Peer Review File

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Reviewer A

1. The authors are requested to provide the intricate molecular signal transduction mechanism(s) in support of their claims.

Answer: We found that FHL2 can regulate the expression level of VEGFA mRNA, but whether this regulation is direct or indirect, we will continue to explore in subsequent studies.

2. The authors are also advised to provide some relevant human samples related in vitro data to establish their observations.

Answer: The UALCAN database showed that FHL2 protein was elevated in both lung adenocarcinoma and lung squamous cell carcinoma (Figure S3). We will further confirm this data in the follow-up study.

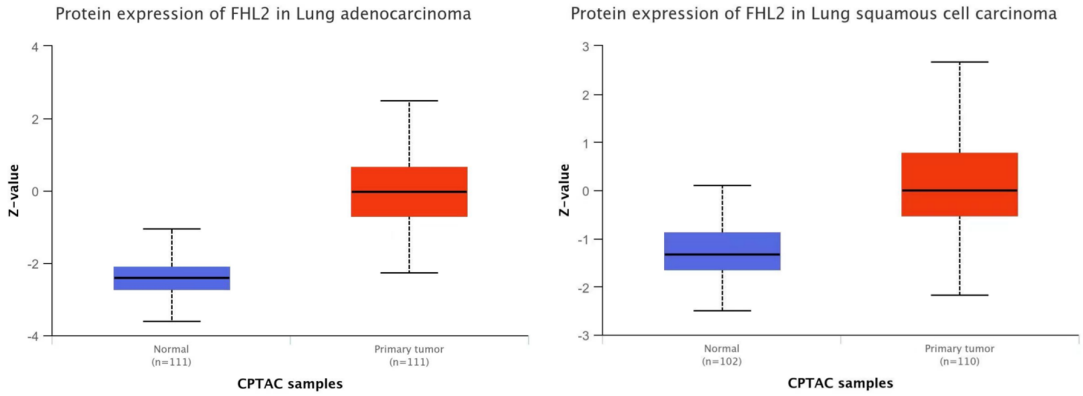


Figure S3

Reviewer B

In the present study, the authors start from the premise that anti angiogenetic therapy is one of the efficient approaches for non-small cell lung cancer (NSCLC) treatment. In addition, considering that FHL2 was identified primarily as a biomarker of lung adenocarcinoma, and that FHL2 modulates cell growth and metastasis, the authors explored FHL2 in NSCLC angiogenesis. First, they explored mRNA level of FHL2 from the TCGA database and FHL2 expression level in NSCLC cell lines by using qPCR analysis. Then, a xenograft model was used to investigate the effects of FHL2 on NSCLC progression in vitro and in vivo. Transwell invasion, and tube formation, were used to determine the roles of FHL2 in angiogenesis vascular permeability; and VEGFA enzyme-linked ELISA assay, to investigate the specific mechanism mediated by FHL2. They demonstrated that FHL2 was significantly upregulated in NSCLC tissues and cell lines and associated with poor prognosis. FHL2 overexpression

promoted proliferation, migration, invasion, and tube formation. Mechanistically, they demonstrated that FHL2 activated the AKT-mTOR signaling pathway by promoting VEGFA synthesis from NSCLC cells to induce angiogenesis and vascular permeability. FHL2 also promoted NSCLC tumor growth in vivo.

Major concern

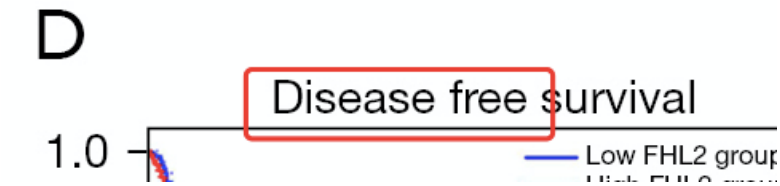
The study is innovative, well-described, employing adequate methodology, and thereby of interest to the reader. My only concern with the study was the lack of in vitro experiments, documenting the histology of the tumors and the expression of the factors studied by immunohistochemistry, thus providing a tool that can be used in the pathologist's diagnostic routine when evaluating NSCLC. This would be, in my opinion, the most important message of the study for patients, oncologists and pathologists.

