RESEARCH ARTICLE

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# Clinical Significance of Gli-1 And Caveolin-1 Expression in the Human Small Cell Lung Cancer

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## Abstract

**Background:** Lung cancer is the leading causes of cancer-related deaths around the world. Abnormal activation of the hedgehog (Hh) signaling pathway has been found to be involved in the occurrence, invasion, and metastasis of cancers. Autophagy also plays a significant role in the growth and metastasis of cancers. However, the correlation between the Hh signaling pathway and autophagy in small cell lung cancer (SCLC) is still poorly understood. This study aimed to investigate the significance of Hh signaling pathway and autophagy in SCLC. **Materials and Methods:** The expression of the Hh-induced transcriptional factor, glioma associated oncogene-1 (Gli-1) and the autophagy-related molecule caveolin-1 (Cav-1) and their clinical significance was performed to detect and assay by immunohistochemistry in tissue microarray including 70 patients with SCLC. **Results:** In our study, 47 (67.1%) patients had positive Gli-1 expression, 49 (70.0%) patients had positive Cav-1 expression, and 44 (62.9%) patients had negative fibroblastic Cav-1 expression. In SCLC, Gli-1 expression increased markedly, and was closely associated with decreased fibroblastic Cav-1 expression. Furthermore, we also found that Gli-1 expression was closely associated with increased Cav-1 expression. **Conclusions:** Our findings suggested that abnormal activation of the Hh signaling pathway is closely related to autophagy in SCLC. We envision that novel targets may come with the further investigation of Gli-1 and Cav-1 in carcinogenesis of SCLC.

**Keywords:** Small cell lung cancer- Gli−1- caveolin−1- hedgehog pathway- autophagy

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## Introduction

Lung cancer is one of the most frequently diagnosed cancers and the leading causes of cancer-related deaths around the world, especially in less developed countries, accounting for about 13% of newly diagnosed cancers and 18% of the total number of deaths worldwide (Torre et al., 2015). Small cell lung cancer (SCLC), accounting for 10% of clinical lung cancer cases, is an aggressive malignancy, strongly correlated with smoking (Koinis et al., 2016). Patients with SCLC can be cured by treated with chemotherapy in combination with radiotherapy currently. Nevertheless, drug resistance inevitably occurs. They relapse sometimes incredibly quick, succumbing to the disease ultimately. Because of this dismal prognosis, it is urgent to conduct more basic research about the molecular mechanism of SCLC (Santarpia et al., 2016).

The hedgehog (Hh) signaling pathway is recognized as the most significant homologue during embryonic development of vertebrates, particularly for the regulation of pattern formation and cell proliferation in numerous tissues (Ingham and McMahon, 2001). However, abnormal activation of Hh signaling pathway may cause excessive cell proliferation resulting in the development of cancer (Cochrane et al., 2015). It also allows for the modulation of the microenvironment to prepare a tumor-suitable niche, thus creating an enabling environment for cancer progression and metastasis (Hanna and Shevde, 2016). Present research reports that glioma associated oncogene-1 (Gli-1) exhibits a strong positive activating effect of downstream target genes of the Hh pathway (Lei et al., 2015). Aberrant expression of Gli-1 is involved in various types of tumors, such as gastric cancer, breast cancer, non-small cell lung cancers and so on. Recently, more and more researches regard Gli-1 as a therapeutic target for intervention of cancer metastasis (Hong et al., 2014; Wang et al., 2014; Lei et al., 2015).

Mediated by the lysosomal degradation pathway, autophagy degrades superfluous or damaged organelles, misfolded proteins, and invading micro-organisms, in order to maintain quality control, sustain cell homeostasis as well as provide energy and nutrients. This self-digestion to some extent is a process potently triggered by fasting (Levine and Kroemer, 2008; Martinez-Outschoorn et al., 2010). Autophagy can also promote tumor in established cancer through autophagy-mediated intracellular recycling

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(White, 2012). During this process, cancer cells induce autophagy by secreting oxidative stress factors into the tumor microenvironment, which elevates glycolysis in cancer-associated fibroblasts. Cancer cells can utilize the elevated production of aerobic glycolysis, such as pyruvate, ketone bodies and L-lactate, for anabolic growth and metastasis (Prabhu et al., 2012). Caveolin-1 (Cav-1) participates in regulating various cellular physiological and pathological processes including tumorigenesis and tumor development. And it has been clarified that the loss of stromal Cav-1 significantly correlates with autophagy (Martinez-Outschoorn et al., 2014).

