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Article

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Expression of Lurap1 and Dvl1 in Non Small Cell Lung Cancer and Their Clinicopathological Significance

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Abstract

Background. This study aimed to detect the expression levels of leucine repeat adaptor protein 1 (Lurap1), Dishevelled Segment Polarity Protein 1 (Dvl1), as well as downstream effectors of the Wnt/β-catenin signaling pathway including AXIN2, TCF7 and LEF1 in non-small-cell lung cancer (NSCLC) tissues and paired adjacent normal tissues. We further analyzed their correlations with clinicopathological characteristics, identified prognostic factors for overall survival (OS) of NSCLC patients, and explored the underlying molecular mechanisms, so as to provide experimental evidence for diagnosis, treatment and prognostic evaluation of NSCLC.

Methods. Immunohistochemical staining was performed to detect the positive expression of Lurap1, Dvl1, AXIN2, TCF7 and LEF1 in 120 NSCLC tissue specimens. Clinicopathological parameters and postoperative survival data of enrolled patients were collected simultaneously.

Results. The positive expression rate of Lurap1 was significantly lower in NSCLC tissues than in paired adjacent normal tissues, whereas Dvl1, AXIN2, TCF7 and LEF1 exhibited markedly higher expression in cancer tissues ($P < 0.05$). Low Lurap1 expression was significantly correlated with poor tumor differentiation, lymph node metastasis and advanced TNM stage ($P < 0.05$). Lurap1 expression was negatively correlated with Dvl1, AXIN2, TCF7 and LEF1 expression ($P < 0.05$). Survival analyses revealed that patients with low Lurap1 expression or high expression of Dvl1, AXIN2, or TCF7 had remarkably shortened OS. Multivariate Cox regression demonstrated that low Lurap1 expression, high Dvl1 expression, lymph node metastasis, and TNM stage Ⅲ-Ⅳ were independent risk factors for unfavorable prognosis in NSCLC patients.

Conclusion. Aberrant low expression of Lurap1 and high expression of Dvl1 may facilitate invasion and metastasis of NSCLC via activating the Wnt/β-catenin signaling pathway. Lurap1 and Dvl1 may serve as potential molecular biomarkers for evaluating malignancy and postoperative prognosis of NSCLC.

Keywords. Lurap1; Dvl1; non small cell lung cancer; Wnt/β-catenin signaling pathway; invasion; metastasis

Introduction

Non small cell lung cancer (NSCLC) accounts for 80%-85% of all lung cancer cases. It is characterized by insidious onset, high malignancy, strong invasive and metastatic potential, high

postoperative recurrence rate and poor prognosis[1]. Current therapeutic modalities for NSCLC include surgical resection, radiotherapy, chemotherapy, targeted therapy and immunotherapy. Nevertheless, owing to complex pathogenesis and dysregulated molecular regulatory networks, most patients are diagnosed at intermediate-advanced stages and prone to drug resistance and distant metastasis. NSCLC remains one of the most lethal malignancies worldwide[2]. Therefore, identifying key molecular mechanisms driving malignant progression of NSCLC and screening specific prognostic biomarkers and therapeutic targets are of great clinical importance to improve patient outcomes.

Leucine repeat adaptor protein 1 (Lurap1) is a cytoplasmic adaptor protein enriched in leucine-rich repeats (LRR). Composed of conserved leucine-repeat domains and protein-binding motifs, Lurap1 is highly evolutionarily conserved. It mediates protein-protein interactions and acts as a negative regulator of multiple signaling cascades, participating in fundamental biological events including cell proliferation, epithelial polarity maintenance, cell migration and apoptosis[3]. The leucine-repeat domain is essential for Lurap1 function: it specifically recognizes and binds Dvl family proteins, promotes Dvl ubiquitination-mediated degradation and blocks Dvl oligomerization, thereby dually restraining Dvl-dependent Wnt signaling. Lurap1 is thus an important endogenous tumor-suppressive modulator of the canonical Wnt/β-catenin pathway[4]. Under physiological conditions, Lurap1 is widely expressed in normal respiratory and pulmonary epithelial cells. It maintains basal Wnt pathway activity, guarantees normal epithelial differentiation and sustains tissue homeostasis. Downregulation or functional loss of Lurap1 abolishes its inhibitory effect on Dvl, leading to intracellular Dvl accumulation, persistent downstream cascade activation, uncontrolled cell proliferation, enhanced migratory-invasive capacity and epithelial-mesenchymal transition[5]. Cumulative biochemical and cellular experiments have validated the tumor-suppressive role of Lurap1 in multiple solid tumors. In gastrointestinal and breast cancers, Lurap1 is significantly downregulated. Reduced Lurap1 expression relieves Dvl repression and drives aberrant Wnt pathway activation to accelerate tumor progression. Restoring Lurap1 expression decreases Dvl abundance and suppresses tumor cell proliferation and invasion[6].