Answer: It is necessary to record the expression of tumor-associated proteins in histology and immunohistochemistry, and we will supplement relevant experiments in subsequent studies.

Reviewer C

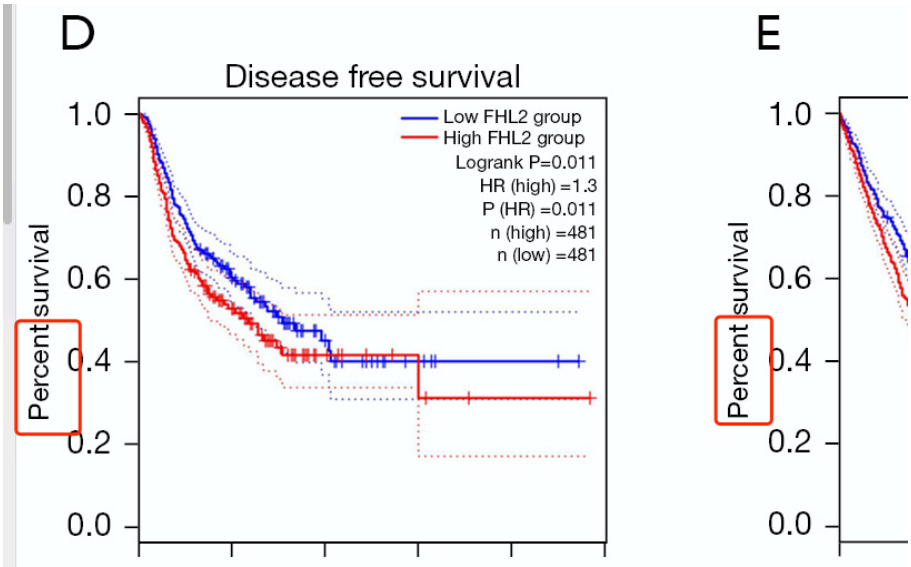
1. Figure 1

a. Please revise "Disease free" to "Disease-free".



Answer: Have been modified.

b. Please delete the 'percent', as the numbers are range from 0-1.



Answer: Have been modified.

2. Figure 2

The figure 2 you submit as a separate file is different with the version in the paper and does not match the figure legend. Please confirm which version is correct, and send the right one to us.

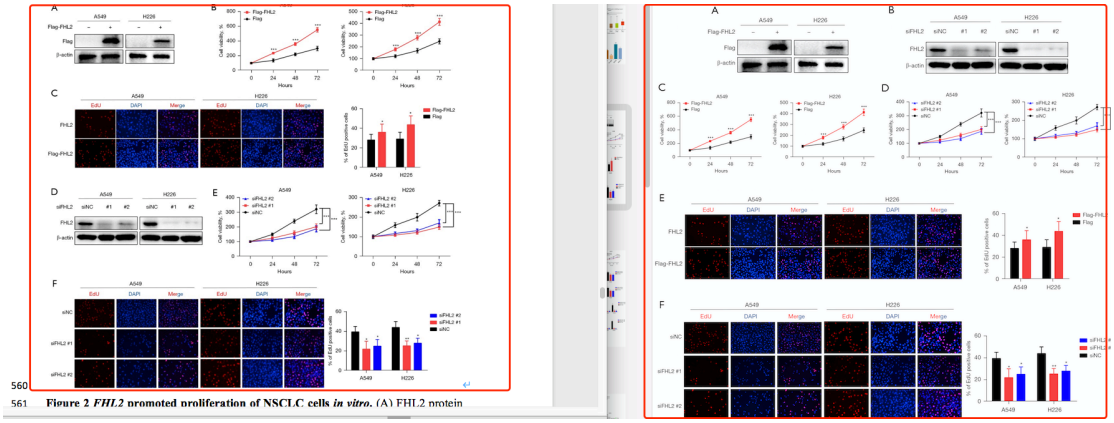


Figure 2 *FHL2* promoted proliferation of NSCLC cells *in vitro*. (A) FHL2 protein

Answer: Have been modified.

