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Commentary

Plasma HSP90α and liver cancer: a potential biomarker?

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Liver cancer comprises multiple kind of primary liver cancers (cancers that rise from the liver) as well as secondary liver cancers (cancers that rise from other organs). Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and is also one of the most lethal cancer in the world (Waller et al., 2015). Other types of primary liver cancers include intrahepatic cholangiocarcinoma (CC) which represents about 10% of cases, and angiosarcoma, hemangiosarcoma and hepatoblastoma which are rare. There are currently limited therapeutic options for patients with primary liver cancer and recurrence rates after surgery are elevated. Survival rates are also very low with an average 5 year-survival rate of 17.6% in the US and <6% worldwide. Indeed, most cases are being diagnosed at an advance stage: only 43% of cases at diagnosis are localized diseases (5 year-survival rate of 31.1%), 27% are regional (5 year-survival rate of 10.1%), 18% are distant (5 year-survival rate of 2.8%) and 12% are unstaged/unknown (5 year-survival rate of 6.4%) [data for US population, SEER website]. Thus, the development of sensitive biomarkers for diagnosis and response to therapy is highly needed.

Because of the steady increase in incidence of liver cancer (over 2% per year), there has been a global push to expand our knowledge and understanding of primary liver cancers, especially HCC. Recently, large scale genomic studies have identified multiple mutations and delineated potential therapeutic targets (Ally et al., 2017; Schulze et al., 2015; Totoki et al., 2014). However, these findings have yet to be translated into the clinic. Until then, early detection of all primary liver cancers is critical. Several serological, molecular and pathological biomarkers have been used and/or proposed for liver cancer (Behne and Copur, 2012). For example, alpha-fetoprotein (AFP) has been a standard serological biomarker, but its lack of sensitivity and specificity are prompting the development of more potent biomarkers.

HSP90α is a molecular chaperone involved in multiple physiological and pathological signaling pathways. In multiple cancers, HSP90α is overexpressed (including in HCC) and can be secreted outside the tumor cells (Eustace et al., 2004; Lu et al., 2015) Although the extracellular role of HSP90a is still not fully understood, it is known to promote metastases (Eustace et al., 2004).

In *EBioMedicine*, Fu and collaborators recently investigated whether levels of plasma HSP90α in liver cancer patients could improve diagnosis accuracy and be predictive of response to therapy (Fu et al., 2017). This report follows an earlier publication evaluating the role of extracellular HSP90α in tumor malignancy and the regulation of its secretion. The authors accessed HSP90α concentrations in the plasma of patients with malignant tumors (breast, lung, pancreas, liver) vs healthy volunteers. Plasma HSP90α concentrations were significantly elevated (>50 ng/mL) in most malignant samples (including in the plasma of 20 out of 29 liver cancer patients) and were significantly higher in patients having metastatic disease (Wang et al., 2009). These data suggested that extracellular HSP90α might be a potential diagnostic marker for tumor malignancy although the sample size of the study was small and further investigation was necessary. Fu and collaborators then analyzed the data from a large-scale multicenter clinical trial (NCT02324127) enrolling over 1600 patients divided in 2 cohorts to assess (1) whether plasma HSP90α could be used as a diagnostic marker for liver cancer and how it compares to AFP; and (2) whether plasma HSP90α could be predictive of response to therapy. The first cohort [auxiliary diagnosis study] included 782 patients with liver cancer (531 HCC, 57 CC, 65 HCC-CC, and 129 other/non-defined), 171 patients with at-risk liver disease (e.g. hepatitis) and 572 healthy volunteers. Quantification of plasma HSP90α was significantly higher in patients with liver cancer tumors (including non-HCC tumors and tumors under 3 cm) compared to at-risk and healthy patients. Using the same dataset, plasma HSP90α appears also to be more sensitive and specific than AFP in its ability to detect liver cancers. Although further validation of these results is necessary, these data suggest that plasma HSP90α might be a promising early diagnosis marker for liver cancer. The second cohort [efficacy monitoring study] included 122 liver cancer patients, 86 of which received surgery and 36 received interventional therapy. Although preliminary, the quantification of plasma HSP90α in this cohort seems to correlate with tumor size. These encouraging results suggest that plasma HSP90α might be predictive of response to therapy.

Before plasma HSP90α could be used in the clinic as a serological biomarker for liver cancer, further work and validation will be necessary including a study using a blind validation test group. Several important questions are also raised by this interesting work: are plasma HSP90α levels specific to the tumor cells or could the immune cells and/or microenvironment be involved? Is plasma HSP90α elevated in benign liver tumors? Could interventional therapies aberrantly affect HSP90α expression levels and thus biased the results as an indicator of response to therapy? Because plasma HSP90α is elevated in multiple cancers, could it be used for secondary liver cancer diagnosis? And if so, how could one distinguish between primary and secondary liver cancers? It would also be interesting to know whether these results are translatable to other populations as the etiology of liver cancer is variable.

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In conclusion, based on the study presented by Fu and collaborators, using quantitative plasma HSP90α levels as a potential early detection biomarker for liver cancer appears to be promising.

Disclosure

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