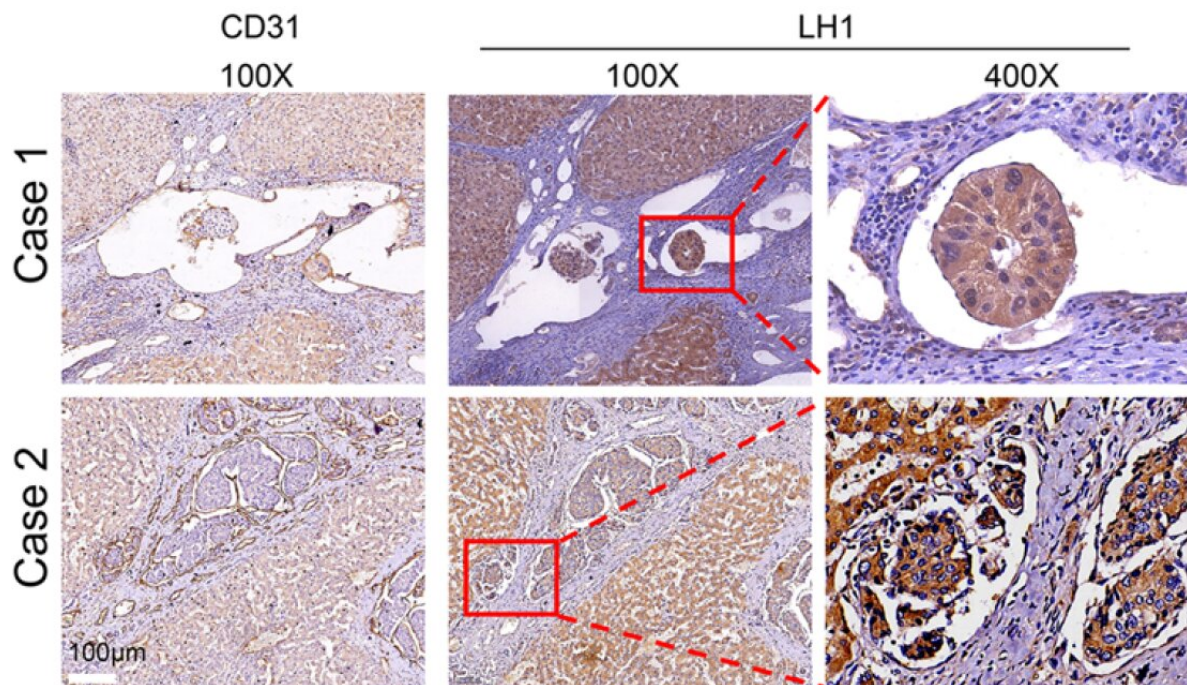


Researchers identify a protein that promotes cancer metastasis, providing a new potential treatment target

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They also demonstrated that LH1 could bind and stabilize Septin2 (SEPT2), a protein that plays an essential role in preparing the cells for high mechanical migration demand, to enhance the formation of an actin network. The actin network is the most dynamic element of the cytoskeleton, is distributed throughout the cell cytoplasm, and controls cell mechanics and motility. Thus, the enhanced formation of the actin network can promote the confined migration and metastasis of HCC and PDAC cells. LH1 was strongly expressed in HCC tumour embolus. Credit: *Molecular Cancer* (2023). DOI: 10.1186/s12943-023-01727-9

Cancer metastasis is a major cause of cancer-related death. A research team at City University of Hong Kong (CityU) recently identified a protein that triggers the migration of liver and pancreatic cancer cells and metastasis and is correlated with shortening the survival time of patients.

The research findings were verified by in vitro and in vivo models, supported with [clinical data](#), and are expected to provide a new potential target for [cancer therapy](#). The study was published in the journal *Molecular Cancer*, under the title "Lysyl hydroxylase LH1 promotes confined migration and metastasis of [cancer](#) cells by stabilizing Septin2 to enhance actin network."