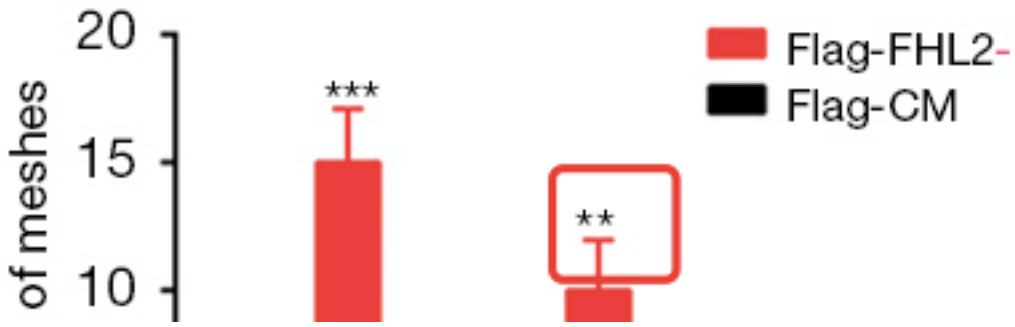
3. Figure 3

a. Please indicate the observation method in the figure legend G, H.

cells on HUVECs. Crystal-violet-stained HUVECs (magnification ×100). (G,H) The effects of CM from *FHL2*-overexpressed (G) or *FHL2*-silenced (H) NSCLC cells on tube formation in HUVECs (magnification ×100). The number of meshes are shown

Answer: Have been modified.

b. Please also indicate the meaning of "**" in figure legend.



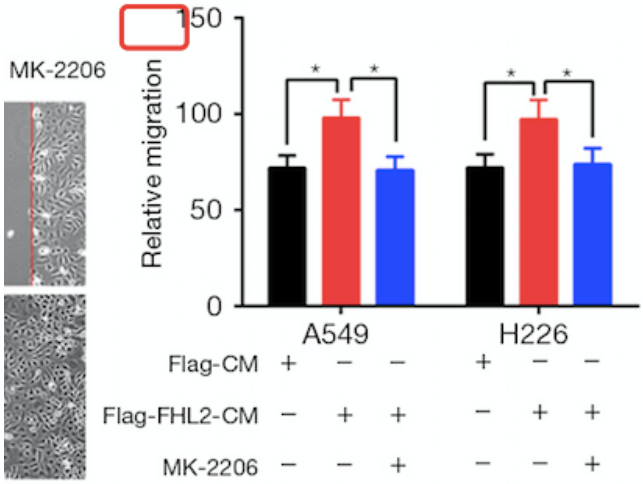
Answer: Have been modified.

4. Figure 4

a. Please also indicate the meaning of "****" in figure legend.

Answer: Have been modified.

b. If applicable, please add the unit in the Y-axis of figure 4G.



Answer: Have been modified.

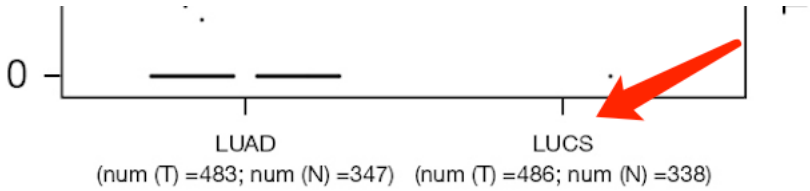
c. Please indicate the observation method in the figure legend I.

611 Crystal-violet-stained HUVECs (magnification ×100). (I) Tube formation ability of
612 HUVECs was examined after coculture with MK-2206 and the CM from
613 *FHL2*-silenced NSCLC cells for 24 h (magnification ×100). The number of meshes

Answer: Have been modified.

5. Figure 1A

LUSC or LUCS? Please check and revise.



Reply: We have modified it.