Editorial

Circulating cancer stem cells: a novel prognostic predictor of hepatocellular carcinoma

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Not only tumor progression but also metastasis are the major causes of mortality from a wide range of cancers, including hepatocellular carcinoma (HCC). In general, tumor cells frequently leave the primary tumor and form metastatic lesions in distant organs. It has been believed that tumor infiltration of blood vessels at the primary tumor site is responsible for the dissemination of tumor cells and the formation of metastatic lesions in distant organs. Circulating tumor cells (CTCs) are extremely rare cells found in the blood stream of patients with tumors and it has been believed that these cells contribute to cancer dissemination and lead to the development of metastasis (1). Although CTCs were first detected roughly 140 years ago (2), recent progress in molecular biology and technology has successfully achieved the identification of CTCs in a variety of cancers. Initially, mRNA extracted from peripheral blood mononuclear cells was frequently subjected to reverse transcription-polymerase chain reaction (RT-PCR) for the detection of these cells using various tumor markers. In HCC patients, RT-PCR for α-fetroprotein or albumin has been utilized to detect circulating liver cancer cells (3,4); however, this approach is considered inappropriate to produce consistent findings because of the lack of specificity for tumor cells.

Recently, the CellSearch System (Veridex LLC, Raritan, NJ) has been widely used to detect CTCs in a variety of cancers. In order to distinguish tumor cells from hematopoietic cells, this system targets epithelial cell adhesion molecule (EpCAM)+pan-cytokeratin (CK)+ 4'-6-diamidino-2-phenylindole (DAPI)+CD45- cells. Currently, quantification of these cells has been utilized as a less invasive diagnostic and prognostic tool in metastatic breast, prostate, colon cancers (5). At the same time, some difficulties have been pointed out concerning this approach. The sensitivity and specificity of this assay are not necessarily favorable in early stage cancers. In addition, EpCAM down-regulation has been observed in epithelial-mesenchymal transition (EMT), which is deeply involved in metastasis (6). Of importance, it has been reported that EpCAM expression is detected in less than 50% of primary HCC tissues (7). Concordant with these findings, there are few reports concerning the CellSearch System for the detection of CTCs in HCC. The CellSearch System should therefore be used, taking into consideration both the cancer type and the progression stage.

On the other hand, the "cancer stem cell (CSC)" hypothesis has attracted attention over recent years (8). According to the concept, tumors consist of a minor component of tumorigenic cells and a major component of non-tumorigenic cells. The minor population, termed CSCs or tumor-initiating cells (TICs), is able to self-renew and generate differentiated progenies to organize a hierarchical cell system in a similar fashion to normal stem cells. These cells exhibit pronounced tumorigenic activity in xenograft transplantation using immunodeficient mice, which indicates the important role of the cells in the development of cancer. Additionally, there is increasing evidence that CSCs could play a crucial role in recurrence after treatment and metastasis (9).

Advancements in stem cell biology have facilitated the identification and characterization of CSCs in a variety of tumors, including HCC (10). Fan and colleagues reported that CD45-CD90+ cells engraft in the livers of severe

combined immunodeficient /Beige mice and function as CSCs in HCC (11). In addition, they demonstrated that CD45-CD90+ cells were detected in blood samples of more than 90% of HCC patients and there was no difference in tumorigenicity between CD45-CD90+ cells from blood samples and those from primary tumor tissues. Recently, they quantified CD45-CD90+CD44+ cells in the peripheral blood of HCC patients 1 day before hepatic resection and investigated whether the frequency of these cells serves as a predictor of prognosis (12). In this study, they successfully detected CD45-CD90+CD44+ cells in 56 of 82 blood samples of HCC patients (68.3%), and found that patients with circulating CSCs ≤0.01% showed significantly more favorable prognosis than those with circulating CSCs >0.01% in recurrence-free survival and overall survival. Moreover, multivariable analysis revealed that CSCs >0.01% was the most significant risk factor in view of recurrence after hepatectomy. Taken together, these results indicate that circulating CSCs could predict the postoperative recurrence of HCC. On the other hand, additional treatment appeared to be essential for HCC patients with a high number of circulating CSCs. The development of adjuvant therapy using molecularly targeted drugs such as sorafenib might be useful for the prevention of early HCC metastasis.

The authors successfully demonstrated the strong correlation of the number of circulating CSCs with recurrence and survival in HCC, but there are still some issues to be resolved. In particular, it is well known that EMT is required for tumor cells to gain motility and invasiveness to enter the blood stream for distant metastasis (13). Although CD90 is a characteristic marker of mesenchymal stem cells, they reported that CD90 expression in circulating CSCs was lower than that in primary tumor CSCs. It is important to confirm whether circulating CSCs undergo EMT. Considering that a recent report showed that EMT could turn differentiated progeny into CSCs (6), it should be examined whether circulating CSCs derived from the primary tumor CSCs. Meanwhile, the authors documented that metastasis in post-operative remnant liver occurred with greater frequency than in distant organs such as the lung, lymph node, and bone. It is possible that intra-hepatic metastasis had already developed prior to the surgery in some cases; however, it has been reported that CTCs could not only cause distant metastasis but also re-infiltrate back into the primary organ in breast cancer (14). These findings might support the possibility that circulating liver CSCs preferentially contribute to intra-hepatic metastasis.

In summary, this study by Fan *et al.* highlighted the importance of circulating liver CSCs as a prognostic tool for early recurrence after hepatectomy. Further analyses of circulating liver CSCs are of paramount importance to both the elucidation of mechanisms underlying metastasis and the establishment of novel therapeutic approaches targeting these cells.

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