The canonical Wnt/β-catenin signaling pathway is a core driver of tumor initiation and progression. Its persistent abnormal activation is extensively involved in NSCLC cell proliferation, epithelial-mesenchymal transition, invasion-metastasis, cancer stemness maintenance and adverse clinical outcomes[7]. Dishevelled Segment Polarity Protein 1 (Dvl1), encoded by the gene located at 1p36, is an indispensable upstream hub protein of the canonical Wnt/β-catenin cascade. Possessing three conserved domains (DIX, PDZ and DEP), Dvl1 transduces signals from membrane-bound Wnt receptors, inhibits the β-catenin destruction complex, promotes β-catenin nuclear translocation, and triggers transcription of downstream targets including AXIN2, TCF7 and LEF1 to modulate cell proliferation, migration and differentiation. Physiologically, Dvl1 preserves pulmonary epithelial homeostasis. In malignancies, however, Dvl1 overexpression causes excessive and sustained Wnt pathway activation, which promotes tumor invasion-metastasis, chemoresistance and poor prognosis[8]. Multiple studies have reported upregulated Dvl1 in primary lung cancer and brain metastatic lesions. Dvl1 overexpression enhances proliferation and invasion of NSCLC cells, and high Dvl1 expression correlates with lymph node metastasis, advanced TNM stage and shortened patient survival, marking it as a potential oncogenic biomarker[9-10]. Existing investigations mainly focus on the oncogenic function of

Dvl1 alone. Large-sample clinical evidence is lacking regarding upstream tumor-suppressive regulators of Dvl1, co-expression patterns of Dvl1 together with full sets of Wnt downstream molecules, and whether Lurap1 restrains NSCLC progression and prognosis by negatively modulating Dvl1-dependent Wnt signaling.

Accordingly, the present study enrolled 120 surgically resected NSCLC specimens. Immunohistochemistry was applied to detect protein expression of Lurap1, Dvl1, and Wnt/β-catenin downstream factors AXIN2, TCF7 and LEF1 in cancer and paired adjacent non-tumor tissues. We analyzed associations between these protein profiles and clinicopathological parameters as well as overall survival, and explored expression correlations among Lurap1, Dvl1 and Wnt pathway components. This work clarifies the clinicopathological significance and potential regulatory mechanisms in NSCLC progression, and provides novel experimental and theoretical basis for malignancy evaluation, prognostic prediction and targeted therapy for NSCLC.

Methods

Clinical Samples

One hundred and twenty patients who underwent radical lung cancer resection at the Department of Thoracic Surgery between January 2019 and December 2020 were retrospectively enrolled. Tumor tissues and paired adjacent normal lung tissues (≥5 cm away from tumor margin and histologically confirmed tumor-free) were collected.

Inclusion criteria: Histopathological diagnosis of NSCLC (adenocarcinoma or squamous cell carcinoma); No preoperative anti-tumor interventions including radiotherapy, chemotherapy, targeted therapy or immunotherapy; Complete clinical, imaging and pathological records; Complete postoperative follow-up data. Exclusion criteria: Patients complicated with other primary malignancies, severe organ dysfunction, incomplete clinical information or loss to follow-up. This study involving human participants was reviewed and approved by the First Affiliated Hospital of Bengbu Medical University Institutional Ethics Committee ([2025]KY003X01). All research procedures were carried out in accordance with the principles of the Helsinki Declaration and relevant official research guidelines and regulations. Informed consent was obtained from all participants and/or their legal guardians before the implementation of the study.

Clinicopathological data including gender, age, tumor differentiation, maximum tumor diameter, lymph node metastasis and TNM stage were retrieved. Post-operative follow-up was performed via outpatient re-examination and telephone interviews. The follow-up deadline was December 2025. Death was defined as the survival endpoint, and overall survival (OS) was the primary observational outcome (**Table 1**).

Reagents and Experimental Procedures

All tissue specimens were fixed in 4% paraformaldehyde, subjected to routine dehydration, embedded in paraffin, and cut into 4 μm serial sections. Immunohistochemical SP staining was used to detect protein expression of Lurap1, Dvl1, AXIN2, TCF7 and LEF1. Briefly, sections were deparaffinized and rehydrated. Antigen retrieval was performed using citrate buffer under high-pressure heating. Endogenous peroxidase activity was blocked with 3% hydrogen peroxide at room temperature, followed by goat serum incubation to block non-specific binding. Sections were incubated with primary antibodies against Lurap1, Dvl1, AXIN2, TCF7 and LEF1 overnight at 4° C. After rewarming, secondary antibodies were applied at room temperature. DAB

chromogenic reaction was conducted, followed by hematoxylin counterstaining, gradient dehydration, transparency and mounting with neutral balsam. Known positive tissues served as positive controls, and PBS substituting primary antibodies was set as negative controls (**Table 2** for antibody information).