The Hh signaling pathway may be one of the signaling pathways in the tumor microenvironment that involves autophagy. However, the correlation between the Hh signaling pathway and autophagy in SCLC is still poorly understood. In the present study, the expression of Gli-1 and Cav-1 proteins were detected in patients with SCLC, and clinicopathological information was collected to analyze the relation of the Hh signaling pathway with autophagy.

## Materials and Methods

*Selection of patients and tissue microarray construction*

A total of seventy patients receiving surgical intervention due to SCLC were recruited from the Department of Pathology, Zhongnan Hospital of Wuhan University. The clinical and pathological information of each patient were recorded, including age, gender, depth of invasion, depth of tumor invasion (T), lymph node metastasis (N), distant metastasis (M), and pTNM stage (UICC/AJC TNM staging system, 2016) (Goldstraw et al., 2016). Age at diagnosis ranged from 19 to 73 years (average: 54 years). This study was approved by the Institute Research Medical Ethics Committee of Zhongnan Hospital of Wuhan University. Written informed consent was obtained from all the patients preoperatively.

Seventy SCLC and ten matched adjacent noncancerous lung tissues were collected from each patient, fixed in 10% buffered formalin, embedded in paraffin. Hematoxylin and eosin stained slides were screened for the most representative tumor tissues and matched adjacent noncancerous tissues. Two tissue microarray (TMA) slides with a diameter of 1.5mm were constructed with a tissue manual arraying instrument. Each TMA slide consisted of 160 specimens of 70 SCLC tissues and 10 matched adjacent noncancerous lung tissues (each case has two specimens).

*Immunohistochemistry*

Immunohistochemistry was performed to detect the expression of Gli-1 (rabbit anti-human polyclonal antibody, H-300, 1:50 dilution; GenWay Biotech, CA, USA), and Cav-1 (rabbit anti-human polyclonal antibody, sc-894, 1:150 dilution; Santa Cruz, USA) proteins, according to manufacturer's instructions. HRP-conjugated second antibody and DAB kit (Dako, Agilent Technologies, CA, USA) were used to visualize antibody binding. Briefly, TMAs were deparaffinized in xylene and rehydrated in graded alcohol washes. Antigen retrieval was performed in citric acid (10 mM, pH 6.0) at 95 °C for 15 min by microwave, followed by cooling for 30 min. TMAs were washed in PBS and treated with 0.3% hydrogen peroxide for 30 min, in order to block endogenous peroxide activity, and then washed again in PBS. TMAs were first incubated in 2% BSA buffer at 37 °C for 30 min, and then at 4 °C overnight in rabbit anti-Cav-1 polyclonal antibody and rabbit anti-Gli-1 polyclonal antibody respectively, to permit antibody binding. TMAs were then washed three times with PBS for 5 min each time and incubated in HRP-conjugated second antibody at 37 °C for 30 min. The sites of peroxidase activity were visualized by using DAB. TMAs were then counterstained with haematoxylin. Immunostaining reactivity was observed by using light microscopy (Olympus BX-53 with CCD DP73). The standard positive control provided by the manufacturer served as a positive control, and the primary antibody was replaced with PBS in negative controls.

*Determination of the proportion of cells positive for each marker*

We counted the Cav-1- or Gli-1-stained tumor tissues of each specimen at high magnification (200×) and estimated the positive area (PA) that was determined independently by two pathologists (Zhao XD and Chen HL) who were blinded to the clinical features independently. PA was graded as follows: 0 (PA ≤ 20%), 1 (PA 21%–40%), 2 (PA 41%–60%), 3 (PA 61%-80%) and 4 (PA > 81%). Then the intensity of staining (IS) was evaluated in hot spots at high-power magnification and was scored as: 0 (negative), 1 (weak), 2 (moderate) and 3 (strong). The Cav-1 and Gli-1 intensity distribution (ID) scores for each case were calculated by the following equation: ID = PA × IS, where ID ≤ 4 represented negative (−) or low expression and ID > 4 represented positive (+) or high expression. This standard was applied for Cav-1 and Gli-1, which could well present the relationship between the markers and the clinical characteristics.

