Editorial

TIE2-expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis

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Abstract: Hepatocellular carcinoma (HCC) is the third most common cause of cancer-related deaths worldwide. In the past few years, the mechanisms of hepato-carcinogenesis have been elucidated and the involvement of a number of pathways, including angiogenesis, aberrant signal transduction, and dysregulated cell cycle control have been demonstrated. Myeloid lineage cells, such as macrophages and monocytes, have been reported to regulate angiogenesis in mouse models. TIE2, a receptor of angiopoietins, conveys pro-angiogenic signals and identifies a monocyte/macrophage subset with pro-angiogenic activity. Recently, one study suggests that TIE2-expressing monocyte/macrophage (TEMs) frequency can be used as a diagnostic marker for HCC.

Keywords: Hepatocellular carcinoma (HCC); markers; TIE2-expressing monocyte/macrophage (TEMs)

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Hepatocellular carcinoma (HCC) is a relevant health problem, being the sixth most common cancer worldwide in terms of incidence with 626,000 new cases per year, accounting for 5.7% of all new cancer cases (1). Due to the poor prognosis of the disease, the number of deaths per year is almost the same as new cases [598,000], making HCC the third most common cause of cancer-related death (1).

Prognosis and feasibility of treatments for HCC patients largely depend not only on tumor characteristics, but also on the severity of the underlying chronic liver disease that affects the majority of cases (2,3). Prognosis is relatively better for the subset of patients eligible for surgery (tumor resection or orthotopic liver transplantation) or for local ablation strategies with potentially curative aim (e.g., percutaneous ethanol injection or radiofrequency ablation). Outcome is significantly worse for those patients who can be treated only with palliative loco-regional treatments, such as transcatheter arterial chemo-embolization, or who are affected by advanced disease. Unfortunately, curative strategies are currently limited to a minority of patients, those who present at diagnosis with small nodules, disease confined to the liver, good performance status and well preserved liver function. The proportion of patients presenting with these characteristics is currently no more than about 30-40% (4). In the experience of the Cancer of the Liver Italian Program (CLIP) group, in a series of 650 patients diagnosed in the years 1994-1999, 59% of patients at diagnosis were not treatable by surgery or percutaneous ablation (5). However, the proportion of small, early tumors is expected to significantly increase in the next years, together with the diffusion of surveillance procedures of high-risk patients, allowing tumor diagnosis at an earlier stage (4).

However, early stage HCC is difficult to detect by non invasive imaging, and AFP as "surveillance biomarker" has been dropped in current guidelines because of low sensitivity and specificity (6).

In a recent issue of hepatology, Matsubara *et al.* (7) reported on the significance of circulating TIE2-expressing monociytes (TEMs) as biomarkers for the detections of both early- and late-stage HCC.

In their study, the authors analyzed the occurrence and kinetics of TEMs in 168 HCV-infected patients including 89 with HCC, examining the frequency of TEMs, defined as CD14+CD16+TIE2+, in the peripheral blood and liver.

They found that the frequency of circulating TEMs was significantly higher in HCC patients than non-HCC patients and being higher in the liver than in the blood. Interesting the authors serially examined the frequency of TEMs in HCC patients who underwent RFA therapy or tumor resection and found that in patients without HCC recurrence, the frequency of TEMs decreased after successful HCC ablation or resection, instead in patients with subsequent HCC recurrence, TEMs increased before the apparent radiological identification of HCC, therefore, TEM frequency dynamically changes in patients in correlation with the presence or recurrence of HCC.

To assess the clinical significance of TEMs as tumor biomarkers, the authors compared various clinical parameters in patients with high or low TEM frequency and found that elevated TEM frequency in the peripheral blood is associated with a deterioration of liver function in HCC patients and suggesting that the assessment of TEMs frequency in the blood holds prognostic value.

Matsubara *et al*. also identified TEMs in HCC specimens and observed that these cells preferentially localize in perivascular tumor areas, in agreement with findings in mouse models of cancer (8). Furthermore, it was found that higher TEM infiltration correlated with increased microvessel density in the tumors, possibly suggesting that HCC-infiltrating TEMs are proangiogenic.

These new findings reported by Matsubara *et al*. provide further evidence that BM-derived cells may serve as biomarkers for HCC, also the data suggest that these cells could be involved in the pathogenesis of HCC and have the potential to regulate HCC angiogenesis and progression, possibly by releasing proangiogenic growth factors (9).

Indeed, detecting small HCCs during screening procedures will translate into survival benefits but further studies should be conducted to confirm the role of this biomarker before such prognostic marker can be used in clinical practice.

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