Immunohistochemical (IHC) Staining

Two experienced pathologists independently evaluated all sections in a double-blind manner. Discrepancies were resolved by joint review. A composite scoring system combining staining intensity and positive cell percentage was adopted:① Staining intensity: 0 = no staining; 1 = light yellow; 2 = yellowish-brown; 3 = dark brown.② Percentage of positive cells: 0 = ＜5%; 1 = 5%-25%; 2 = 26%-50%; 3 = 51%-75%; 4 = ＞75%.Total score = staining intensity score × positive-cell-proportion score. Specimens with total scores of 0-2 were regarded as negative, and scores of 3-12 as positive.

Statistical Analysis

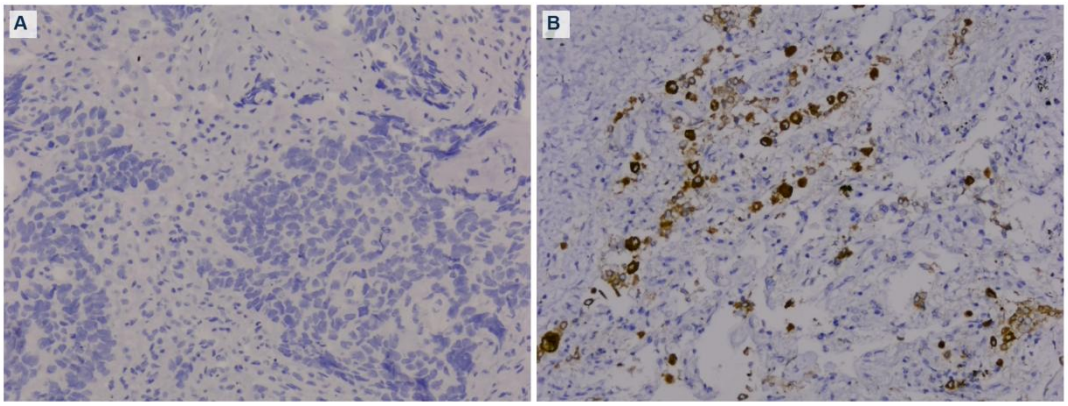
SPSS 26.0 software was utilized for statistical analyses. Count data were presented as cases (percentages). Paired χ^2 test was applied to compare protein expression between tumor and adjacent tissues. Associations between protein expression and clinicopathological features were analyzed using χ^2 test. Spearman correlation analysis was performed to evaluate inter-protein expression correlations. Kaplan-Meier survival curves were plotted, and Log-rank tests were used for survival-difference comparisons. Univariate and multivariate Cox proportional-hazards regression models were constructed for prognostic analyses. $P < 0.05$ was considered statistically significant.

Results

Differential Expression of Lurap1, Dvl1 and Wnt Pathway Downstream Molecules in NSCLC Tissues

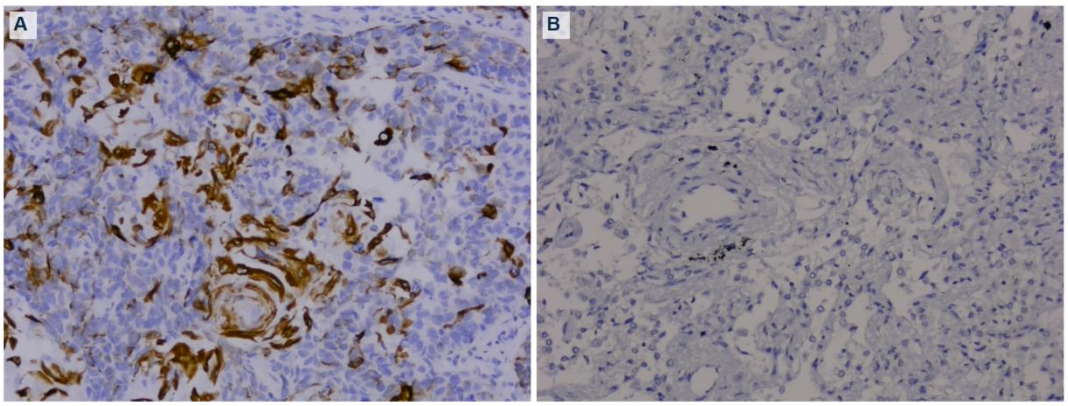
Immunohistochemical results showed that Lurap1 was predominantly localized in the cytoplasm of lung cells. Its positive rate in NSCLC tissues was significantly lower than that in paired adjacent normal lung tissues (Fig. 1). Dvl1 was mainly distributed on cell membranes and in the cytoplasm of tumor cells, with significantly higher positive expression in NSCLC tissues than in adjacent tissues (Fig. 2). AXIN2 (Fig. 3), TCF7 (Fig. 4) and LEF1 (Fig. 5) were predominantly nuclear proteins in tumor cells, and their positive rates were markedly elevated in cancer tissues relative to adjacent non-tumor tissues. All above differences reached statistical significance (all $P < 0.05$).

Fig. 1 Immunohistochemical staining of Lurap1 in NSCLC tissue sections (original magnification 100×).



