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Letter to the Editor

Comment on: Stathmin1 overexpression associated with polyploidy, tumor-cell invasion, early recurrence, and poor prognosis in human hepatoma

Dear Editor,

we read with great interest the paper by Liu et al[1] regarding the interaction between the serine/threonine-protein kinase Hippo pathway, also known as the Salvador-Warts-Hippo (SWH) pathway, and Stathmin 1 (STMN 1) or oncoprotein-18 in the progression of liver cancer. STMN1 overexpression may be an early event of liver carcinogenesis and can be used as a marker for the diagnosis and treatment of liver cancer. Primary liver cancer is the third leading cause of cancer-related death worldwide, and hepatocellular carcinoma (HCC) is the most common type[2]. HCC is an important complication of Hepatitis C virus (HCV), HBV and non-alcoholic fatty liver diseases (NAFLD) related cirrhosis and is reported with an average incidence of 1-4% year[3-6]. The appearance of HCC is mainly related to two conditions: the first is cirrhosis itself, with its necro-inflammatory activity, and the second is the failure of immune surveillance with escape mechanisms. To date, the onset of HCC in patients with HCV, which have achieved sustained virological response (SVR) after treatment with direct-acting antivirals (DAA), is still subject of study and debate[7]. Also, interesting is the role of miR-877-5p in the mechanism of HCC. In fact, the authors found that miR-877-5p expression was under-regulated in tissues and HCC cell lines and it was associated with histological grade, TNM status, and lower survival rate[8]. Nowadays, some authors[9] focus on the use of microRNAs in the diagnosis and treatment of various diseases, including Parkinson. Furthermore, the downregulation of pro-apoptotic factors, such as the cellular tumor antigen p53 and TNF-related apoptosis-inducing ligand (TRAIL), are considered genetic deregulation events that lead the normal hepatocytes to transform into cancer cells. p53 plays a fundamental role in the onset, progression, and reactivity of liver cancer. Although gene therapy is still a long way from common therapeutic use due to safety concerns, sonoporation may represent a viable alternative for the delivery of suicide genes, such as p53 and TRAIL into liver cancer cells[10]. An increase in serum chromogranin A in patients with HCC has also been reported by Biondi et al[11]. Therefore, molecular markers, such as chromogranin A, could be very useful tools for the diagnosis of HCC. Like HCC, cholangiocarcinoma (CCA) is a malignant and aggressive liver tumor. It is characterized by early lymph node involvement and distant metastasis, with 5-year survival rates of 5%-10%. The identification of new biomarkers with diagnostic, prognostic or predictive value is particularly important as resection (surgical or combined with a liver transplant) has shown promising new therapies[12] (Figure 1). In the present study, STMN1 is known as an oncogene encoding 18 kDa cytosolic phosphoprotein involved in microtubule destabilization[13]. The Hippo/Yes-associated protein 1 (Yap) network plays an important role in cell proliferation and survival[14]. The downstream effectors of this pathway are the transcriptional co-activators YAP1 and a very similar protein WW domain-containing transcription regulator protein 1 (TAZ). In the presence of the Hippo pathway, YAP and TAZ are phosphorylated by large tumor suppressor kinases 1/2 (LATS1/2)[15], maintained in the cytoplasm, and subsequently degraded by the proteosomal pathway. However, when YAP/TAZ escape Hippo's control, they move to the nucleus and interact with transcription factors, such as those belonging to the TEA domain family member (TEAD) and the cAMP response element-binding protein (CREB) family, leading to the activation of genetic programs[16]. Although the deregulated Hippo/Yap pathway has been observed in many other types of tumors, Perra et al[17] and Yimlamai et al[18] demonstrated that the overexpression of YAP was an early event in liver cancer, thus as happens for STMN1. The interaction between STMN1 and the YAP1 protein was evaluated

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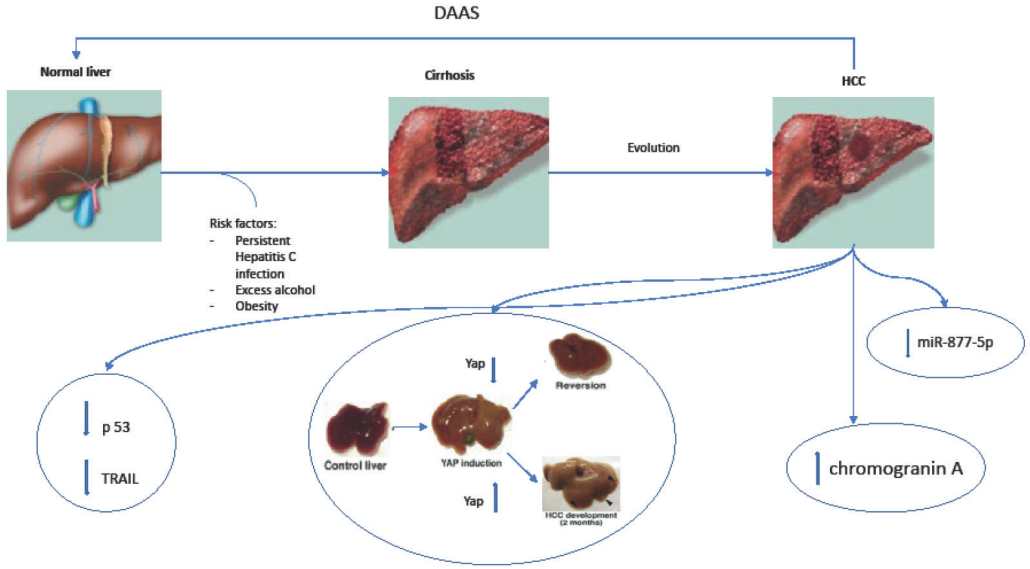

Figure 1. Factors affecting HCC carcinogenesis.

using immunoprecipitation and immunofluorescence techniques. The results showed that cell proliferation increased and apoptosis decreased when STMN1 was upregulated in HepG2 and SNU-398 cells. Globally, kinases are involved in the regulation of cell proliferation and survival and play an important role in many cancers[19].

The current study shows that the upregulation of STMN1 promotes the onset and development of liver cancer through the activation of YAP1 signaling, therefore STMN1 acts as an oncogene by promoting the expression of YAP1.

Conflict of interest

The Authors declare that they have no conflict of interests.

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