC cases (79%), and only two cases of SCLC (6%) showed grade 3 expression. On the other hand, there was a strong immunohistochemical expression (grade 3) of emerin in 25 out of 34 adenocarcinomas (74%), 25 out of 30 squamous cell carcinomas (84%), and 5 out of 8 large cell carcinomas (62%). These findings suggest that immunohistochemical expression of emerin is downregulated in SCLC as compared to that in non-SCLC. In addition, lamin A/C and lamin B expression were also downregulated in SCLC. Of note, mutations in A-type lamins, as well as emerin, cause a spectrum of human diseases (laminopathies) that include Emery-Dreifuss muscular dystrophy, limb-girdle muscular dystrophy,

Table 4 Immunohistochemical expression of lamin A/C in lung carcinoma

Histological type	*n*	Immunohistochemical grade			
		Negative	1	2	3
SCLC	33	8 (24%)	22 (67%)	3 (9%)	0
Non-SCLC					
AC	34	0	1 (3%)	5 (15%)	28 (82%)
SCC	30	0	1 (3%)	7 (23%)	22 (74%)
LCC	8	0	0	5 (63%)	3 (37%)

Grade 1, focal (1 to 9% of cells positive); grade 2, intermediate (10 to 50% of cells positive); grade 3, diffuse (more than 51% of cells positive)

SCLC, small cell lung carcinoma; *AC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *LCC*, large cell carcinoma

Table 5 Immunohistochemical expression of lamin B in lung carcinoma

Histological type	*n*	Immunohistochemical grade			
		Negative	1	2	3
SCLC	33	0	9 (27%)	14 (42%)	10 (31%)
Non-SCLC					
AC	34	0	2 (6%)	9 (26%)	23 (68%)
SCC	30	0	3 (10%)	12 (40%)	15 (50%)
LCC	8	0	0	3 (37%)	5 (63%)

Grade 1, focal (1 to 9% of cells positive); grade 2, intermediate (10 to 50% of cells positive); grade 3, diffuse (more than 51% of cells positive)

SCLC, small cell lung carcinoma; *AC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *LCC*, large cell carcinoma

Table 6 Immunohistochemical expression of LAP 2 in lung carcinoma

Histological type	*n*	Immunohistochemical grade			
		Negative	1	2	3
SCLC	33	0	0	5 (15%)	28 (85%)
Non-SCLC					
AC	34	0	1 (3%)	1 (3%)	32 (94%)
SCC	30	0	0	0	30 (100%)
LCC	8	0	0	0	8 (100%)

Grade 1, focal (1 to 9% of cells positive); grade 2, intermediate (10 to 50% of cells positive); grade 3, diffuse (more than 51% of cells positive)

SCLC, small cell lung carcinoma; *AC*, adenocarcinoma; *SCC*, squamous cell carcinoma; *LCC*, large cell carcinoma

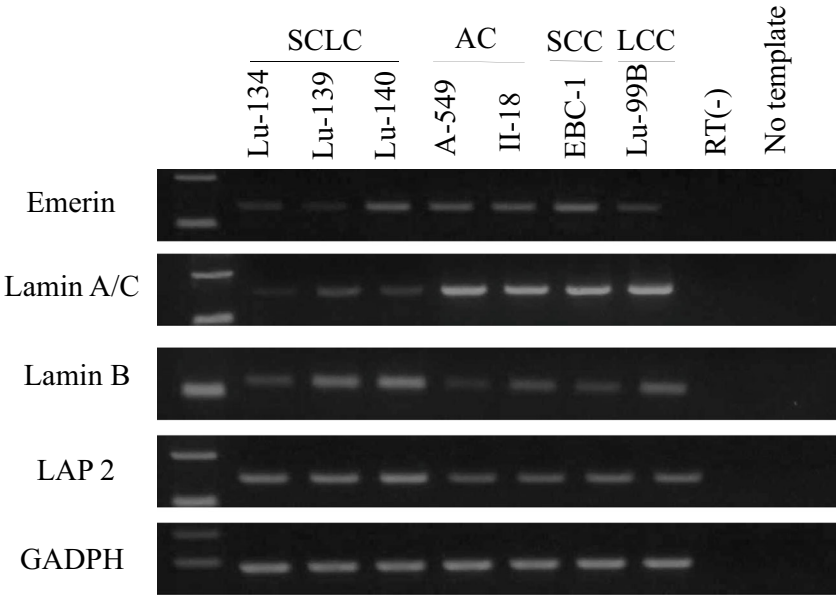

Fig. 3 Messenger RNA (mRNA) expression of emerin, lamin A/C, lamin B, and LAP2 in lung carcinoma cell lines. The expression levels of emerin (2/3) and lamin A/C were distinctly lower in SCLC cell lines than in other histological types of lung carcinoma cell lines. SCLC, small cell carcinoma; AC, adenocarcinoma; SCC, squamous cell carcinoma; LCC, large cell carcinoma

dilated cardiomyopathy, Dunnigan-type familial partial lipodystrophy, and Hutchinson-Gilford Progeria syndrome [35, 36]. In many cases, cells from affected patients show characteristic features such as misshapen nuclei, increased nuclear fragility, and herniations [37].