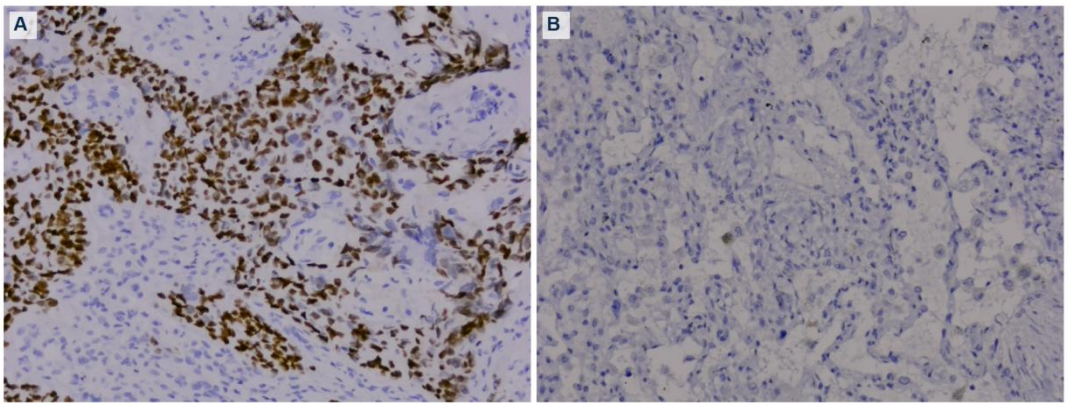
1A Lurap1 shows negative expression in normal tissue adjacent to cancer; **1B** Lurap1 shows positive cytomembrane staining with strong intensity in approximately 80% of tumor cells.cytoplasm.

Fig. 2 Immunohistochemical staining of DVL1 in NSCLC tissue sections (original magnification 100×).



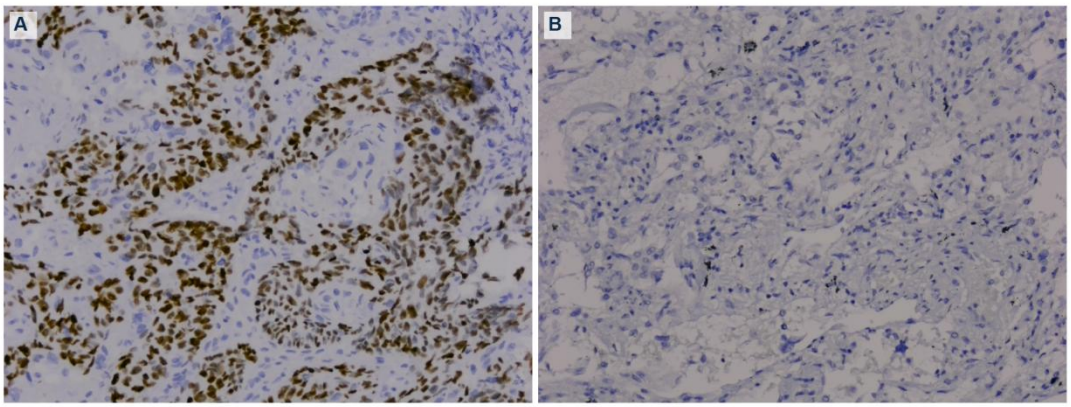
2A DVL1 shows positive cytomembrane staining with strong intensity in approximately 60% of tumor cells; **2B** ZEB1 shows negative expression in normal tissue adjacent to cancer.

Fig. 3 Immunohistochemical staining of AXIN2 in NSCLC tissue sections (original magnification 100×).



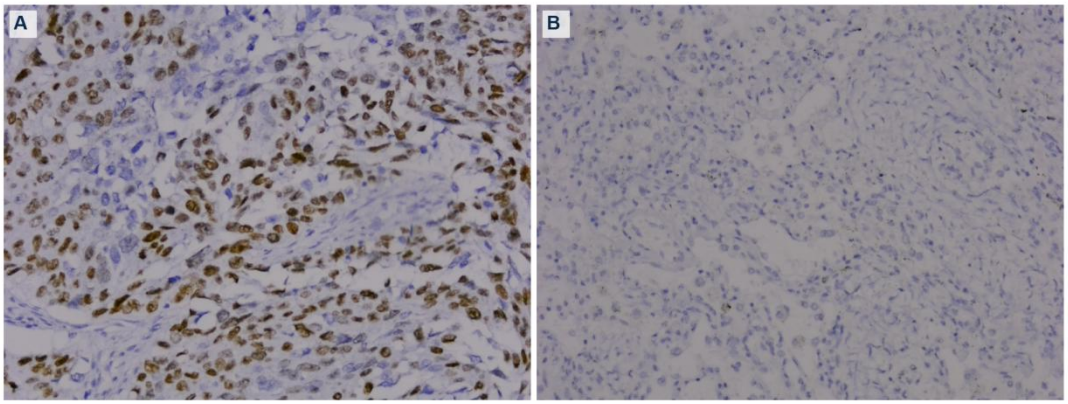
3A AXIN2 shows positive nuclear staining with strong intensity in approximately 90% of tumor cells; **3B** AXIN2 shows negative expression in normal tissue adjacent to cancer;

Fig. 4 Immunohistochemical staining of TCF7 in NSCLC tissue sections (original magnification 100×).



