

Targeting late SV40 factor: Is the achilles heel of hepatocarcinogenesis revealed?

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Author contributions: Shlomai A collected the material and wrote the manuscript

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Received: May 7, 2012 Revised: May 29, 2012

Accepted: June 7, 2012

Published online: December 14, 2012

Key words: Oncogene addiction; Hepatocellular carcinoma; Late SV40 factor; Transcription factor; Multi-kinase inhibit

Peer reviewers: Mara Massimi, PhD, Department of Basic and Applied Biology, University of L'Aquila, Via Vetoio-Coppito, 67100 L'Aquila, Italy; Dr. Matthias Ocker, MD, Professor, Institute for Surgical Research, Philipps-University Marburg, Baldingerstrasse, 35033 Marburg, Germany

Shlomai A. Targeting Late SV40 factor: Is the achilles heel of hepatocarcinogenesis revealed? *World J Gastroenterol* 2012; 18(46): 6709-6711 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v18/i46/6709.htm> DOI: <http://dx.doi.org/10.3748/wjg.v18.i46.6709>

Abstract

Hepatocellular carcinoma (HCC) is a dreadful cancer and a major cause of death among patients with chronic liver disease and cirrhosis. The apparent alterations in a diversity of intracellular pathways found in HCC has set the rationale for developing molecular-directed drugs that simultaneously inhibit multiple pathways, such as the multi-kinase inhibitor Sorafenib. However, recently this concept has been challenged by showing that HCC is heavily dependent on a single oncogene designated late SV-40 factor (LSF), a transcription factor that is over-expressed in liver cancer cells and that its expression is strongly correlated with tumor grade and aggressiveness. Furthermore, using an intensive screening for drugs that inhibit LSF activity, Grant *et al* have found a molecule designated factor quinolinone inhibitor 1 that can specifically block the ability of LSF to bind its target promoters, resulting in a massive death of HCC cells both *in vitro* and *in vivo*. The innovative findings of HCC representing "oncogene addiction" to LSF and the ability of a single molecule to block the activity of this oncogene resulting in tumor abolishment are encouraging and provide us with the hope that the "Achilles heel" of HCC has been found.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh in women, and its incidence has been sharply rising during the last two decades^[1]. Whereas patients with localized disease can benefit from curative therapeutic modalities, such as liver resection, liver transplantation or radiofrequency ablation, until recently little could be offered to patients with advanced disease, whose survival was often measured in a few months^[2].

MULTIPLE PATHWAYS ARE DISTORTED IN HEPATOCELLULAR CARCINOMA

Disruption of a variety of cellular pathways, as well as mutations in tumor suppressors and oncogenes have been described in patients with HCC^[3]; mutations in the genes encoding for *TP53* and β -catenin, amplifications of the vascular endothelial growth factor (VEGF) and Cyclin D1 (*CCND1*) genes, silencing of E-Cadherin tumor suppressor and activation of the myelocytomatosis viral oncogene are a partial list. Indeed, the more effort

invested in elucidating molecular mechanisms underlying HCC, the clearer it became that the complexity and diversity of such mechanisms make the development of potential gene-targeted drugs a highly complicated task.

SORAFENIB-THE FIRST APPROVED MOLECULAR-DIRECTED DRUG FOR HEPATOCELLULAR CARCINOMA

In 2008, Llovet *et al*^[4] have published the results of a phase 3 multi-center placebo control trial showing that the multi-kinase inhibitor Sorafenib prolongs survival in patients with advanced HCC. The rationale for using a multi-kinase inhibitor that simultaneously blocks Raf, VEGF, platelet-derived growth factor and c-Kit signaling is to “cover” as much diverse signaling pathways involved in hepatic carcinogenesis as possible. However, although the introduction of this first molecular-directed drug is a major breakthrough in the field of HCC, the results are still far from optimal as reflected by the only modest improvement in life expectancy of 2.8 mo on average in the price of often-severe adverse events^[5,6].

