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HKU Biologists Uncover How a Genetic Player Fuels Liver Cancer by Disrupting Fat Metabolism

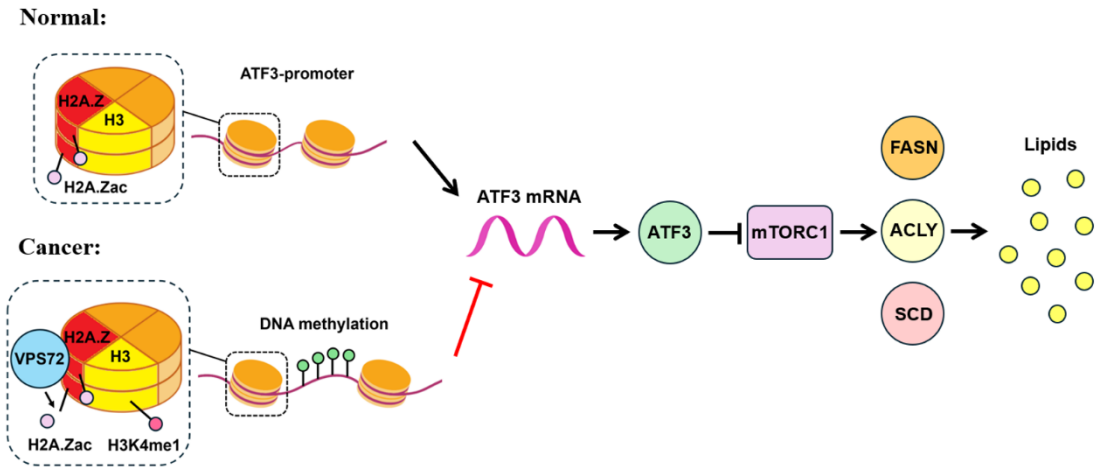

Figure 1. Mechanism of how genetic player VPS72 impacts liver cancer. Too much VPS72 in cells activates the cancer-promoting pathway, which increases fat production and helps liver cancer grow. This study shows a new connection between fat buildup and liver cancer, suggesting new treatment possibilities. Image adapted from the respective paper at *Advanced Science.*

Liver cancer is a lethal disease with limited treatment options for advanced stages. While risk factors such as viral hepatitis, alcohol use, and obesity increase the likelihood of hepatocellular carcinoma (HCC, the progression of liver cancer), scientists are racing to uncover the hidden biological mechanisms that fuel tumour growth. Recent research led by Professor Jiangwen ZHANG of the School of Biological Sciences at The University of Hong Kong (HKU) has uncovered how a key genetic culprit, VPS72, drives the development of liver cancer by disrupting fat metabolism and manipulating gene activity. The team's findings have been published in *Advanced Science*.

The Fat-Liver Cancer Connection

The liver is the body's metabolic powerhouse, responsible for balancing fat production and breakdown. In healthy individuals, this process is tightly controlled. However, in HCC, liver cells accumulate excessive fat droplets, fuelling tumours to grow uncontrollably. This fat buildup is largely controlled by a key cellular pathway known as mTORC1, a molecular switch that activates fat-producing genes, and by SREBP proteins, which act as master regulators that directly control enzymes involved in fat synthesis. In cancer cells, mTORC1 becomes hyperactive, ramping up fat production and creating a vicious cycle that promotes tumour growth.

The Role of Genetic Driver VPS72 in Liver Cancer Development

Professor Zhang and his team discovered that VPS72, a gene that modifies how DNA is packaged inside cells, is overactive and abnormally amplified (i.e., present in extra copies) in over 50% of HCC patients. This amplification is linked to poorer survival rates, suggesting that this genetic player plays a central role in cancer progression. Here is how the mechanism works:

- **DNA Packaging:** VPS72 helps attach specific proteins to DNA, which affects whether certain genes are turned on or off.
- **Suppressing Protective Genes:** VPS72 adds chemical tags to the promoter of gene ATF3, which normally helps prevent cancer growth. This tagging shuts down the production of ATF3, leading to the overactivity of a cancer-promoting pathway called mTORC1.
- **Increasing Fat Production:** When mTORC1 is overactive, it boosts proteins that increase the production of fats. This results in cancer cells being flooded with fats, providing them with energy and materials needed to grow rapidly.

In short, this genetic player acts like a rogue conductor: it silences protective genes, promotes the cancer pathway and forces liver cells to overproduce fat —a perfect storm for cancer.