4A TCF7 shows positive nuclear staining with strong intensity in approximately 90% of tumor cells; **4B** TCF7 shows negative expression in normal tissue adjacent to cancer.

Fig. 5 Immunohistochemical staining of LEF1 in NSCLC tissue sections (original magnification 100×).



5A LEF1 shows positive nuclear staining with strong intensity in approximately 80% of tumor cells; **5B** LEF1 shows negative expression in normal tissue adjacent to cancer.

Associations of Lurap1 and Dvl1 Expression with Clinicopathological Features of NSCLC

Reduced Lurap1 expression was closely correlated with poor tumor differentiation, lymph node metastasis and TNM stage Ⅲ-Ⅳ ($P < 0.05$), whereas no significant correlations were observed between Lurap1 and age, gender or tumor size ($P > 0.05$). High Dvl1 expression was significantly associated with poor differentiation, lymph node metastasis and advanced TNM stage ($P < 0.05$), while no correlations were found with age or gender. These findings indicated that Lurap1 downregulation and Dvl1 upregulation were closely linked to malignant progression, invasion and metastasis in NSCLC (**Table 3**).

Associations between Wnt/β-catenin Pathway Downstream Molecules and Clinicopathological Characteristics of NSCLC

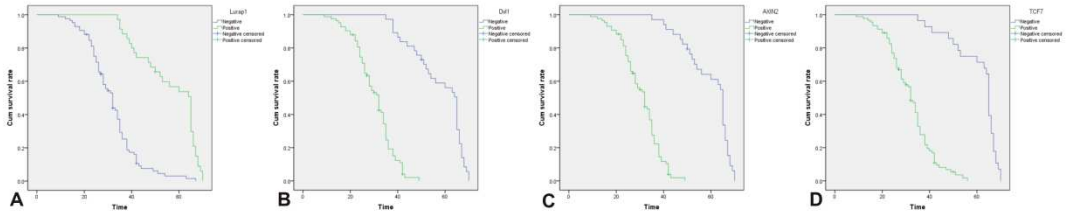
AXIN2 expression showed no statistical correlations with gender, age, smoking history, tumor size or tumor differentiation ($P > 0.05$), but was significantly associated with lymph node

metastasis and pTNM stage ($P < 0.05$). TCF7 expression was only correlated with lymph node metastasis ($P < 0.05$), with no significant relationships to gender, age, smoking history, tumor size, differentiation or pTNM stage ($P > 0.05$). LEF1 expression exhibited no significant differences across subgroups stratified by gender, age, smoking history, tumor size or tumor differentiation ($P > 0.05$), yet it was significantly related to lymph node metastasis and pTNM stage ($P < 0.05$) (**Table 4**).

Univariate Prognostic Analysis and Multivariate Cox Regression Analysis

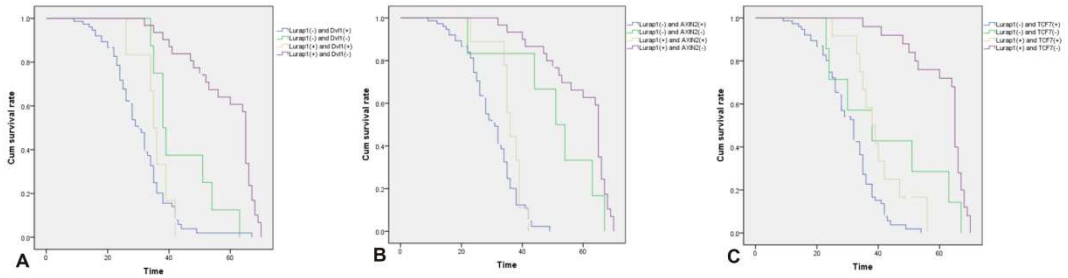
Kaplan-Meier survival analysis demonstrated that patients with low Lurap1 expression, high Dvl1 expression, high AXIN2 expression or high TCF7 expression exhibited significantly shorter overall survival compared with corresponding control groups (all $P < 0.05$) (Fig. 6). Patients with lymph node metastasis or TNM stage Ⅲ-Ⅳ also had worse prognosis. Combined-marker univariate survival analysis revealed that concurrent abnormal expression of Lurap1 and Dvl1 yielded the strongest predictive power for poor prognosis ($HR = 7.983$, $P < 0.001$). Combined Lurap1-AXIN2 expression ($HR = 6.465$, $P < 0.001$) and combined Lurap1-TCF7 expression ($HR = 1.522$, $P = 0.003$) were also significantly associated with survival (Fig.7). By contrast, combined Lurap1-LEF1 expression had no prognostic value ($HR = 0.986$, $P = 0.427$).