*Statistical analysis*

SPSS Statistics software package, version 19.0 (Chicago, IL, USA) was used for the statistical analysis. Demographic characteristics were summarized by count and percentage for categorical variables, and comparisons were performed by Chi-square test or Fisher's exact test. For binary categorical data, the phi coefficient, a measurement of the degree of association between two binary variables, were used to determine association between two markers. All statistic assessments were evaluated at a two-sided P value of 0.05.

## Results

*Demographics and clinical characteristics*

Demographic and clinical characteristics of SCLC patients were summarized in Table 1. Seventy SCLC patients entered the study, including 13 (18.6%) women and 57 (81.4%) men. The largest group of patients in the study was younger than 60 years of age (62.9%). Fifty-eight (82.9%) had shallow (T1/T2) invasion. Forty-two (60.0%) had no lymph node invasion. Fifty-nine (84.3%) had

Table 1. Patient Characteristics (N=70)

| Characteristics | Sub-characteristics | Value (%) |
|---|---|---|
| Age (years) | | 54 (range = 19-73) |
| Gender | Male | 57 (81.4) |
| | Female | 13 (18.6) |
| Invasion deep (T) | T1 | 1 (1.4) |
| | T2 | 57 (81.5) |
| | T3 | 11(15.7) |
| | T4 | 1 (1.4) |
| Lymph node metastasis (N) | N0 | 42 (60.0) |
| | N1 | 25 (35.7) |
| | N2 | 3 (4.3) |
| Distant metastasis (M) | M0 | 69 (98.6) |
| | M1 | 1 (1.4) |
| pTNM stage | I | 29 (41.4) |
| | II | 30 (42.9) |
| | III | 10 (14.3) |
| | IV | 1 (1.4) |
| Tatal | | 70 (100) |

pTNM stage I / II SCLC.

*Expression of Gli-1, Cav-1 and fibroblastic Cav-1*

Gli-1 was mainly expressed in SCLC tissues, was primarily localized in the cytoplasm and or cell nucleus. There was almost negative Gli-1 expression in the stromal fibroblasts of SCLC or inflammatory cells, but there was positive Gli-1 expression in vascular endothelial cell (Figure 1). In normal alveolar and bronchial epithelium,

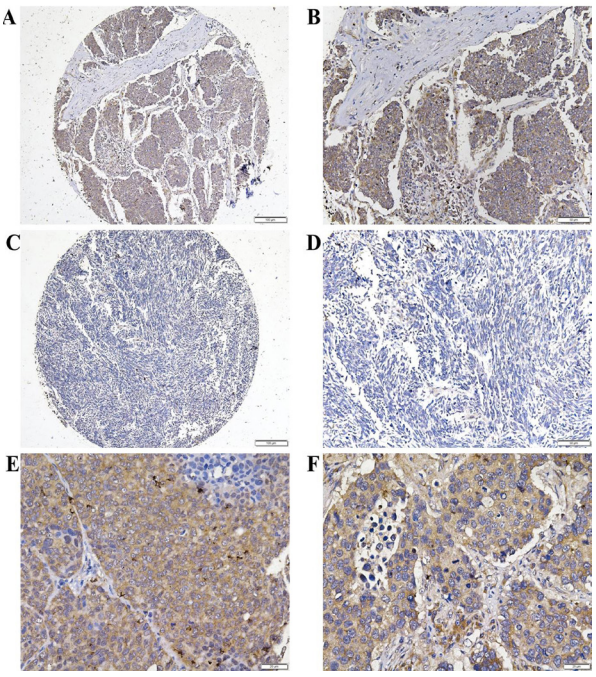


Figure 1.Gli-1 Protein Expression in SCLC Tissues: A, B, Gli-1 positive expression in SCLC tissues; C, D, weak Gli-1 expression in SCLC tissues; E, F, Gli-1 positive expression in SCLC tissues with low or negative Gli-1 expression in the stromal fibroblasts of SCLC or inflammatory cells (A, C, 100×magnification; B, D, 200×magnification; E, F, 400×magnification).