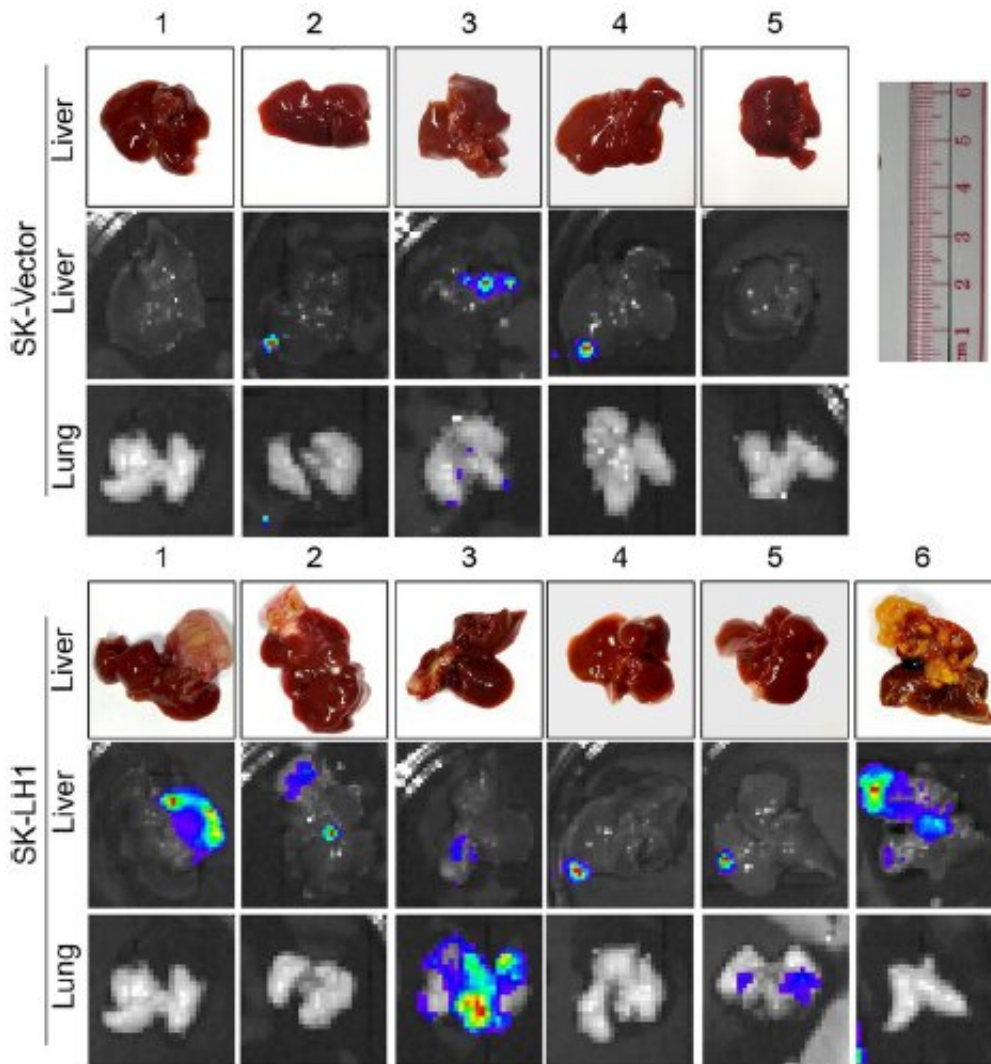
"Cancer metastasis is a complex process. Stiffness in tumors and the surrounding tissues is known to increase along with the tumor growth, which creates confined spaces or channel-like tracks of pores for tumor cell migration and metastasis in multiple cancer types. But the mechanism of this confined migration remains unclear," said Professor Michael Yang Mengsu, Vice-President (Research and Technology) and Yeung Kin Man Chair Professor of Biomedical Sciences at CityU, who led the cross-institutional research. "We aim to deeply study the [cancer metastasis](#) mechanism and identify novel genes and proteins related to it."