Fig. 6 Kaplan-Meier analysis of the survival rate of patients with bladder cancer.



A Overall survival of all patients in relation to Lurap1 expression(HR=3.239，P＜0.001); **B** Overall survival of all patients in relation to DVL1 expression(HR=1.761，P=0.002); **C** Overall survival of all patients in relation to AXIN2 expression (HR=1.458，P=0.007); **D** Overall survival of all patients in relation to TCF7 expression (HR=1.397, P=0.046).

Fig. 7 Kaplan-Meier analysis of the survival rate of patients with bladder cancer.



A Overall survival of all patients in relation to the combined expression of Lurap1 and Dvl1 (HR=7.983，P＜0.001); **B** Overall survival of all patients in relation to the combined expression of Lurap1 and AXIN2 (HR=6.465，P＜0.001); **C** Overall survival of all patients in relation to the combined expression of Lurap1 and TCF7 (HR=1.522，P=0.003).

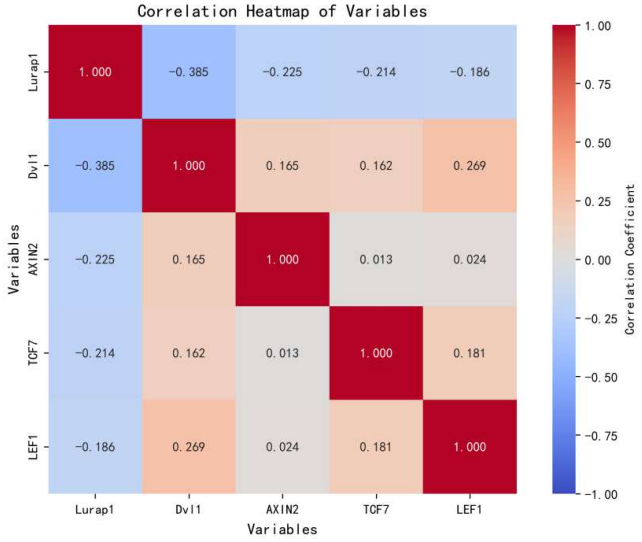
Variables with statistical significance in univariate analysis were incorporated into the Cox proportional-hazards regression model. Multivariate analysis identified low Lurap1 expression,

high Dvl1 expression, lymph node metastasis, and TNM stage Ⅲ-Ⅳ as independent adverse prognostic risk factors for postoperative OS in NSCLC patients (all $P < 0.05$). Concurrent abnormal expression of Lurap1 and Dvl1 was also an independent prognostic risk factor (HR = 3.755, $P < 0.001$). After adjustment for confounding factors, combined expression of Lurap1 with AXIN2, TCF7 or LEF1 lost independent prognostic significance (all $P > 0.05$) (**Tables 5-6**).

Expression Correlations between Lurap1 and Dvl1 as well as Wnt/β-catenin Pathway Downstream Molecules

Spearman correlation analysis indicated that Lurap1 protein expression was significantly negatively correlated with Dvl1, AXIN2, TCF7 and LEF1 in NSCLC tissues ($P < 0.05$) (Fig. 8). These results suggested that Lurap1 downregulation was accompanied by activation of Dvl1-dependent Wnt/β-catenin signaling, and Lurap1 might negatively modulate Wnt/β-catenin pathway activity (**Table 7**).

Fig.8 Pearson correlation heatmap.



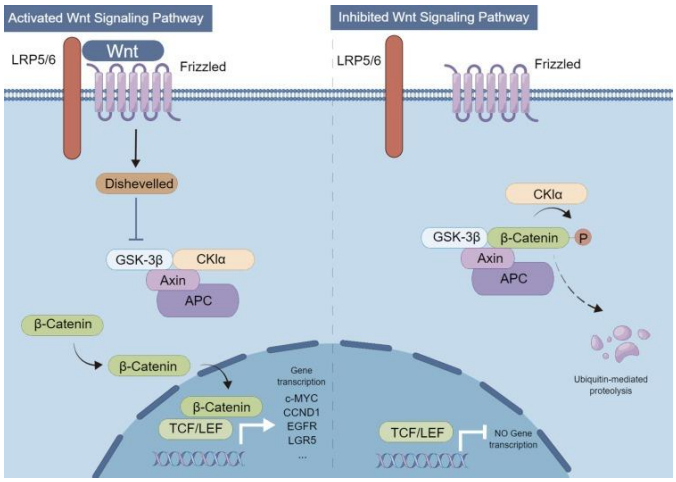
Discussion

NSCLC constitutes the major subtype of lung cancer. Compared with small-cell lung cancer, NSCLC progresses insidiously with atypical early-stage symptoms. Many patients are diagnosed with local invasion, lymph node or distant metastasis and miss optimal surgical opportunities[11]. Despite wide application of surgery, radiotherapy, chemotherapy, targeted therapy and immunotherapy, malignant proliferation, invasion-metastasis and therapeutic resistance remain major contributors to tumor recurrence and dismal prognosis in NSCLC patients[12]. Hence, dissecting key molecules and signaling cascades driving NSCLC progression and clarifying oncogenic mechanisms is of great clinical and scientific significance for identifying novel therapeutic targets and improving patient outcomes.

