Commentary

# Making cancer fat: reprogramming of lipid metabolism by CD147 in hepatocellular carcinoma

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Over the past few years, *de novo* lipogenesis has taken central stage in the field of cancer metabolism (1). Large amount of lipids is needed for synthesis of membranes, signaling molecules, lipoproteins, etc. to support rapidly growing tumor cells (2-4). Reports have shown that neoplastic tissues show aberrant activation of *de novo* lipogenesis and that inhibition of different enzymes within the fatty acid biosynthesis pathway can block cancer cell growth (2,5-9). Meanwhile, the importance of fatty acid oxidation (FAO) in cancer metabolism is being increasingly recognized. FAO is the catabolic process by which lipids are utilized to produce energy. Recent studies implicated that the key regulatory enzymes in FAO such as carnitine palmitoyltransferase 1 (CPT1) and peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) regulate cancer development (10,11). The underlying mechanisms for the regulation of *de novo* lipogenesis and FAO in cancers are, however, still incompletely understood. Thus, it would be of a high scientific and clinical interest to elucidate the lipid metabolism in cancer.

Multiple independent laboratories discovered that CD147, a transmembrane glycoprotein, is highly expressed in hepatocellular carcinoma (HCC) cells and is strongly associated with tumor progression (12,13). Licartin, an $^{131}$Iodin-labeled antibody fragment targeting the HCC-associated antigen HAb18G/CD147, has been approved by the Chinese Food and Drug Administration (FDA) and enters into clinical use for HCC treatment (14-16). To date, studies have shown that CD147 contributes to the metabolism of cancer cells via glycolysis (17-19). However, a paper recently published in the *Journal of Hepatology* by Li *et al*. reports that CD147 regulates the lipid metabolism in cancer cells (20).

By analyzing four public datasets of mRNA expression in HCC tissues and performing experiments using two different HCC cell lines, Li *et al*. demonstrated that CD147 significantly contributed to the reprogramming of fatty acid metabolism in HCC cells. They investigated the levels of expression of lipogenic enzymes and sterol regulatory element binding proteins (SREBPs), and activation of Akt/mTOR signaling pathways in tumor cells with different CD147 expression levels. Their data showed that CD147 activated the Akt/mTOR signaling pathway and subsequently up-regulated SREBP1c, leading to the increase in transcription of major lipogenic genes, FASN and ACC1 to promote *de novo* lipogenesis.

Next, they analyzed the signaling pathway involved in CD147-induced peroxisome proliferator-activated receptor alpha (PPARα) regulation. To test whether CD147 inhibits the expression of PPARα via activation of P38 MAPK signaling pathway, they treated P38 inhibitor SB203580 to CD147-wild type, CD147-knockout and CD147-overexpression HCC cells. They found that the inhibition of P38 MAPK activity up-regulated PPARα in CD147-wild type and CD147-overexpression cells. As well, the treatment with SB203580 led to the activation of FAO and decreases in the contents of triglyceride, phospholipids and neutral lipids. The results suggest that the inhibition of P38 MAPK reversed the down-regulation of FAO by CD147 through the up-regulation of PPARα in HCC cells. Lastly, they found that CD147 knockout or knockdown significantly inhibited the proliferation, migration and invasion of HCC cells, determined via the MTT assay, wound-healing migration assay, trans-well invasion assay, and orthotopic

xenograft models. Li *et al*. verified that CD147 increased the aggressiveness of HCC cells through the Akt/mTOR/SREBP1c and P38/PPARα pathways, leading to the up-regulation of fatty acid synthesis and down-regulation of fatty acid oxidation (*Figure 1*).

Tumors expressing high levels of CD147 include carcinomas of the urinary bladder, breast, lung, oral cavity, esophagus, skin, and etc. (21-29). It would be interesting to see if CD147 functions likewise as a critical regulator of fatty acid metabolism in other types of cancer. The study by Li *et al*. is expected to provide new insights into understanding the mechanisms underlying the reprogramming of lipid metabolism in HCC and its association with HCC proliferation and progression, as wells as new strategies for future drug development for HCC treatment.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest to declare.

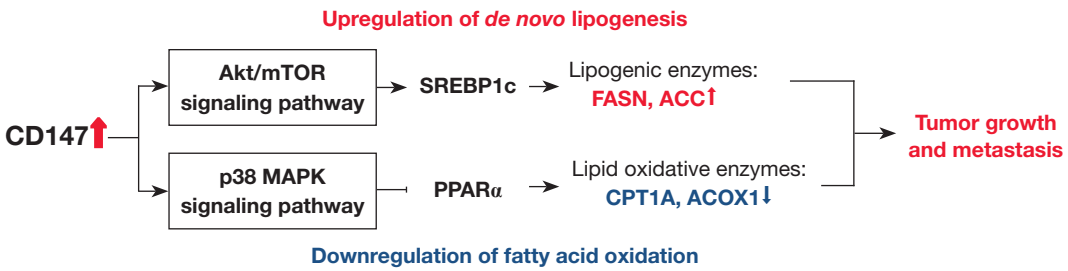


**Figure 1** Regulation of fatty acid metabolism by CD147 in HCC cells. Modified from reference (20).

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