A New Target for Liver Cancer Treatment

These findings offer new hope for targeted therapies. One approach is to design drugs that block VPS72's interaction with H2A.Z proteins, potentially stopping the DNA changes that lead to cancer. Another strategy involves using existing drugs that inhibit mTORC1, a pathway already targeted in other cancers, which could be repurposed for liver cancer patients with increased VPS72 activity. By focusing on VPS72 and the pathways it affects, Professor Zhang's team hopes to stop cancer from progressing.

"Our research shows that the gene VPS72 plays two key roles in liver cancer (HCC): it affects both how genes are controlled and how fat metabolism goes wrong. The findings help explain how liver cancer develops and suggest new ways to treat cancers driven by abnormal fat metabolism," said Professor Jiangwen Zhang, corresponding author of the study.

This research uncovers a critical link between genetic regulation, fat metabolism, and liver cancer. By targeting the genetic player VPS72 and its cancer-promoting pathway, scientists hope to open the door to more precise and effective treatments—potentially turning off a key fuel supply that liver tumours depend on.

The full research paper can be accessed at:
https://advanced.onlinelibrary.wiley.com/doi/10.1002/advs.202411368

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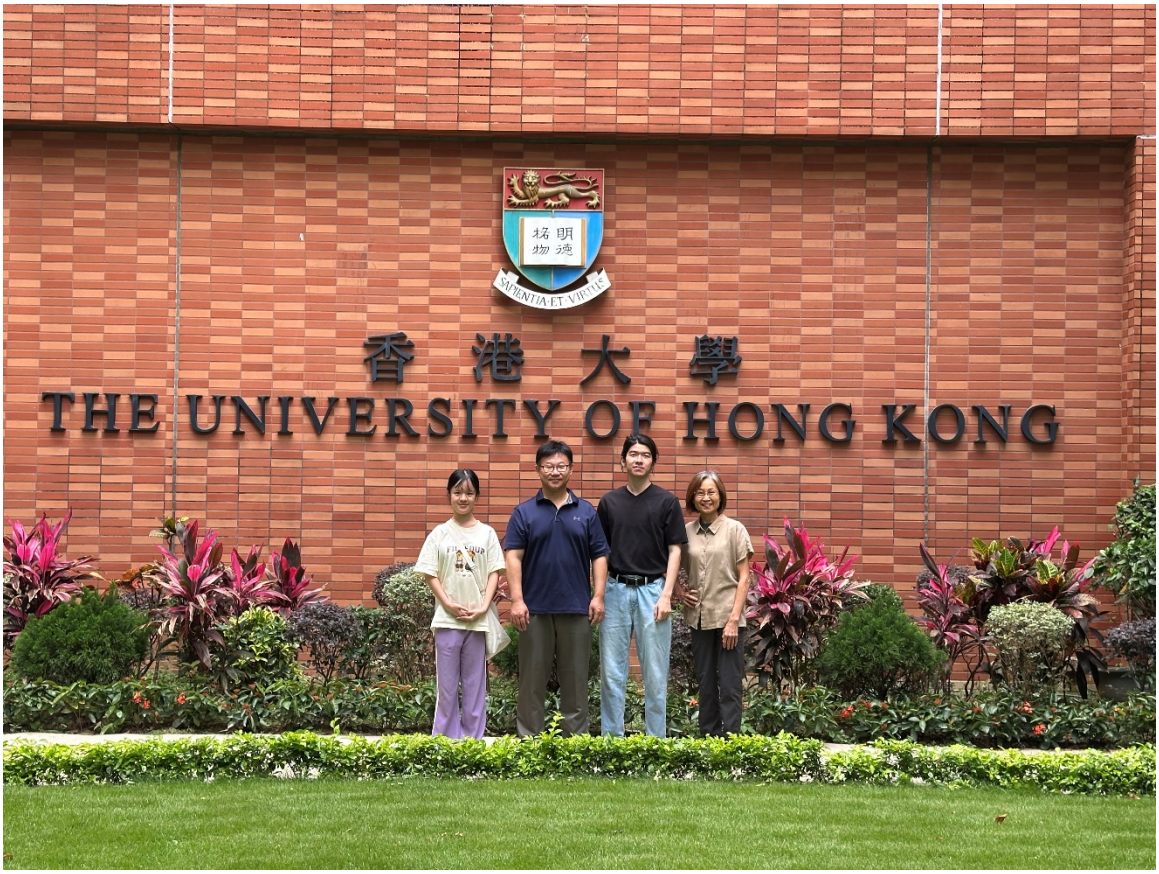

Figure 2. Professor Jiangwen ZHANG (second from the left) from HKU School of Biological Sciences and his research team.