Editorial

TIE2-expressing monocytes: a possible cellular diagnostic and prognostic biomarker for hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is one of the most prevalent malignancies and the third leading cause of cancer-related deaths worldwide (1). Major risk factors for HCC include chronic infection by hepatitis B virus (HBV) or hepatitis C virus (HCV) and alcoholic liver cirrhosis.

Advanced and symptomatic HCC disease is not amenable to curative surgery, therefore screening programs for high-risk populations are implemented to increase early detection and effective surgical treatment of HCC (2).

However, a definitive diagnosis of HCC requires concordant findings from several invasive and non-invasive diagnostic parameters, including liver biopsy, serum alpha-fetoprotein (AFP) levels, computed tomography, or magnetic resonance imaging (2). Nevertheless, noninvasive imaging is not sufficiently sensible for detecting an early-stage HCC, similarly AFP has low sensitivity and specificity to be used as a screening biomarker (3). In this framework, effective biomarkers for the early detection as well the progression of HCC are greatly needed.

Matsubara *et al*. in Hepatology (4) described the possible significance of circulating CD14+CD16+ monocytes expressing Tyrosine kinase with Ig and EGF homology domains 2 (TIE2) [TIE2-expressing monocytes (TEMs)] as biomarkers for the detection of both early- and late-stage HCC. Indeed, TIE2 is mainly expressed on endothelial cells and binds all the known angiopoietins (ANGs) and TEMs are peripheral as well as tumor-infiltrating myeloid cells presumed to be characterized by a profound pro-angiogenic activity (5-7). In particular, TEMs have been reported in tumors of the kidney, colon, pancreas and lung, as well as in soft tissue sarcomas (7) where angiogenesis is known to be important for tumor progression.

In this framework, HCC is a highly vascularized tumor, the progression of early lesions to overt HCC is strongly associated with increase of vasculature (8,9) and the antiangiogenic drug, sorafenib prolongs to a certain extent survival of patients with advanced HCC.

Matsubara *et al*. (4) report on the frequency of circulating TEMs in a cohort of 168 HCV-infected patients, of which 89 were with HCC. The investigators found that the frequency of TEMs was significantly higher in patients with HCC than HCV-infected patients without HCC or healthy subjects. No difference was found among HCC patients at different stages of the disease, thus establishing TEMs as a stage-independent, diagnostic biomarker for HCC. In addition, higher blood TEM levels correlate to a worse recurrence-free survival after HCC resection or radiofrequency ablation (RFA) therapy, suggesting a role for TEMs also as prognostic biomarker. Furthermore, they also identified TEMs in HCC tumor lesions preferentially localized in perivascular tumor areas correlating with increased microvessel density in the tumors. Therefore, it's possibly suggesting that HCC-infiltrating TEMs are proangiogenic. Moreover, high circulating and intratumoral TEM levels correlate with a more advanced Child-Pugh stage, suggesting that TEM frequency correlates positively with the degree of liver inflammation/stage of cirrhosis and negatively with liver function.

The biology underlying TEM's involvement in human tumor angiogenesis and progression is essentially unknown and several questions need to be addressed in order to possibly improve HCC anti-angiogenetic therapy. Indeed, the proangiogenic activity exerted by TEMs in HCC may represent one of the reasons for the limited efficacy of

sorafenib or other antiangiogenic treatments. Furthermore, elevated circulating levels of the TIE2 ligand, ANG2, correlate with a worse prognosis in untreated HCC patients and predict shorter survival in HCC patients treated with Sorafenib (10).

The study by Matsubara *et al.* (4) is the first to present evidence suggesting that circulating TEMs may be a diagnostic biomarker for both early- and late-stage HCC, although they are not strictly peculiar of HCC but detectable also in other tumors (5,7). These very interesting findings need to be validated on a larger scale of HCC patients to confirm the relevance of TEMs as diagnostic/prognostic marker for HCC as well as therapeutic target for improving the efficacy of current treatments for HCC.

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