Hepatocellular carcinoma (HCC) is the most common type of the second leading cause of cancer death worldwide—liver cancer. Pancreatic ductal adenocarcinoma (PDAC) is another highly aggressive cancer with a five-year survival rate of less than 10%. Both of them have a typical feature of solid tumors with excessive extracellular matrix (ECM) deposition containing confined pores or channel-like tracks that enable cancer cell migration. So the team chose these two different cancer types

as the study subjects.

Developing methods to study the migration mechanism

In collaboration with the Second Affiliated Hospital of Chongqing Medical University (CQMU), Professor Yang's team first collected HCC and PDAC specimens for analysis from 153 and 63 patients, respectively, who had not received chemotherapy or radiotherapy before surgery. The team also obtained human liver cancer and pancreatic cancer cell lines from the National Institutes of Health in the U.S..



The research team observed that the LH1 overexpressing group had significantly larger tumours in the liver of a mice model with liver orthotopic injection.
 Credit: *Molecular Cancer* (2023). DOI: 10.1186/s12943-023-01727-9

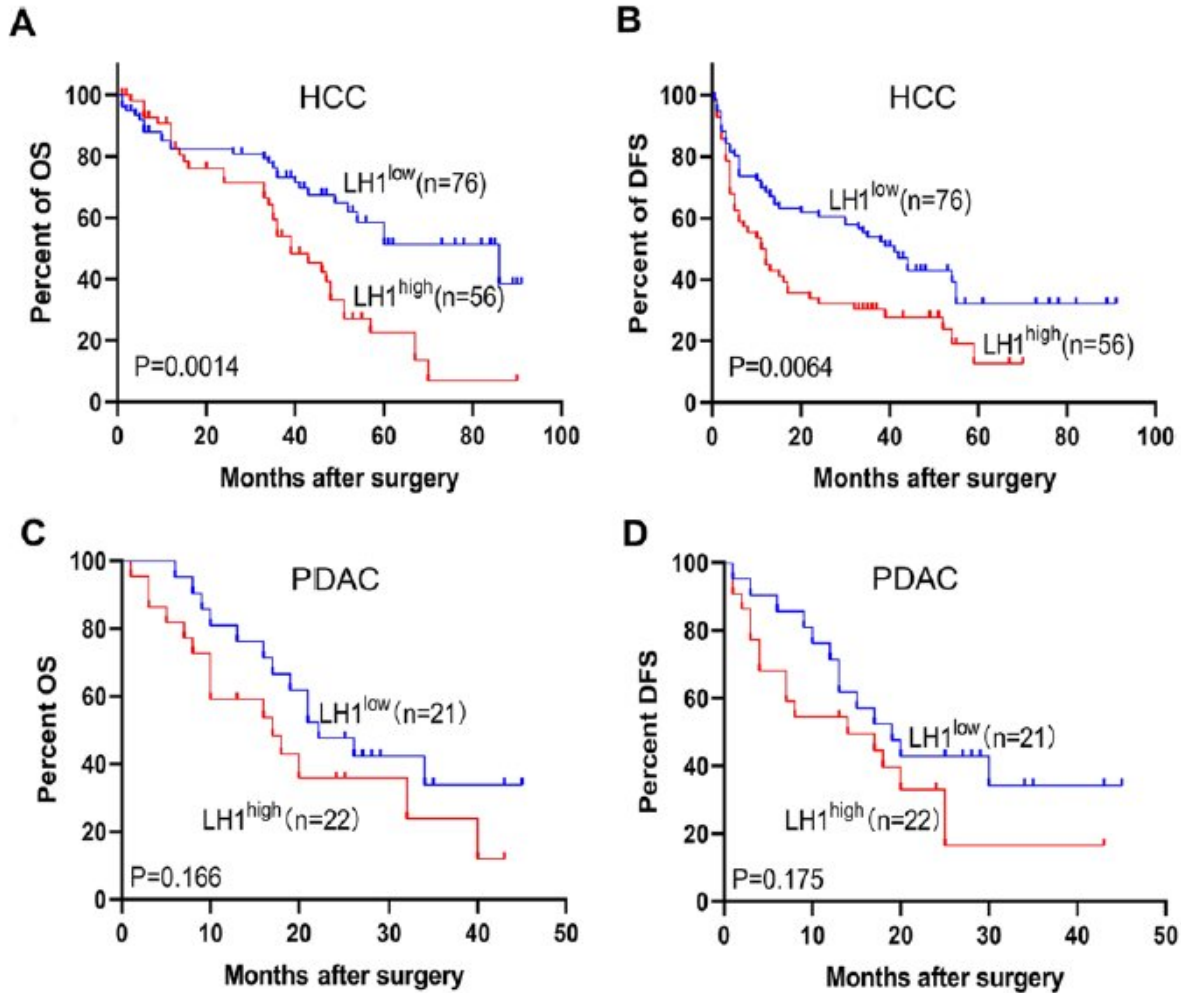
"The main challenge was to simulate the complex cancer microenvironment," explained Professor Yang. "But there is a lack of study models for cell migration in confined environment. So we developed a series of multidimensional platforms and 2D and 3D in vitro and in vivo models to comprehensively study the cell migration process."

