

# CD147/Basigin: a Warburg oncogene in hepatocellular carcinoma?

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Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide, ranking fifth in incidence and second in mortality (1). Although HCC cases mainly occurred in South-East Asia and Southern Africa in the past, the incidence of this disease has been on the rise in the Western countries over the forty last years (1). Despite the advances in the diagnostic techniques and novel therapies, HCC remains a tumor with a dismal prognosis (2-4). While the detection of HCC at an early stage allows the employment of potentially curative treatments, such as liver transplantation, surgical resection and tumor ablation, over two thirds of patients are diagnosed at a late stage of the disease, when conventional therapeutic approaches are ineffective (2-4). Furthermore, administration of the multikinase inhibitor Sorafenib, the only drug approved by the Food and Drug Administration (FDA) for targeted therapy of advanced HCC, provides only limited benefits to HCC patients in terms of overall survival (2-4). Thus, in order to improve significantly the effectiveness of therapeutic strategies against liver cancer, a deeper understanding of the molecular pathogenesis of this deadly disease is necessary.

Among potential target proteins for innovative treatments against liver cancer is cluster of differentiation 147 (CD147). Also known as Basigin (BSG) or extracellular matrix metalloproteinase inducer (EMMPRIN), CD147 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily (5-7) that is highly expressed on the cell surface of many tumor types, including HCC. Mounting evidence indicates that CD147 modulates tumor cell proliferation, apoptosis, migration, angiogenesis, metastasis, and differentiation (8,9). At the molecular level, a number of studies have shown that CD147 acts as a cellular adhesion molecule and induces the secretion of matrix metalloproteinases (MMPs) and the release of cytokines

(8,9). Of note, CD147 was found to play a pivotal role in the reprogramming of tumor cell metabolism. It has been clearly established that cancer cells exhibit elevated rates of glucose consumption and high lactate production under aerobic conditions, a phenomenon known as the “Warburg effect” (10,11). In the latter setting, cancer cells rapidly proliferate, using glycolysis for energy, and excessive lactate is transported by monocarboxylate transporters (MCTs) for tumor cell survival (11). Importantly, recent investigation have demonstrated that CD147 is an important modulator of the Warburg effect in various cancer types by sustaining glycolysis and inhibiting mitochondrial biogenesis and oxidative phosphorylation in tumor cells (12). In HCC cell lines, CD147 induces the expression of MCT1 for the export of lactate, which induces the activation of the protein kinase B (Akt)/Mouse double minute 2 homolog (MDM2) cascade, thus triggering the proteolysis of the p53 tumor suppressor (13). Altogether, these experimental observations strongly suggest a pivotal role of CD147 as a “Warburg oncogene” in cancer.

Additional evidence supporting a metabolic oncogenic role of CD147 in HCC comes from a recent paper by Li *et al.* entitled “CD147 reprograms fatty acid metabolism in hepatocellular carcinoma cells through Akt/mTOR/SREBP1c and P38/PPAR $\alpha$  pathways” (14). In the latter study, the authors investigated in human HCC the importance of CD147 on *de novo* lipogenesis (14), another fundamental process related to the glycolytic pathway and the Warburg effect in transformed cells (15). In contrast to normal cells that use exogenous fatty acids for their needs, most cancer cells—including malignant hepatocytes—exhibit elevated levels of fatty acid biosynthesis. In rapidly proliferating transformed cells, sustained *de novo* lipogenesis is necessary for membrane production as well as for energy generation

and post-translational modifications of proteins that support tumor growth (15). Through a series of elegant experiments, the study by Li *et al.* shows that CD147 promotes *de novo* fatty acid synthesis in HCC through the upregulation of the master lipogenic enzymes, acetyl-CoA carboxylase (ACC1) and fatty acid synthase (FASN), via the Akt/mammalian target of rapamycin (mTOR)/sterol regulatory elementary binding protein1c (SREBP1c) signaling pathway (14). Furthermore, the authors found that CD147 suppresses fatty acid oxidation (FAO) in HCC cells via downregulation of peroxisome proliferation activated receptor alpha (PPAR $\alpha$ ) and its downstream effectors (14). The authors hypothesize that inhibition of FAO by CD147 contributes to HCC growth and metastasis as suppression of FAO impairs the catabolism of lipids that are necessary for the metabolic needs of HCC cells. At the molecular level, CD147 was found to exert its suppressive effect over FAO by inhibiting the PPAR $\alpha$  transcriptional program in a p38 MAPK signaling pathway-dependent manner (14).

The significant study by Li *et al.* provides novel and seminal insights to better understand the role of CD147 in hepatocarcinogenesis. In particular, the authors uncovered a molecular mechanism, namely the control of lipid biosynthesis and FAO, whereby CD147 might crucially contribute to HCC onset and progression. In addition, the present findings offer a possible molecular explanation for the uncostrained activation of the Akt/mTOR signaling pathway, whose pro-lipogenic function in experimental and human HCC is well established (16), in liver cancer. Thus, CD147 might represent the pivotal upstream inducer of the Akt/mTOR cascade in this biologically aggressive tumor type. Nonetheless, as both CD147 and *de novo* lipogenesis are highly induced in a wide variety of tumors, the present findings might have broader implications in cancer, not limited to HCC.