Our previous study suggested that the nuclear proteins most frequently expressed at high levels in papillary thyroid carcinomas were emerin (82% positive), lamin A/C (64%), and LAP2 (82%) [25]. In contrast, our current study demonstrated that emerin, lamin A/C, and lamin B were clearly downregulated in SCLCs but not in non-SCLCs. Interestingly, while some cancers frequently show a downregulation of lamin A/C, other cancers have upregulated levels of lamin A/C. Furthermore, for some cancers such as colon cancer, both increased and decreased levels of lamin A/C have been reported [30]. Capo-chichi et al. suggested that the loss of emerin may be the basis of nuclear morphological deformation and subsequently the cause of aneuploidy in ovarian carcinoma cells [38]. Therefore, the alteration of nuclear membrane proteins may be the underlying mechanism of the morphological deformation that can occur in malignant cells. Since A-type lamins are not expressed in early embryos and several non-terminally differentiated cells, and B-type lamins are expressed to some extent in essentially all normal somatic cells [39], we suggest that a downregulated or absent lamin A/C expression might indicate an undifferentiated nature of SCLC cells and be associated with their high growth rate and nuclear morphological deformation.

Lamina-associated polypeptide 2 (LAP2) is a nuclear protein that connects the nuclear lamina with chromatin. In the current study, we frequently observed strong immunohistochemical expression (grade 3) in the SCLC samples (85%) as well as in adenocarcinomas (94%), squamous cell carcinomas (100%), and large cell carcinomas (100%). Hyun-Jung Kim et al. reported that LAP2 regulates motility of cancer cells, and it is widely overexpressed in diverse digestive tract cancers [29]. The high expression of LAP2 in SCLCs and non-SCLCs also may be related to cancer cell motility.

RT-PCR analysis revealed that the mRNA expressions of emerin and lamin A/C were lower in SCLC cell lines than in non-SCLC cell lines, which supports our immunohistochemical findings. However, lamin B and LAP2 expressions were higher in SCLC cell lines than in non-SCLC cell lines. This only partially supports our immunohistochemical results and may reflect the lack of a consistent correlation between the expression level of mRNA and quality of protein.

Diagnosing SCLC remains challenging when biopsies are small and crushed; this is not uncommon in this type of tumor due to the fragile nature of the tumor cells [40]. In this respect, our findings suggest a hypothesis that the crush artifact (smearing of chromatin) may be related to abnormalities of nuclear membrane proteins which leads to nuclear fragility and/or weakness.

As we know, the nuclear envelope (NE) consists of an inner and an outer membrane, nuclear pore complexes (NPCs), and the underlying nuclear lamina, a filamentous scaffold structure formed by lamins [3]. In the current study, we have demonstrated the different expressions of the nuclear membrane proteins but except the nuclear pore complexes in SCLC and USCLC. Nuclear pore complexes (NPCs) perforate the nuclear envelope and serve as the primary transport gates for molecular exchange between nucleus and cytoplasm [41], and play an important role in maintaining the nuclear structure and functions. The relationship between the nuclear pore complexes and lung carcinomas, however, remains to be explained.

In conclusion, we suggest that profiles of nuclear membrane proteins in SCLC cells are characteristic of and possibly

associated with SCLC's biological and/or clinical nature. In addition, the abnormal nuclear protein profile in SCLC cells may contribute to the crush artifact and possibly facilitate the histological diagnosis of this tumor in pulmonary biopsy specimens.

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Contributions Wang Jieying, Tetsuo Kondo, and Ryohei Katoh conceived and designed the study, and wrote, edited, and reviewed the manuscript. Wang Jieying and Tetsuo Kondo performed the experiment. Tadao Nakazawa, Naoki Oishi, and Kunio Mochizukia researched and analyzed data. All authors gave final approval for publication.

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Compliance with ethical standards

The study protocols were approved by the Institutional Ethics Board of the University of Yamanashi, Yamanashi, Japan. The study complies with all ethical standards as stated in the Ethical Responsibilities of Authors on the *Virchows Archiv* webpage (https://www.springer.com/medicine/pathology/journal/428).

