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P2.157: Abnormal phosphorylation of human LRH1 at Ser510 predicts poor prognosis and promotes cell viability in lung squamous cell carcinoma

H. Mine, A. Enta, Y. Maruya, S. Inomata, M. Watanabe, Y. Ozaki, N. Okabe, K. Hamada, H. Suzuki

Department of Thoracic Surgery, Fukushima Medical University Hospital, Fukushima, Japan

*Correspondence : H. Mine, E-mail : hayato@fmu.ac.jp

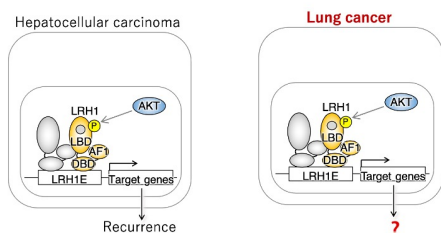


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INTRODUCTION

The nuclear receptor liver receptor homolog 1 (LRH1)/NR5A2 is aberrantly expressed in diverse cancer types, including liver and lung cancers^{1,2}. We recently developed a monoclonal antibody specific for phosphorylated human LRH1 at S510 (hLRH1^{pS510}). Since we previously showed that excessive phosphorylation of human LRH1 at S510 (hLRH1^{pS510-high}) is predictive of hepatocellular carcinoma recurrence³, we clarified the clinicopathological and biological significance of hLRH1^{pS510-high} in lung cancer (Fig 1).

Fig 1



METHODS

By immunohistochemistry using an anti-hLRH1^{pS510} monoclonal antibody, we evaluated the hLRH1^{pS510} signals in 151 and 150 cases of lung adenocarcinoma (LUAD) and lung squamous cell carcinoma (LUSC) tissues, respectively, and performed clinicopathological analysis. The Allred score (0–8) was calculated as the sum of staining intensity (0–3) and proportion scores (0–5), and samples were classified as hLRH1^{pS510-low} (score ≤7) or hLRH1^{pS510-high} (score = 8).

To examine the biological significance of hLRH1^{pS510} in LUSC, we generated LK-2 and RERF-LC-AI cells expressing wild-type LRH1, LRH1S510A (an S510 phosphorylation-deficient LRH1 mutant), or LRH1S510E (an S510 phosphorylation-mimetic LRH1 mutant), and assessed its effect on cell viability by phenotypic comparison (Fig 2).

Fig 2



RESULTS

Fig 3

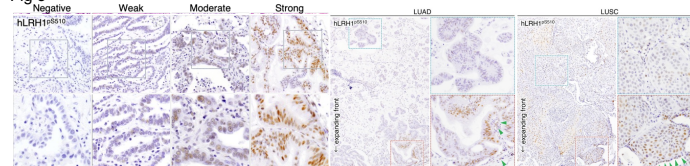


Fig 4

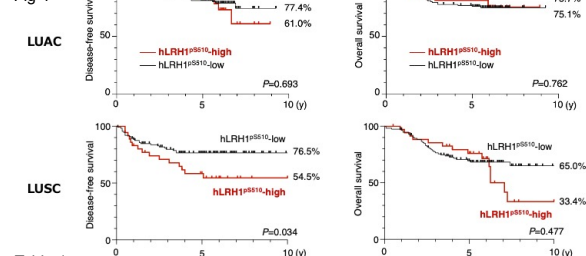
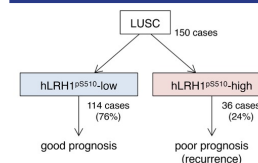


Table 1

Variable	Univariate analysis			Multivariate analysis		
	HR	95%CI	P-value	HR	95%CI	P-value
Age	≥ 75	0.905	0.476–1.719	0.760		
Gender	Female	1.043	0.409–2.664	0.930		
Extent of resection	Lobectomy	0.469	0.229–0.961	0.039	0.194	0.077–0.485
Tumor size	> 3 cm	1.770	0.945–3.313	0.074		
pT	T2/T3/T4	1.907	0.984–3.697	0.056	1.591	0.595–4.257
Pathological grade	G2/G3	1.781	0.698–4.546	0.228		
Vascular invasion	(+)	1.903	0.950–3.812	0.069		
Lymphatic invasion	(+)	2.191	1.170–4.103	0.014	1.839	0.866–3.908
Pleural invasion	(+)	3.362	1.850–6.264	< 0.001	3.582	1.578–8.130
Lymph node metastasis	N1/N2	2.516	1.298–4.878	0.006	2.004	0.889–4.515
Pathological stage	II/III	1.534	0.825–2.855	0.177		
hLRH1 ^{pS510}	high	1.970	1.038–3.737	0.038	2.668	1.337–5.325

HR, hazard ratio; CI, confidence interval

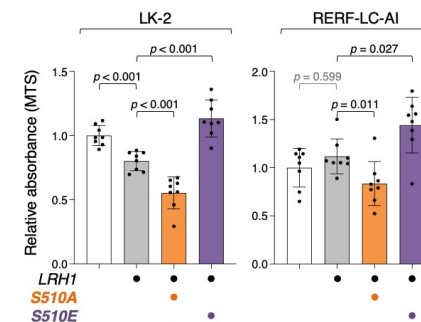
DISCUSSION AND CONCLUSION



Our findings indicate that hLRH1^{pS510} is associated with poor prognosis and enhanced cell viability in LUSC, suggesting its potential as a therapeutic target.

The strong hLRH1^{pS510} signal was occasionally detectable in LUAD and LUSC cells at the expanding tumor edges (Fig 3). A semi-quantitative analysis revealed that 28 (18.4%) and 36 (24.0%) of LUAD and LUSC cases, respectively, exhibited hLRH1^{pS510-high}. hLRH1^{pS510-high} was associated with significantly worse DFS in LUSC, with a 10-year DFS rate of 54.5% compared with 76.5% in hLRH1^{pS510-low} (Fig 4). hLRH1^{pS510-high} represented an independent biomarker for the DFS of LUSC patients by multivariate analysis (Table 1). In LK-2 and RERF-LC-AI cells expressing wild-type LRH1, LRH1S510A, or LRH1S510E, cell viability was significantly decreased in LRH1S510A-expressing cells and increased in LRH1S510E-expressing cells, indicating that LRH1 S510 phosphorylation promotes LUSC cell viability (Fig 5).

Fig 5



REFERENCES

- 1)Nadolny C, et al. Cancer Biol Ther. 2015;16:997–1004.
- 2)Meisohn M-C, et al. Physiol Rev. 2019;99:1249–79.
- 3)Nishimagi A, et al. Clin Exp Med. 2023;23:4985–95.

AI USE DISCLOSURE

ChatGPT (OpenAI) was used solely for English language editing. All scientific content was prepared and verified by the authors.