Together with deciphering the role of CD147 on lipid metabolism reprogramming in malignant hepatocytes, the data by Li *et al.* further support the importance of this protein as a therapeutic target in human HCC. Indeed, the present and previous findings strongly suggest that suppression of CD147 might target both aberrant glycolysis and *de novo* lipogenesis, thus impairing the major energy sources of HCC cells with consequent strong growth restraint of the tumor. In addition, since CD147 significantly contributes to various hallmarks of cancer, including proliferation, resistance to apoptosis, epithelial-mesenchymal transition (EMT), angiogenesis, chemoresistance, invasion and metastasis (8,9), its inhibition

might be deleterious for the survival of liver cancer cells. In accordance with the latter hypothesis, targeting CD147 has shown encouraging results in the treatment of human HCC patients. Indeed, administration of the radioimmunotherapeutic drug Licartin, which was generated by labeling <sup>131</sup>Iodine onto murine monoclonal antibody against CD147, was found to significantly decrease the recurrence rate and to increase the survival length of HCC patients subjected to liver transplantation in a randomized controlled trial (17). Furthermore, the combination of Licartin and chemoembolization appeared to extend survival in patients with unresectable HCC compared with historical controls (18).

Altogether, the data from the study by Li *et al.* and previous investigations indicate that CD147 possesses multiple oncogenic properties in liver cancer, thus representing a promising therapeutic target in this deadly disease. However, although the importance of CD147 inhibition for the treatment of liver cancer is underscored by recent experimental and clinical data, additional lines of investigation are required. First, the proteins modulating CD147 expression and the signaling cascades regulated by CD147 should be further characterized, in order to better understand the oncogenic activity of CD147 along hepatocarcinogenesis as well as to identify new potentially targetable proteins. Second, *in vitro* and *in vivo* models would be highly needed to unravel the possible compensatory mechanisms triggered by HCC cells to survive following CD147 inhibition. Third, reliable serological and/or molecular biomarkers predicting the clinical response to CD147 suppression should be identified for the stratification of HCC patient. Finally, the synergistic anti-cancer efficacy of anti-CD147 in combination with chemotherapy, targeted therapies, resection, or radiation therapy should be determined.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

## References

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics.

- CA Cancer J Clin 2011;61:69-90.
2. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012;379:1245-55.
  3. Wrzesinski SH, Taddei TH, Strazzabosco M. Systemic therapy in hepatocellular carcinoma. *Clin Liver Dis* 2011;15:423-41, vii-x.
  4. Villanueva A, Llovet JM. Targeted therapies for hepatocellular carcinoma. *Gastroenterology* 2011;140:1410-26.
  5. Kasinrerk W, Fiebigler E, Stefanová I, et al. Human leukocyte activation antigen M6, a member of the Ig superfamily, is the species homologue of rat OX-47, mouse basigin, and chicken HT7 molecule. *J Immunol* 1992;149:847-54.
  6. DeCastro R, Zhang Y, Guo H, et al. Human keratinocytes express EMMPRIN, an extracellular matrix metalloproteinase inducer. *J Invest Dermatol* 1996;106:1260-5.
  7. Simon-Chazottes D, Matsubara S, Miyauchi T, et al. Chromosomal localization of two cell surface-associated molecules of potential importance in development: midkine (Mdk) and basigin (Bsg). *Mamm Genome* 1992;2:269-71.
  8. Xiong L, Edwards CK 3rd, Zhou L. The biological function and clinical utilization of CD147 in human diseases: a review of the current scientific literature. *Int J Mol Sci* 2014;15:17411-41.
  9. Tang X, Guo N, Xu L, et al. CD147/EMMPRIN: an effective therapeutic target for hepatocellular carcinoma. *J Drug Target* 2012. [Epub ahead of print].
  10. Warburg O. On respiratory impairment in cancer cells. *Science* 1956;124:269-70.
  11. Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. *Cancer Cell* 2008;13:472-82.
  12. Le Floch R, Chiche J, Marchiq I, et al. CD147 subunit of lactate/H<sup>+</sup> symporters MCT1 and hypoxia-inducible MCT4 is critical for energetics and growth of glycolytic tumors. *Proc Natl Acad Sci U S A* 2011;108:16663-8.
  13. Huang Q, Li J, Xing J, et al. CD147 promotes reprogramming of glucose metabolism and cell proliferation in HCC cells by inhibiting the p53-dependent signaling pathway. *J Hepatol* 2014;61:859-66.
  14. Li J, Huang Q, Long X, et al. CD147 reprograms fatty acid metabolism in hepatocellular carcinoma cells through Akt/mTOR/SREBP1c and P38/PPAR $\alpha$  pathways. *J Hepatol* 2015;63:1378-89.
  15. Menendez JA, Lupu R. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. *Nat Rev Cancer* 2007;7:763-77.
  16. Calvisi DF, Wang C, Ho C, et al. Increased lipogenesis, induced by AKT-mTORC1-RPS6 signaling, promotes development of human hepatocellular carcinoma. *Gastroenterology* 2011;140:1071-83.
  17. Xu J, Shen ZY, Chen XG, et al. A randomized controlled trial of Licartin for preventing hepatoma recurrence after liver transplantation. *Hepatology* 2007;45:269-76.
  18. Wu L, Yang YF, Ge NJ, et al. Hepatic arterial iodine-131-labeled metuximab injection combined with chemoembolization for unresectable hepatocellular carcinoma: interim safety and survival data from 110 patients. *Cancer Biother Radiopharm* 2010;25:657-63.

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