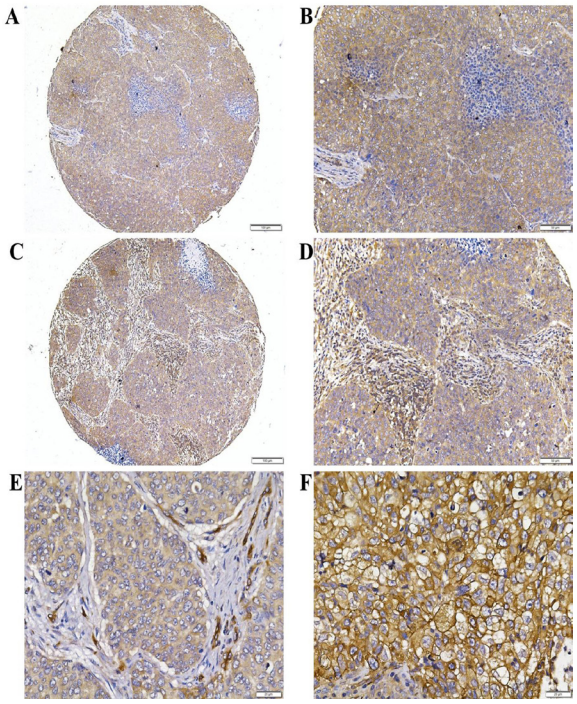


Figure 2.Cav-1 Protein Expression in SCLC Tissues: A, B, Cav-1 negative stromal fibroblasts of SCLC; C, D, Cav-1 positive expression in stromal fibroblasts of SCLC; E, Cav-1 positive expression in SCLC tissues with negative expression in stromal fibroblasts; F, Cav-1 positive expression on the cell membrane of SCLC tissues (A, C, 100×magnification; B, D, 200×magnification; E, F, 400×magnification).

Gli-1 expression was present only at a low level. In SCLC, 67.1% (47/70) of the specimens were positive for Gli-1, which was a significantly higher than that in normal lung tissues.

Cav-1 was expressed in both SCLC tissues and normal alveolar and bronchial epithelium. In tumor tissues, Cav-1 was predominantly expressed on the cell membrane or in the cytoplasm. In normal lung tissues, Cav-1 was also expressed in the fibroblasts, however, Cav-1 was absent at most of stromal fibroblasts of SCLC. There was negative Cav-1 expression in inflammatory cells, but positive expression in vascular endothelial cell (Figure 2). Our results showed that forty-nine (70.0%) patients had positive Cav-1 expression, and forty-four (62.9%) patients had negative fibroblastic Cav-1 expression.

We also evaluated the clinicopathological significance between negative and positive groups for these markers. From Table 2 showed, just found both of Gli-1 and Cav-1 positive expression group in the tumor cells had a higher percentage with pTNM stage III/IV of SCLC (both $P \leq 0.05$).

*Association between Gli-1 expression with Cav-1/fibroblastic Cav-1 expression in SCLC*

The association between Gli-1 and Cav-1 expression was shown in Table 3. There was a positive association between Gli-1 and Cav-1 expression ($P < 0.001$, phi coefficient = 0.737); and a negative association between Gli-1 and fibroblastic Cav-1 expression ($P < 0.001$, phi

Table 2. Demographics and Clinical Characteristics of SCLC Patients According to their Gli-1 and Cav-1 Expression