These platforms and models include [microfluidic chips](#) for single-cell and collective [cell migration](#), and hydrogels of various stiffness for 3D invasion assays to simulate the in vivo environment. The team also utilized next-generation sequencing (NGS) and liquid chromatography-mass spectrometry (LC-MS) to determine the differentially expressed genes and proteins in cancer tissues.

LH1 as a key factor in promoting confined migration of HCC and PDAC cells

Based on the transcriptomic analysis with NGS and proteomic analysis with LC-MS, the team identified a protein called lysyl hydroxylase 1 (LH1) as one of the most significantly overexpressed proteins in HCC tissues. The microfluidic chips and 3D invasion models they developed demonstrated LH1's capability to promote confined migration at multidimensional levels, including speed and invasion capacity of HCC and PDAC cells. The effects can be suppressed by knocking down the expression of LH1.

They also demonstrated that LH1 could bind and stabilize Septin2 (SEPT2), a protein that plays an essential role in preparing the cells for high mechanical migration demand, to enhance the formation of an actin network. The actin network is the most dynamic element of the cytoskeleton, is distributed throughout the cell cytoplasm, and controls cell mechanics and motility. Thus, the enhanced formation of the actin network can promote the confined migration and metastasis of HCC and PDAC cells.



The figures show that patients with high LH1 protein expression level had a shorter overall survival and disease-free survival time with HCC (fig. A&B) and PDAC (fig. C&D). Credit: *Molecular Cancer* (2023). DOI: 10.1186/s12943-023-01727-9

High LH1 expressed level results in poor prognosis for cancer patients

The research team also analyzed the correlation between LH1 and

prognosis (i.e., the development of disease and chance of relapse) of HCC and PDAC patients. The clinical samples showed that patients with higher LH1 expression, along with [poor prognosis](#), had only half of the survival rate of the low LH1 expression group.

Moreover, HCC and PDAC patients with high LH1 expression experienced a shorter overall survival time from the date of diagnosis to death of 39 and 17 months, respectively, compared to 86 and 22 months for patients with a lower level of LH1. Also, their disease-free survival time from primary treatment to relapse of the disease was 11.5 and 14 months, respectively, compared to 41 and 19 months for patients with a lower LH1 level.

"The platforms and methods we developed provide a unique approach to study the confined migration of cancer cells," said Professor Yang. "We demonstrated that LH1 promotes confined migration and metastasis of cancer cells by stabilizing SEPT2, and that high LH1 is associated with poor prognosis of HCC and PDAC patients. The findings are expected to provide a potential new target for cancer diagnosis and drug development."

More information: Zihan Yang et al, Lysyl hydroxylase LH1 promotes confined migration and metastasis of cancer cells by stabilizing Septin2 to enhance actin network, *Molecular Cancer* (2023). [DOI: 10.1186/s12943-023-01727-9](https://doi.org/10.1186/s12943-023-01727-9)

Provided by City University of Hong Kong

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