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Ubiquitin-specific protease 22 promotes lipogenesis contributing to Hepatocellular Carcinoma pathogenesis

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Hepatocellular carcinoma (HCC), accounting for nearly 90% of liver malignancy, is the third most lethal human cancer worldwide with more than 830,000 deaths in 2020 [1]. Due to the complexity and heterogeneity of HCC, most patients are diagnosed at an advanced stage. While several phase III trials have been carried out for HCC therapy, limited clinical benefits were obtained because of quickly acquired drug resistance or considerable toxicity [2]. It remains an urgent need to explore effective novel strategies to combat HCC.

Dysregulation of cellular metabolism is a hallmark of cancers, especially HCC. Of note, the rapid increase of HCC cases is partly due to the epidemic of obesity, and the subsequent development and progression of metabolic-associated fatty liver disease (MAFLD), which made metabolic disorders a major risk factor for HCC [3–15]. Elevated de novo lipogenesis is a significant factor for the development of MAFLD and HCC [16]. Unfortunately, there is no substantial progress in therapeutic agents targeting lipid synthesis due to toxicity or complications [17]. It is of utmost importance to find more effective targets for fatty acid synthesis.

In the recent study published in Nature Communications, Ning et al. analyzed and observed that a variety of lipids including fatty acids, phospholipids and sphingomyelin were significantly enriched in HCC tissues compared with adjacent normal tissues using non-targeted metabolomics [18]. They found that the deubiquitinase ubiquitin-specific protease 22 (USP22), rather than the other USP members highly correlated with the abnormal upregulation of lipid synthesis [18]. Ning et al. performed Immunoprecipitation pulldown-Mass spectrometry (IP-MS) assay to reveal the regulatory mechanism and identified Peroxisome proliferator-activated receptor gamma (PPARγ) as a reliable candidate substrate of USP22, which was further confirmed by endogenous immunoprecipitation assay. PPARγ is a key transcription factor that regulates lipid synthesis through the transcriptional activation of lipid synthesis enzymes such as acetyl-CoA carboxylase (ACC) and ATP citrate lyase (ACLY). PPARγ is highly expressed in adipocytes, being implicated in lipid uptake, synthesis, and storage [19]. Ning et al. found that PPARγ contributes to USP22-mediated ACC and ACLY upregulation and discovered a previously undescribed PPAR binding motif in the *ACACA* (the gene encoding ACC) promoter in HCC cells [18].

In addition, Ning et al. showed that USP22 deubiquitinated and stabilized PPARγ by removing K48-linked ubiquitin chain which was catalyzed by E3 ligases $CRL4B^{AhR}$ and pVHL [18]. Genetic and pharmacological inhibition of PPARγ abolished the regulatory effect on ACC and ACLY transcription, and significantly decreased lipogenesis and tumorigenesis caused by USP22 expression both in HCC cells and xenograft tissues. Furthermore, an in silico analysis revealed that HCC patients with upregulated USP22 and elevated levels of PPARγ or ACC/ACLY exhibit poor prognosis and overall survival [18].

Taken together, in this study, Ning et al. demonstrated that USP22 promotes de novo synthesis of fatty acids and tumorigenesis by deubiquitinating PPARγ in HCC (Fig. 1) [18]. Considering the limitation of clinical therapeutic options for HCC, emerging molecular targets are urgently needed. Findings from this research may provide a new option for targeting fatty acid synthesis that could yield therapeutic benefits to HCC patients with high USP22 expression.

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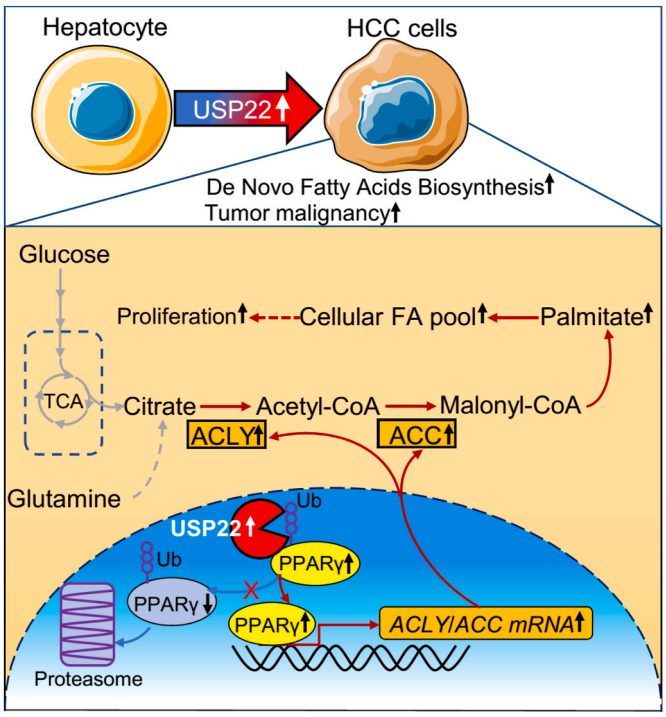

Fig. 1. USP22 regulates abnormal lipidome accumulation by lipogenetic mechanisms involving the PPARγ-ACLY/ACC axis in HCC pathogenesis. This may provide a rationale for therapeutic targeting lipogenesis via USP22 inhibition.
Abbreviations: ACC: acetyl-CoA carboxylase; ACLY: ATP citrate lyase; HCC: Hepatocellular Carcinoma; PPARγ: Peroxisome proliferator-activated receptor gamma; USP22: ubiquitin-specific protease 22.

Declaration of competing interest

None.

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