| Parameters | All patients | Gli-1 | | | Cav-1 | | | Fibroblastic Cav-1 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | (n=70) | Negative (n=23) | Positive (n=47) | P value | Negative (n=21) | Positive (n=49) | P value | Low (n=44) | High (n=26) | P value |
| Age | | | | 0.81 | | | 0.914 | | | 0.737 |
| <60 years | 44 (62.9) | 14 (60.9) | 30 (63.8) | | 13 (61.9) | 31 (63.2) | | 27 (61.4) | 17 (65.4) | |
| ≥60 years | 26 (37. 1) | 9 (39.1) | 17 (36.2) | | 8 (38.1) | 18 (43.9) | | 17 (38.6) | 9 (34.6) | |
| Gender | | | | 0.145 | | | 0.283 | | | 0.288 |
| Women | 13 (18.6) | 7 (30.4) | 6 (12.8) | | 6 (28.6) | 7 (14.3) | | 6 (13.6) | 7 (26.9) | |
| Men | 57 (81.4) | 16 (69.7) | 41 (87.2) | | 15 (71.4) | 42 (85.7) | | 38 (86.4) | 19 (73.1) | |
| Invasion deep | | | | 0.33 | | | 0.146 | | | 0.53 |
| T1/T2 | 58 (82.9) | 21 (91.3) | 37 (78.7) | | 20 (95.2) | 38 (77.6) | | 35 (79.5) | 23 (88.5) | |
| T3/T4 | 12 (17.1) | 2 (8.7) | 10 (21.3) | | 1 (4.8) | 11 (22.4) | | 9 (20.5) | 3 (11.5) | |
| Lymph node metastasis | | | | 0.7 | | | 0.831 | | | 0.84 |
| N0 | 42 (60.0) | 14 (60.9) | 28 (59.6) | | 13 (61.9) | 29 (59.2) | | 26 (59.1) | 16 (61.5) | |
| N1/N2 | 28 (40.0) | 9 (39.1) | 19 (40.4) | | 8 (38.1) | 20 (40.8) | | 18 (40.9) | 10 (38.5) | |
| pTNM stage | | | | 0.029* | | | 0.045* | | | 0.079 |
| I/II | 59 (84.3) | 23 (100.0) | 36 (76.6) | | 21 (100.0) | 38 (77.6) | | 34 (77.3) | 25 (96.2) | |
| III/IV | 11 (15.7) | 0 (0.0) | 11 (23.4) | | 0 (0.0) | 11 (22.4) | | 10 (22.7) | 1 (3.8) | |

Data expressed as count and percentage for categorical variables, and were performed by Chi-square test or Continuity correction; *P <0.05 between negative and positive groups

Table 3. Association between Gli-1 with Cav-1 and Fibroblastic Cav-1 Expression

| | Gli-1 | | *P* value | The phi coefficient |
|---|---|---|---|---|
| | Negative | Positive | | |
| Cav-1 | | | | |
| Negative | 18 (78.3%) | 3 (6.4%) | <0.001* | 0.737 |
| Positive | 5 (21.7%) | 44 (93.6%) | | |
| Fibroblastic Cav-1 | | | | |
| Low | 2 (8.7%) | 42 (89.4%) | <0.001* | -0.784 |
| High | 21 (91.3%) | 5 (10.6%) | | |

**P*<0.05 between Gli-1 with Cav-1and fibroblastic Cav-1 expression

coefficient = -0.784).

## Discussion

SCLC is an aggressive malignancy belonging to lung cancer, which remains the first cause of death in the malignant carcinomas. In this study, we assessed the expression of Gli-1 and Cav-1 in SCLC for the first time, and the results revealed that forty-seven (67.1%) patients had positive Gli-1 expression, and forty-four (62.9%) patients had negative fibroblastic Cav-1 expression. Gli-1 was related to TNM stage of SCLC (P = 0.029). What's more, we first revealed the relationship between the Hh signaling pathway and autophagy in SCLC: the Hh pathway marker Gli-1 increased markedly and was found to be associated with the autophagy-related marker fibroblastic Cav-1 in a negative way(P < 0.001, phi coefficient = -0.784).

The Hh signaling pathway plays an important role in embryonic development, formation of mature organs, and maintenance of morphology. Abnormal activation of the Hh signaling pathway is closely related to the occurrence, invasion, and metastasis of some cancers, including SCLC. Watkins et al., (2003); Abe and Tanaka, (2016) Gli proteins, belong to the zinc finger protein family and act as the downstream regulatory factors of classic Hh signaling pathway. Hui and Angers, (2011) Gli proteins are vital for embryogenesis and adult homeostasis. Matise and Joyner, (1999) On the other hand, as a member of Gli families, the aberrant expression of Gli-1 will promote carcinogenesis, according to epithelial-mesenchymal transition or angiogenesis or other channels. Cui et al., (2012) Abnormal expression of Gli-1 has been discovered in various types of tumors. In recent years, more and more researches focus on Gli-1 and take it as therapeutic targets. Inhibitor of classical Hh pathway such as cyclopamine is also further explored in cancer targeted therapy (Chen, 2016)

