

Editorial

PHACTR4/STAT3 axis as a possible target therapy for hepatocellular carcinoma treatment

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Hepatocellular carcinoma (HCC) affects predominantly patients with chronic liver diseases such as hepatitis B, hepatitis C, conditions known as hyper carcinogenic state¹. Currently, the treatment of HCC provides several options including local treatment, surgical resection, liver transplantation, radiofrequency ablation, chemoembolization, and chemotherapy². In patients with advanced HCC, sorafenib treatment, significantly increases overall survival and reduces the progression of the disease³. However, despite such new advances in the treatment of HCC, the outcome of HCC remains poor. Therefore, understanding the molecular signaling underlying HCC progression and metastatic process is of great relevance in order to provide new pharmacological agents. To this regard, several signaling mechanisms have been so far investigated: AKT/mTOR and RAS/RAF/MAPK, Wnt/ β -catenin and glutamine synthetase, IGF, STAT3, NF-kappaB and hTERT, and hepatocyte growth factor receptor (c-MET)⁴. In this context, the recent findings of Cao et al⁵ appear to be of great relevance. In the present research article, the authors evaluated the expression profile of PHACTR4 in HCC compared to normal liver tissue. Also, the authors investigated the effect of such pleiotropic protein on the proliferation migration and invasion of HepG2 cell line. The authors' main findings are that PHACTR4 is decreased in HCC tissues compared to normal liver samples and that overexpression of PHACTR4 results in a significant decrease in HepG2 cell proliferation and migration. The authors' findings are of great scientific relevance and interest for the scientific community since they confirmed the importance of such protein also in HCC. PHACTR4 was found to play a major role in other cancer types by previous studies examining the whole-genome and exome sequencing data from 2,451 solid tumors (breast, biliary tract, large intestine, lung, kidney, ovary, and skin cancers). These set of experiments revealed 11 somatic loss-of-function (frameshift or nonsense) and 16 missense mutations of PHACTR4. Notably, Solimini et al⁶ showed that PHACTR4 depletion increased proliferation similar to the levels observed with a positive-control shRNA targeting p21, and the strongest depletion correlated with the most robust proliferation phenotype. These results are consistent with the work of Cao et al⁷ showing that PHACTR4 overexpression results in a significant decrease of cell proliferation by preventing STAT-3 phosphorylation and thus reduction of key molecules involved in cell proliferation control such as cyclin D1. In particular, STAT3 is involved in the mechanism of signal transduction of various cytokines, growth factors, and oncogenes. STAT3 activation plays a pivotal role in tumorigenesis mechanisms by upregulation of genes involved in apoptosis, proliferation, and angiogenesis. Recent studies⁸ have shown that sorafenib inhibits tumor growth by a mechanism independent from the RAF-MEK-MAPK mechanism and that the drug may target directly STAT3 inhibiting tumor growth and metastasis.

Taken all together these data suggest that the PHACTR4/STAT3 axis represents an important target, warranting further investigation to provide promising treatment for HCC.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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