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Berk JM, Tifft KE, Wilson KL (2013) The nuclear envelope LEM-domain protein emerin. Nucleus 4:298–314. https://doi.org/10.4161/nucl.25751
2. Dittmer TA, Misteli T (2011) The lamin protein family. Genome Biol 12:222. https://doi.org/10.1186/gb-2011-12-5-222
3. Foisner R (2003) Cell cycle dynamics of the nuclear envelope. Sci World J 3:1–20. https://doi.org/10.1100/tsw.2003.06
4. Manilal S, Nguyen TM, Sewry CA, Morris GE (1996) The Emery-Dreifuss muscular dystrophy protein, emerin, is a nuclear membrane protein. Hum Mol Genet 5:801–808
5. Paulin-Levasseur M, Blake DL, Julien M, Rouleau L (1996) The MAN antigens are non-lamin constituents of the nuclear lamina in vertebrate cells. Chromosoma 104:367–379
6. Foisner R, Gerace L (1993) Integral membrane proteins of the nuclear envelope interact with lamins and chromosomes, and binding is modulated by mitotic phosphorylation. Cell 73:1267–1279
7. Lin F, Blake DL, Callebaut I et al (2000) MAN1, an inner nuclear membrane protein that shares the LEM domain with lamina-associated polypeptide 2 and emerin. J Biol Chem 75:4840–4847
8. Gerace L, Huber MD (2012) Nuclear lamina at the crossroads of the cytoplasm and nucleus. J Struct Biol 177:24–31. https://doi.org/10.1016/j.jsb.2011.11.007
9. Burke B, Stewart CL (2013) The nuclear lamins: flexibility in function. Nat Rev Mol Cell Biol 14:13–24. https://doi.org/10.1038/nrm3488
10. Andres V, Gonzalez JM (2009) Role of A-type lamins in signaling, transcription, and chromatin organization. J Cell Biol 187:945–957. https://doi.org/10.1083/jcb.200904124
11. Gant TM, Harris CA, Wilson KL (1999) Roles of LAP2 proteins in nuclear assembly and DNA replication: truncated LAP2beta proteins alter lamina assembly, envelope formation, nuclear size, and DNA replication efficiency in Xenopus laevis extracts. J Cell Biol 144:1083–1096
12. Ho CY, Jaalouk DE, Vartiainen MK, Lammerding J (2013) Lamin A/C and emerin regulate MKL1-SRF activity by modulating actin dynamics. Nature 497:507–511. https://doi.org/10.1038/nature12105
13. Holaska JM, Wilson KL (2007) An emerin "proteome": purification of distinct emerin-containing complexes from HeLa cells suggests molecular basis for diverse roles including gene regulation, mRNA splicing, signaling, mechanosensing, and nuclear architecture. Biochemistry 46:8897–8908. https://doi.org/10.1021/bi602636m
14. Segura TM, Kowalski AK, Craigie R et al (2002) Barrier-to-autointegration factor: major roles in chromatin decondensation and nuclear assembly. J Cell Biol 158:475–485
15. Shtivelman E, Hensing TS, Dennis GR et al (2014) Molecular pathways and therapeutic targets in lung cancer. Oncotarget 5:1392–1433. https://doi.org/10.18632/oncotarget.1891
16. Idowu MO, Powers CN (2010) Lung cancer cytology: potential pitfalls and mimics. Int J Clin Exp Pathol 3:367–385
17. Davidson MR, Gazdar AF, Clarke BE (2013) The pivotal role of pathology in the management of lung cancer. J Thorac Dis 5:S463–S478. https://doi.org/10.3978/j.issn.2072-1439.2013.08.43
18. Travis WD, Muller-Hermelink HK et al (2004) Pathology and genetics of tumours of the lung, pleura, thymus and heart. WHO/IASLC classification of lung and pleural tumours. IARC Press, Lyon
19. Ganti AK, West WW, Lackner RP, Kessinger A (2010) Current concepts in the diagnosis and management of small-cell lung cancer. Oncology 24:1034–1039
20. Cohen MH, Matthews MJ (1978) Small cell bronchogenic carcinoma: a distinct clinicopathologic entity. Semin Oncol 5:234–243
21. Ganti AK, West WW, Zhen W (2013) Current concepts in the management of small cell lung cancer. Indian J Med Res 137:1043–1051
22. Asioli S, Maletta F, Pacchioni D, Lupo R, Bussolati G (2010) Cytological detection of papillary thyroid carcinomas by nuclear membrane decoration with emerin staining. Virchows Arch 457:43–51. https://doi.org/10.1007/s00428-010-0910-z
23. Asioli S, Bussolati G (2009) Emerin immunohistochemistry reveals diagnostic features of nuclear membrane arrangement in thyroid lesions. Histopathology 54:571–579. https://doi.org/10.1111/j.1365-2559.2009.03259.x
24. Kinsella MD, Hinrichs B, Cohen C, Siddiqui MT (2013) Highlighting nuclear membrane staining in thyroid neoplasms with emerin: review and diagnostic utility. Diagn Cytopathol 41:97–504. https://doi.org/10.1002/dc.22870
25. Wang J, Kondo T, Yamane T, Nakazawa T, Oish N, Mochizuki K, Katoh R (2015) Expression of nuclear membrane proteins in normal, hyperplastic, and neoplastic thyroid epithelial cells. Virchows Arch 467:427–436. https://doi.org/10.1007/s00428-015-1816-6
26. Coradeghini R, Barboro P, Rubagotti A, Boccardo F, Parodi S, Carmignani G, D'Arrigo C, Patrone E, Balbi C (2006) Differential expression of nuclear lamins in normal and cancerous prostate tissues. Oncol Rep 15:609–613
27. Sun S, Xu MZ, Poon RT, Day PJ, Luk JM (2010) Circulating Lamin B1 (LMNB1) biomarker detects early stages of liver cancer in patients. J Proteome Res 9:70–78. https://doi.org/10.1021/pr9002118
28. Venables RS, McLean S, Luny D, Moteleb E, Morley S, Quinlan RA, Lane EB, Hutchison CJ (2001) Expression of individual lamins in basal cell carcinomas of the skin. Br J Cancer 84:512–519. https://doi.org/10.1054/bjoc.2000.1632

