Editorial

Can TIE-2 expressing monocytes represent a novel marker for hepatocellular carcinoma?

Barbara Dapas[1], Mario Grassi[2], Gabriele Grassi[1,3]

[1]Department of Life Sciences, [2]Department of Engineering and Architecture, University of Trieste, Trieste, Italy; [3]Department of "Scienze Mediche, Chirurgiche e della Salute", University of Trieste, Cattinara Hospital, Italy

Correspondence to: Gabriele Grassi, M.D., Ph.D. Department of Life Sciences, University Hospital of Cattinara, Strada di Fiume 447, 34100 Trieste, Italy. Email: ggrassi@units.it.

Abstract: Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, is a global health problem representing the sixth most common cancer and the third cause of cancer related death worldwide. The number of deaths per year in HCC is comparable to the incidence number, underlying the aggressive behavior of HCC and the modest efficacy of available curative treatments. Effective HCC treatment is problematic also due to the lack of early and specific diagnostic markers. In this regard, particular interest has been put on the tyrosine kinase with Ig and endothelial growth factor (EGF) homology domains 2 (TIE2), a receptor of angiopoietins, predominantly present on endothelial cells but also observed on monocytes [TIE-2-expressing monocytes (TEMs)]. Recently, a work by Matsubara *et al*. showed that the amount of circulating TEMs is higher in hepatitis virus C (HCV)/HCC patients compared to HCV patients or healthy subjects. Additionally the authors showed that TEMs have a diagnostic potential for HCC. Whereas the molecular mechanisms responsible for this observation remain elusive and further studies are necessary to confirm this finding, the work of Matsubara *et al*. may contribute to the identification of a novel HCC prognostic and diagnostic marker.

Keywords: Hepatocellular carcinoma (HCC); tyrosine kinase with Ig and endothelial growth factor (EGF) homology domains 2 (TIE2); TIE-2-expressing monocytes (TEMs); markers

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Hepatocellular carcinoma (HCC), the predominant form of primary liver cancer, is a global health problem (1-4) representing the sixth most common cancer and the third cause of cancer related death worldwide. The HCC occurrence, peaking at 70 years of age, is higher in males compared to women with an estimated ratio of 2.4. HCC incidence is highest in Asia and Africa compared to developed countries. A notable exception is represented by Southern Europe characterized by the highest frequency among the developed countries. The most common risk factors for HCC development are represented by chronic viral hepatitis [hepatitis virus B (HBV) and hepatitis virus C (HCV)], alcohol intake and aflatoxins exposure.

The worldwide number of deaths per year in HCC is comparable to the incidence number, underlying the aggressive behavior of HCC and the modest efficacy of available curative treatments. Effective HCC treatment is problematic also due to the lack of early and specific diagnostic markers. The most commonly used marker serum alpha-fetoprotein (AFP) has only a partial efficacy as monitoring device and for this, recently it has been removed from current guidelines due to low specificity and sensitivity (5). Thus many efforts have been put in the identification of reliable biomarkers useful to predict HCC early diagnoses, progression and aggressiveness. The interest of the scientific community in this field is witnessed by the fact that in 2013, 886 papers appeared in PubMed using the key words: "hepatocellular carcinoma" and "marker".

Among the different HCC diagnostic markers so far studied, it can be included: molecular and biochemical

cellular markers, micro-interfering RNAs, epigenetic variations and tumor stroma (TS) related markers (6). Whereas historically the identification of molecular and biochemical cellular markers represents the first approach to the individuation of HCC markers, the other three classes, holding great promise, have been developed later. miRNAs, small non-coding double-stranded RNAs with the capacity to regulate the expression of target genes (7) have been proved to be dis-regulated in HCC (8) and to represent potential HCC markers (6,9). Epigenetic variations, observed in circulating cell-free tumor DNA of HCC patients, have been shown to relate to tumor stage (10). Finally, in the last years, the cross-talk between tumor cells and their surrounding stroma has gained attention because of the role of stroma in HCC development and progression (11-13).

