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**High-fat diet promotes liver tumorigenesis**

Bu L, Zhang Z, Chen J, et al. [High-fat diet promotes liver tumorigenesis via palmitoylation and activation of AKT](https://gut.bmj.com/content/73/7/1156). Gut 2024; 73: 1156-1168. doi: 10.1136/gutjnl-2023-330826

The phosphoinositide 3-kinase (PI3K)-Akt (Protein kinase B) pathway plays a pivotal role in metabolic homeostasis. Bu et al., investigated the role of Akt in hepatocellular carcinoma (HCC) development in the context of metabolic dysfunction-associated steatohepatitis (MASH), using both in vitro and in vivo models.

They first screened over 500 metabolites and identified palmitic acid (PA) as a key activator of Akt in HEK-293 (Human embryonic kidney 293) cells, an effect inhibited by 2-bromopalmitate (2BP), a palmitoyl transferase inhibitor. Using MASH-HCC mouse models, they showed that a high-fat diet (HFD) and PA increased Akt activity in MASH and HCC. They also demonstrated that palmitoylation of Akt occurs on two cysteine residues, C77 and C224. Supporting this finding, transfection studies with mutated C77 and C224 Akt in HEK-293 cells resulted in reduced PI3K-Akt activity. Similarly, these residues were shown to be important for Akt membrane localization through membrane fractionation with immunoblotting and immunofluorescence.

Given the effects of 2BP on Akt activity, Bu et al., screened for Akt palmitoyl transferases, identifying ZDHHC17 and ZDHHC24 as candidates. These two enzymes were found to be crucial for inducing MASH and associated HCC in vitro and in vivo. Analysis of human HCC tissue showed a similar increase in ZDHHC17/24 protein expression and Akt activation. Bu et al., then targeted pathways of PA synthesis and palmitoylation, demonstrating a reduction in Akt activation and HCC formation.

In summary, the study revealed the regulatory mechanisms of Akt palmitoylation in HCC oncogenesis suggesting that targeting palmitic acid intake, synthesis, and Akt palmitoylation could be plausible therapeutic strategies for MASH-associated HCC.