29. Kim HJ, Hwang SH, Han ME, Baek S, Sim HE, Yoon S, Baek SY, Kim BS, Kim JH, Kim SY, Oh SO (2012) LAP2 is widely overexpressed in diverse digestive tract cancers and regulates motility of cancer cells. PLoS One 7:e39482. https://doi.org/10.1371/journal.pone.0039482
30. Willis ND, Cox TR, Rahman-Casañs SF, Smits K, Przyborski SA, van den Brandt P, van Engeland M, Weijenberg M, Wilson RG, de Bruïne A, Hutchison CJ (2008) Lamin A/C is a risk biomarker in colorectal cancer. PLoS One 3:e2988. https://doi.org/10.1371/journal.pone.0002988
31. Kaufmann SH, Mabry M, Jasti R, Shaper JH (1991) Differential expression of nuclear envelope lamins A and C in human lung cancer cell lines. Cancer Res 51:6
32. Broers JL, Raymond Y, Rot MK, Kuijpers H, Wagenaar SS, Ramaekers FC (1993) Nuclear A-type lamins are differentially expressed in human lung cancer subtypes. Am J Pathol 143:211–220
33. Machiels BM, Broers JL, Raymond Y, de Ley L, Kuijpers HJ, Caberg NE, Ramaekers FC (1995) Abnormal A-type lamin organization in a human lung carcinoma cell line. Eur J Cell Biol 67:328–335
34. Christopher DMF (2007) Diagnostic histopathology of tumors. In: Cesar AM, Saul S (eds) Tumor of the lung and pleura,3 edn. 189
35. Denais C, Lammerding J (2014) Nuclear mechanics in cancer. Adv Exp Med Biol 773:435–470. https://doi.org/10.1007/978-1-4899-8032-8_20
36. Schreiber KH, Kennedy BK (2013) When lamins go bad: nuclear structure and disease. Cell 152:1365–1375. https://doi.org/10.1016/j.cell.2013.02.015
37. Zwerger M, Ho CY, Lammerding J (2011) Nuclear mechanics in disease. Annu Rev Biomed Eng 13:397–428. https://doi.org/10.1146/annurev-bioeng-071910-124736
38. Capo-chichi CD, Cai KQ, Testa JR et al (2006) Loss of GATA6 leads to nuclear deformation and aneuploidy in ovarian cancer. Mol Cell Biol 29:4766–4777. https://doi.org/10.1128/MCB.00087-09
39. Broers JL, Ramaekers FC, Bonne G, Yaou RB et al (2006) Nuclear lamins: laminopathies and their role in premature ageing. Physiol Rev 86:967–1008. https://doi.org/10.1152/physrev.00047.2005
40. Kontogianni K, Nicholson AG, Butcher D, Sheppard MN (2005) CD56: a useful tool for the diagnosis of small cell lung carcinomas on biopsies with extensive crush artefact. J Clin Pathol 58:978–980. https://doi.org/10.1136/jcp.2004.023044
41. Kevin EK, Thomas US (2017) The nuclear pore complex as a flexible and dynamic gate. Cell 164(6):1162–1171. https://doi.org/10.1016/j.cell.2016.01.034