The TS contains a cellular compartment that includes cancer cells, fibroblasts, myofibroblasts, vascular and immune cells (12). TS cells support tumor development by preserving proliferative signaling, preventing growth suppressors, arresting apoptosis, inducing angiogenesis, stimulating invasion and minimizing immune destruction (14,15). Among TS cells, there are tumor-associated macrophages (TAMs) that are able to secrete many soluble factors including cytokines and growth factors necessary for tumor tropism. In particular, a subclass of TAMs named M2 (activated M2 type macrophages) (16) can secrete the pro-angiogenic factors vascular endothelial growth factor (VEGF) or endothelial growth factor (EGF), thus promoting tumor angiogenesis. The fact that HCC is a highly vascularized tumor indicates the role of this cell type in HCC development and the potential role as diagnostic marker. Notably, the levels of VEGF and other pro-angiogenic soluble factors such as angiopoietin-2 (ANG-2), are higher in HCC patients compared to non-HCC subjects and correlate with patients survival (17-19). However, such molecules did not show any significant advantage compared to other clinically available markers for HCC diagnosis (20). These findings prompted the researchers to explore the possibility that the targets of the angiogenic factors rather than the factors *per se*, could have been more informative for HCC diagnosis and monitoring. In this regard, particular interest has been put on the tyrosine kinase with Ig and EGF homology domains 2 (TIE2), a receptor of angiopoietins, predominantly present on endothelial cells but recently also observed on monocytes [TIE-2-expressing monocytes (TEMs)] (20-22). Notably, TEMs presence has been observed in human kidney, colon and pancreas cancers, where angiogenesis plays an important role in tumor progression (20).

No information was available with regard to the significance of TEMs in HCC until the work of Matsubara *et al.* (23). In their work, the authors studied the frequency of TEMs in the peripheral blood of 168-HCV infected patients with 89 of them bearing HCC. The major finding of this work was that the amount of circulating TEMs is higher in HCV/HCC patients compared to HCV patients or healthy subjects. As TEMs levels were not related to tumor stage, TEMs elevation can be considered a stage-independent diagnostic marker for HCC.

Dividing the HCV/HCC patients into two groups with high and low TEMs levels, the authors observed that in the high group, the recurrence-free survival rates were shorter compared to the low group; this suggests for the TEMs circulating level, a strong prognostic value. This consideration was also corroborated by the fact that in patients, which underwent treatment (radio frequency ablation or resection) and had no recurrence, the frequency of circulating TEMs significantly decreased compared to patients that had recurrence. The suggested prognostic value of TEMs is certainly of great potential interest for practical applications; however, further evidences of its efficacy are necessary. For example, an evaluation of the TEM efficacy in the long-term prognosis is required as Matsubara *et al.* limited the observation time to a maximum of two years.

Matsubara *et al*. also suggest that TEMs elevation is HCC and not HCV related. This consideration stems from the observation that TEMs increase was higher in non HCV-infected HCC patients compared to non-HCC patients. However, this aspect has to be further investigated in the future as, for example, it has been reported that TEMs are significantly more elevated in HCV-infected patients without HCC compared to healthy subjects (24). Despite this aspect, in the cohort studied by Matsubara *et al*., the specificity of TEMs levels turned out to be superior to the commonly used AFP and the circulating levels of ANG-2.

Whereas in the next future the above findings may become of clinical practical utility, further studies are required to better define and understand the biological role of TEMs in tumor angiogenesis. In this regard, Matsubara *et al.* suggest that TEMs localizes preferentially in the peri-vascular area of HCC tissue and that TEM frequency correlates with micro-vessel density. Despite being suggestive of a close relation between TEMs and angiogenesis in HCC, this observation needs to be further

confirmed in a higher number of cases, as the cases analyzed by Matsubara *et al*. are limited to twelve. Additionally, mechanistic and molecular evidences of TEM connection to tumor angiogenesis need to be provided in future investigations.

In summary, Matsubara *et al*. have provided evidences that TEMs level may be of clinical utility as a stage-independent diagnostic marker for HCC. The commented work also suggests the possibility of a TEM involvement in the pathogenesis of HCC *via* the up-regulation of tumor angiogenesis. Whereas the molecular mechanisms responsible for this observation remain elusive, it is evident that TEMs and/or molecules they produce may also represent valuable targets for novel anti HCC therapeutic approaches.

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