**Gluconeogenic enzyme PCK1 supports S-adenosylmethionine biosynthesis and promotes H3K9me3 modification to suppress hepatocellular carcinoma progression**

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**Commentator:** Prof. Kung-Chia Young **Location:** Room 601, Med College Building

**Background:** Epigenetic alterations and abnormal gene expression are hallmarks of cancer. Dysregulated posttranslational modifications of histones, such as methylation, are thought to play a crucial role in the development and progression of various cancers. S-adenosylmethionine (SAM) is a critical methyl donor in histone methylation, and its levels are closely linked to cellular metabolism. Recent research indicates that approximately 85% of methylation reactions take place in the liver, highlighting the potential significance of abnormal SAM levels or histone methylation in cancer development. Glycogenesis predominantly occurs in the liver and plays a crucial role in metabolic reprogramming and tumor growth. PCK1, the initial enzyme in hepatic gluconeogenesis, has been implicated in metabolic reprogramming and tumor growth, but its role in histone methylation and cancer progression remains unclear.

**Objective/Hypothesis:** To elucidate the role of PCK1 in histone methylation and its impact on hepatocellular carcinoma (HCC) progression.

**Results:** In this study, authors indicate that PCK1 deficiency leads to reduced levels of H3K9me3 in HCC cells and liver tissues. PCK1 relies on the diversion of TCA cycle intermediates into the serine synthesis pathway (SSP) to increase the production of SAM through the SSP, which in turn facilitates H3K9me3 modification by the methyltransferase SUV39H1. This modification suppresses the oncogene S100A11, thereby decreasing HCC cell proliferation and migration. Supplementing with SAM or knocking out S100A11 alleviates the oncogenic effects caused by PCK1 deficiency. Furthermore, modulation of PCK1 expression affected tumor growth in hepatocellular carcinoma models, highlighting its potential as a therapeutic target.

**Conclusion:** PCK1 plays a crucial role in linking metabolic reprogramming to epigenetic regulation in HCC. By promoting SAM synthesis and H3K9me3 modification, PCK1 suppresses oncogene expression and tumor progression, suggesting that targeting PCK1 may offer new strategies for cancer treatment. These results provide insights into the complex interplay between metabolism and epigenetics in HCC.