Autophagy plays a significant role in maintaining quality control, sustaining cell homeostasis as well as providing energy and nutrients. On the other hand, autophagy can also promote tumor in established cancer through autophagy-mediated intracellular recycling. Levine, (2007) Caveolin-1 (Cav-1), with multiple binding partners, localized in membrane subdomains called caveolae, is a multifunctional scaffolding protein. Fu et al., (2017) Increasing evidence suggests that Cav-1 regulates multiple cancer-associated processes, including cell proliferation, migration and metastasis, cell apoptosis and survival, mutations through the interactions with all these well-known factors, and multidrug resistance. Yeh et al., (2009) It has been reported recently that the loss of Cav-1 in the tumor stroma brings about an activation of tumor microenvironment, which is significantly related to early tumor recurrence, metastasis, and poor clinical outcome in cancer. Shi et al., (2016) Mean while, researches illuminated that tumor proliferation and progression involve autophagy in tumor stromal fibroblasts and Cav-1 expression deficiency. He et al., (2012) In that case, we can draw a conclusion that the loss

of stromal Cav-1 results in the metabolic reprogramming of cancer-associated fibroblasts, primarily caused by activated autophagy in fibroblasts, which has been proved in present investigations (Guan et al., 2016)

In this research, we have explored the association between the expression of Hh signaling pathway and autophagy-related gene in SCLC, and showed that the high expression level of the Hh pathway marker Gli-1 was related to the loss of the autophagy-related marker Cav-1 in the tumor stroma. Consequently, it can be ascertained that in the invasion and metastasis of SCLC, abnormal activation of the Hh signaling pathway is closely related to the induction of autophagy. Hence, we conjecture that Hh signaling pathway may bring about an activation of tumor microenvironment via autophagy, and also provides an alternative therapeutic strategy for SCLC.

Interestingly, during the analysis of the experimental results, a positive association between Gli-1 and Cav-1 expression in tumor cells was discovered. We proposed a possible mechanism to explain this association: Cav-1 mediated Gli-1 expression through PI3K/AKT/mTOR pathway. On the one hand, Cav-1 regulates PI3K/AKT signaling pathway which involved in cancer initiation and progression. PI3K/AKT pathway motivates regulation of proliferation, survival and inhibition of apoptosis, which is important in carcinogenesis. Ersahin et al., (2015) PI3K/AKT pathway is aberrantly activated in different tumor entities, providing a unique foundation for pharmacological target. Li et al., (2016b); Sharma et al., (2017) and Liang et al., (2014) found that Cav-1 activation-induced PI3K/AKT signaling pathway promoted an invasive phenotype in bladder cancer cells. Yang et al., (2016) revealed that Cav-1 could be activated by low shear stress (LSS) to trigger PI3K/AKT/mTOR pathway in breast carcinoma MDA-MB-231 cells. Yang et al., (2016) Consequently, we suppose that PI3K/AKT signaling pathway can be activated by Cav-1 in pathogenesis, invasion and metastasis of tumors. On the other hand, PI3K/AKT pathway also upregulates Gli-1 in a Smo-independent manner. It has been demonstrated that PI3K-AKT can lead to mTORC-mediated phosphorylation of 70S6K, which cause an abolishment of GSK3β-dependent Gli-1-degradation. Kebenko et al., (2015) To be consistent, Smo-independent Gli-1 activation has also been reported in renal cell carcinoma, esophageal adenocarcinoma, and refractory acute myeloid leukemia, which are mediated by the PI3K/AKT signaling pathway. Kebenko et al., (2015); Li et al., (2016a) and Zhou et al., (2016) Therefore, we assume that in the occurrence and metastasis of SCLC, Gli-1 expression is possible to be mediated by the Cav-1 regulation of PI3K/AKT pathway. However, it is better to have some in vitro results to identify this assumption, which is a limitation of this study. Our findings highlight the complicate role of Gli-1 in carcinogenesis. This explains why approaches aiming to block Hh signaling pathway have met with limited success. Thus, we envision that novel targets may come with the further investigation of Cav-1/PI3K/AKT/Gli-1 pathway in carcinogenesis.

In conclusion, this was the first study that demonstrated the expression of Gli-1 and Cav-1 in SCLC patients. Our data elucidated that the high expression level of Gli-1 is related to the low levels of fibroblastic Cav-1 in SCLC, which identified that Hh signaling pathway induced autophagy in the occurrence and metastasis of SCLC. Our results indicate the clinical importance of the expression of Gli-1 and fibroblastic Cav-1 and will potentially attract more attention to the exploration of the complicate tumor microenvironment.

*Conflict of interests*

The authors declare no conflict of interest.

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