Aberrant activation of the Wnt/β-catenin signaling pathway is a core molecular event promoting malignant proliferation, invasion-metastasis and poor prognosis in NSCLC[13]. As an upstream hub molecule, Dvl1 receives Wnt ligands, disrupts the β-catenin destruction complex, facilitates β-catenin nuclear translocation, recruits TCF7/LEF1 transcription factors, and initiates transcription of target genes such as AXIN2 to induce malignant biological behaviors of tumor cells[14-15]. In our study, Dvl1 together with its downstream effectors AXIN2, TCF7 and LEF1

were markedly overexpressed in NSCLC tissues. Their high expression was correlated with poor differentiation, lymph node metastasis, advanced TNM stage and unfavorable survival, further confirming the oncogenic role of Dvl1-mediated Wnt pathway activation in NSCLC progression (Fig. 9).

Fig.9 Signal transduction pathway activation schematic diagram.



Lurap1 is a leucine-repeat-containing adaptor protein. Previous studies have reported that Lurap1 modulates Dvl protein stability via protein-protein interactions and suppresses excessive Wnt/β-catenin signaling, exerting tumor-suppressive functions in multiple malignancies[16]. In the current investigation, Lurap1 was significantly downregulated in NSCLC tumor tissues relative to adjacent normal tissues. Low Lurap1 expression was associated with lymph node metastasis, poor differentiation and advanced TNM stage, implying that loss-of-function of Lurap1 accelerates NSCLC malignant progression. Correlation analyses revealed negative correlations between Lurap1 and Dvl1, AXIN2, TCF7 as well as LEF1, suggesting that Lurap1 may restrain Wnt/β-catenin pathway activation by negatively regulating Dvl1. Upon Lurap1 downregulation, its inhibitory effect on Dvl1 is attenuated, resulting in Dvl1 accumulation and persistent Wnt pathway activation, which consequently promotes NSCLC invasion and metastasis.

Survival analyses demonstrated that patients with low Lurap1 or high Dvl1 expression had significantly shorter OS. Multivariate Cox regression verified that dysregulated expression of Lurap1 and Dvl1 represented independent risk factors for poor prognosis, together with lymph node metastasis and advanced TNM stage. Therefore, Lurap1 and Dvl1 can serve as novel independent molecular biomarkers to evaluate tumor malignancy and predict postoperative prognosis, compensating for limitations of conventional pathological TNM staging.

The present study innovatively demonstrates the tumor-suppressive role of Lurap1 in NSCLC and its regulatory link to Wnt signaling, and clarifies that the Lurap1low/Dvl1high expression pattern participates in NSCLC malignant progression. Nevertheless, this study has limitations. All conclusions are derived from clinical tissue-specimen analyses. Further cellular functional assays and animal-model experiments are warranted to validate the detailed molecular mechanisms by which Lurap1 modulates the Dvl1/Wnt/β-catenin axis to govern NSCLC proliferation and invasion.

Conclusions

Lurap1 is downregulated in NSCLC tissues, while Dvl1 and downstream Wnt/β-catenin

effectors (AXIN2, TCF7, LEF1) are abnormally upregulated. Low Lurap1 expression is closely associated with malignant progression, invasion-metastasis and poor prognosis of NSCLC. Lurap1 expression is negatively correlated with Wnt pathway activity, indicating that Lurap1 may suppress NSCLC progression via negatively regulating the Dvl1/Wnt/β-catenin signaling cascade. Low Lurap1 expression, high Dvl1 expression, lymph node metastasis and advanced TNM stage are independent risk factors for adverse prognosis in NSCLC patients. Lurap1 and Dvl1 are promising novel molecular biomarkers for evaluating malignancy and prognostic stratification of NSCLC, and provide theoretical foundations for targeted therapeutic development for NSCLC.

Data availability statements

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Acknowledgements

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Table 1. Patients characteristics.

Patients characteristics	Frequency (n)	Percentage (%)
Gender		
Male	76	63.3
Female	44	36.7
Ages		
＜ 60y	67	55.8
≥ 60y	53	44.2
Smoking		
No	45	37.5
Yes	75	62.5
Size(cm)		
＜3.0	62	51.7
≥3.0,＜5.0	43	35.8
≥5.0	15	12.5
Grade		
Well	47	39.2
Moderate	49	40.8
Poor	24	20.0
LNM stage		
N0	75	62.5
N1+N2	35	29.2
N3	10	8.3
TNM stage		
I+II	92	76.7
III+IV	28	23.3

Antigen	Clone	Source	Dilution	Position
Lurap1	PA5-56328	rabbit polyclonal	1:50-1:200	Cytoplasm
Dvl1	1A2A5	Mouse polyclonal	1:800-1:1000	Cytomembrane
AXIN2	20540-1-AP	rabbit polyclonal	1:150-1:400	Nucleus
TCF7	C63D9	rabbit polyclonal	1:100-1:400	Nucleus
LEF1	C12A5	rabbit polyclonal	1:100-1:300	Nucleus

Table 2. Antibody information.