LATE SV40 FACTOR-AN ESSENTIAL ONCOGENE IN HEPATOCELLULAR CARCINOMA

Recently, Yoo *et al*^[7] has recognized the Late SV40 factor (LSF) transcription factor as a central oncogene in HCC. LSF, which is induced in the liver via inflammatory cytokines, has a major role in DNA synthesis by transcriptionally activating the rate-limiting enzyme in pyrimidine synthesis, thymidylate synthase, as well as other target genes important for DNA synthesis and cell survival. LSF inhibition results in constraining DNA synthesis, which ultimately leads to cell death. Interestingly, Sarker's group has found that LSF protein is significantly over-expressed in HCC cells as compared to normal human liver cells. Furthermore, the degree of LSF expression revealed a significant correlation with the stage and grade of the tumor. Most importantly, whereas over expression of LSF pushed the tumor towards a more aggressive phenotype, LSF inhibition resulted in abrogation of tumor growth and its metastatic potential, both *in-vitro* and *in-vivo*. Interestingly, among the various genes induced by LSF following its binding to their promoters, *SPP1* gene encoding for the osteopontin (OPN) protein has been found to be induced to the greatest extent. Indeed, the importance of OPN in promoting hepatic carcinogenesis was recently emphasized by a study showing that OPN is much more sensitive than the traditional alpha-fetoprotein as a marker for early HCC^[8]. Whatsoever, Sarker's work as well as a later work by Fan *et al*^[9] strongly indicated that LSF is an essential oncoprotein required for the maintenance and propagation of liver cancer, making it a potentially ideal target for HCC treatment. Furthermore, the merit of these findings lies

in the fact that although multiple genes and signaling pathways are impaired in HCC, the cancerous liver cells are heavily dependent on a single oncogenic protein, the transcription factor LSF, for their survival. This phenomenon, designated “oncogene addiction”, has been recognized in various cancers in the last few years, making the oncogene to which a particular cancer is addicted to an ideal target for anti-cancer therapy^[10,11].

FACTOR QUINOLINONE INHIBITOR 1 SPECIFICALLY INHIBITS LATE SV40 FACTOR ACTIVITY RESULTING IN ABOLISHMENT OF HEPATOCELLULAR CARCINOMA

However, how can one translate experimental abolishment of LSF achieved mainly by dominant negative constructs or knockdown strategies to a drug that inhibits LSF function *in-vivo* and that can be easily delivered to the liver?

A study recently published in the PNAS provided an unexpected and exciting solution to this problem^[12]. By screening for small molecules that could block the interaction of LSF to its DNA binding sites along the genome, Grant *et al*^[12] have revealed a small molecule named factor quinolinone inhibitor 1 (FQI1) that inhibits LSF DNA binding activity both *in-vitro* and *in-vivo*. Functionally, treating HCC cells with FQI1 results in a massive apoptosis of HCC cells whereas normal hepatocytes remain intact. FQI1 treatment results in a robust activity *in-vivo*, as well, reflected by inhibition of tumor growth in mouse HCC xenografts. Importantly, no toxicity was observed in FQI1 treated animals, as evaluated by animals' general well being and by careful examination of various non-hepatic tissues that remained intact following treatment. Noteworthy is the observation that tumors from FQI1-treated animals expressed LSF at similar levels to those of control mice, whereas the expression of a central LSF target gene, OPN, as well the proliferative activity of the tumor were dramatically reduced. This observation reflects the inhibition of LSF activity as a transcription factor by blocking its binding to DNA, rather than reducing its level following FQI1 treatment. Furthermore, the close correlation between the concentrations of FQI1 required for inhibition of LSF transactivation and those required for proliferation inhibition strongly suggest that FQI1 specifically targets LSF and does not share a general non-specific anti proliferative activity.

FQI1 AS AN EMERGING ANTI HEPATOCELLULAR CARCINOMA DRUG-PROMISES AND CHALLENGES

The originality and the importance of the aforementioned studies are dual. First, the identification of a single oncogene serving as a cellular transcription factor to

which HCC is “addicted” and completely dependent on. This finding may completely change the current concept of using drugs inhibiting multiple alternated cellular targets^[5], to a strategy that specifically inhibits a particular target that is essential for HCC maintenance and propagation. Second, in contrast to what was formally considered as an almost impossible target for drug therapy, the efficiency of FQI1 strongly indicates that targeting the activity rather than the level of a transcription factor is an effective and specific mechanism for an anti-cancer drug.

Further studies should address potential caveats and open question remaining before implementing those findings to an efficient anti-HCC drug. The bioavailability of FQI1 in human subjects following treatment should be carefully checked and the long-term consequences in terms of adverse effects should be monitored. The potential for tumor resistance due to mutations in the LSF DNA binding domain is certainly there and should be taken into consideration. In this regard, the combination of the current molecular-targeted drug, Sorafenib, with LSF inhibitors has the potential to minimize the risk of cancer cells “escaping” their oncogene addiction to LSF. Last but not least, the validity of LSF role in HCC should be ascertained for the various etiologies of HCC, including viral, metabolic and toxic.

In summary, the introduction of a small molecule that specifically inhibits the activity of an oncogene on which HCC heavily depends seems as stimulating news to the field. Time will tell whether, similar to the Greek mythology, LSF represents the Achilles heel of HCC, an innovation that can ultimately lead to defeating this deadly cancer.

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S- Editor Shi ZF L- Editor Cant MR E- Editor Xiong L