Charistics	n	Lurap1		P	Dvl1		P
		Negative	Positive		Negative	Positive	
Gender							
Male	76	51	25	0.331	25	51	0.662
Female	44	34	10		12	32	
Age（years)							
< 60	67	48	19	0.987	17	50	0.209

Table 3. Correlations between Lurap1, Dvl1 and clinicopathological variables in NSCLC .

Charistics	n	E-cadherin		P	β-catenin		P	
		reduced	preserved		Negative	Positive		
Lymph node metastasis								
negative	58	33	25	0.001	34	24	0.003	0.151
positive	52	12	40		15	37		
pTNM								
I-II	36	25	11	< 0.001	26	10	< 0.001	0.031
III-IV	74	20	54		23	51		
Lymph node metastasis								
N0	75	61	14	0.002	26	49	0.009	
N1+N2	35	17	18		9	26		
N3	10	7	3		2	8		
pTNM								
I-II	92	60	32	0.027	34	58	0.028	
III-IV	28	25	3		3	25		
⩾60	53	37	16		20	33		
Smoking								
No	45	31	14	0.876	16	29	0.507	
Yes	75	54	21		21	54		
Size(cm)								
< 3.0	62	44	18	0.229	24	38	0.151	
⩾3.0, < 5.0	43	33	10		10	33		
⩾5.0	15	8	7		3	12		
Pathologic differentiation								
Well	47	16	24	< 0.001	21	26	< 0.001	
Moderate	49	38	15		11	38		
Poor	24	15	2		5	19		

Table 4. Correlations between E-cadherin、β-catenin and clinicopathological variables in bladder cancer.

Table 5. Results of Univariate analyses and Multivariate analysis of overall survival (OS) time.

Variable	Univariate analysis			Multivariate analysis		
	HR	P value	95%CI	HR	P value	95%CI
Gender						
Female/Male	0.601	0.182	0.162-1.318	1.042	0.875	0.627-1.732
age（years)						
< 60/≥60	1.246	0.229	0.814-2.328	1.233	0.393	0.762-1.996
Smoking history						
No/Yes	1.129	0.655	0.632-2.061	1.765	0.026	1.070-2.911
T classification						
Ta + T1/T2 + T3	1.284	0.427	0.726-2.447	2.306	< 0.001	1.596-3.331
pathologic differentiation						
Well/Moderate/Poor	1.091	0.634	0.742-1.772	1.266	0.267	0.835-1.920
Lymph node metastasis						
Negative/Positive	4.832	< 0.001	3.017-9.310	1.993	0.009	1.449-3.243
pTNM						
I-II/III-IV	3.213	< 0.001	1.831-6.215	2.306	0.052	0.992-5.359
E-cadherin expression						

Reduced/ Preserved	0.504	0.051	0.248-1.013	0.412	0.120	0.207-0.820
β-catenin expression						
Negative/Positive	1.010	0.648	0.952-1.786	1.632	0.192	0.782-3.408
KlF15 expression						
Negative/Positive	3.228	< 0.001	1.825-6.141	1.926	0.014	1.213-2.725
Slug expression						
Negative/Positive	1.826	0.012	0.989-2.842	1.043	0.782	0.632-2.046
ZEB1 expression						
Negative/Positive	2.012	0.007	1.232-3.445	1.412	0.284	0.767-2.428
Snail expression						
Negative/Positive	1.498	0.025	0.951-2.235	0.734	0.615	0.455-1.346

Variables		KLF15	Slug	ZEB1	Snail	E-cadherin	β-catenin
KLF15	r	1	-0.185	-0.197	-0.217	0.242	-0.248

Table 6. The combined expression results of Univariate analyses and Multivariate analysis of overall survival (OS) time.

Variables	Univariate analysis			Multivariate analysis		
	HR	P value	95%CI	HR	P value	95%CI
KLF15 and Slug expression	7.896	0.009	7.182-9.335	1.207	0.620	0.941-1.510
KLF15 and ZEB1 expression	11.695	< 0.001	9.261-15.226	3.284	0.019	1.163-7.654
KLF15 and Snail expression	9.401	0.006	8.085-13.838	0.926	0.695	0.667-1.320

Table 7. Results of Spearman correlation coefficient analysis.

	P	−	0.026	0.038	0.010	0.012	0.001
Slug	r		1	0.155	0.162	-0.269	0.089
	P		−	0.254	0.068	0.003	0.295
ZEB1	r			1	0.016	-0.242	0.256
	P			−	0.915	0.002	0.005
Snail	r				1	-0.174	0.259
	P				−	0.039	0.011
E-cadherin	r					1	-0.173
	P					−	0.057
β-catenin	r						1
	P						−