Editorial

Stem Cell INVESTIGATION

Identification of molecular transition of hepatocellular carcinoma: a novel method to predict the initiation of metastasis

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Although the most frequently diagnosed cancers and the leading cause of cancer-related deaths vary across the country, hepatocellular carcinoma (HCC) is one of the major cancers and the fourth-leading cause of cancer-related deaths globally following lung, colorectal, and stomach cancers (1). As the majority of liver cancers are associated with hepatitis viruses, alcoholic abuse, and metabolic syndrome leading to nonalcoholic steatohepatitis, a careful check-up of high-risk patients is useful for early diagnosis. However, the strategy of the check-up is under development and the high mortality rate of liver cancer results from the late diagnosis of advanced stages, recurrence after surgical resection, and high incidence of both intrahepatic and extrahepatic tumor metastases (2,3). Extrahepatic metastasis reportedly occurs in 13.5–42% of patients with HCC (4,5), and their prognosis is poor, with less than 1 year of survival time (6-8). Extrahepatic metastatic lesion sites include the lungs, bone, lymph node, adrenal grand, peritoneum, diaphragm, pancreas, skin, brain, muscle, and spinal cord (4,8,9). The most common site of metastasis is the lung (10). Metastasis is a nonlinear (i.e., generally irreversible) and dynamic process that involves cancer cell motility, intravasation, transit in the blood or lymph node, extravasation, and development at a new site (11). Because of the poor prognoses of these patients and the adverse effects on the patients' quality of life, the development of a standard therapeutic strategy and a marker for predicting the tipping point is essential for preventing the initiation of metastasis in the earlier stage.

For the primary lesion and intrahepatic metastatic lesions, surgical treatment, ablation, and embolization could be the options, considering the hepatic reserve function (12). For extrahepatic lesions, surgical removal, systemic chemotherapy including molecular targeting agents (13-17) and possibly immune checkpoint inhibitor, and radiation (9) are considered as therapeutic options. However, for intrahepatic lesions, performance status and hepatic reserve function are the key parameters to be considered. From this standpoint of view, the development of novel therapeutic options for metastatic lesions is essential; at the same time, the predictor of the metastasis, which is the marker by which we can identify the tipping point of primary or tumor cells to metastasize, needs to be developed for preventing the metastasis or for diagnosing it in the earlier phase. Various tumor-related genes, including oncogenes and tumor suppressor genes, show the alteration of expression leading to the gain or loss of function. These changes affect the sequential stages of tumor cell invasion, organ tropism, and growth at a distant site via the signaling networks or pathways where these genes are involved (18). These signaling pathways include the insulin-like growth factor, mitogen-activated protein kinase, phosphatidylinositol-3 kinase/Akt/mammalian target of rapamycin, and Wnt/β-catenin pathways (19).

Traditional biomarkers are also reportedly ineffective in detecting the difference in molecular pathology between nonmetastatic and premetastatic states; however, recent developments in omics technologies has contributed to investigating this tipping point from the perspectives of both network and dynamics (20-23). Yang *et al.* have

recently reported the effect of the dynamic network biomarker (DNB) method in developing a new biomarker for identifying the tipping point of HCC to metastasize (24). They have demonstrated that even if no statistical significance has been observed in the markers at each point, when they are dynamically analyzed, there is a significant difference such that nonmetastatic and premetastatic situations can be defined and novel biomarkers can be identified.

In their work, they have adopted the mathematical method of the DNB model for identifying the difference between nonmetastatic and premetastatic states for developing the new biomarker. Comparing various factors dynamically using omics data, they successfully found that the potential biomarker predicted the lung metastases of HCC as a tipping point (20-23). Specifically, they obtained DNB genes that not only signaled the premetastatic state but were also strongly related to the key molecules of HCC metastasis by analyzing the three DNB statistical conditions of the critical state derived from the nonlinear dynamic theory (20,22,23). Compared with traditional biomarkers detecting the metastatic state on the basis of the differential expression of molecules, a major advantage of the DNB method is that it can identify the premetastatic state or tipping point just before the irreversible transition to the metastasis state in tumor progression. With this method, they have discovered several DNB members as predictive biomarkers that have been shown to play a precursor role in initiating metastasis (20-23) in both animal models and patient samples. They have transplanted HCC cell lines of highly aggressive progression and expressing stable fluorescent protein for easy detection of the dynamics of carcinogenesis and metastasis and analyzed them dynamically in a time-dependent manner. They have shown by analyzing time-series transcriptomic data based on the DNB method the tipping point of metastasis initiation using model mice and found that CALML3, located on chromosome 10 (10p15.1) and encoding a 138-amino-acid residue calcium sensor protein similar in structure to calmodulin 39, is one of the DNB members and plays an important role in metastasis initiation.

CALML3 is highly expressed in the normal differentiation of tissues, including skin, kidneys, breasts, and thyroid. Also, its expression is significantly reduced in cancers of these tissues (25), indicating the tumor-suppressive function of this gene; however, little is known regarding its function in the mechanisms of metastasis initiation. They have performed assays *in vitro*, *in vivo*, and using clinical samples for clarifying the molecular mechanisms of CALML3 and have shown that this gene could indicate metastasis initiation through the biological network and that the loss of this gene function predicts poorer prognosis in patients with HCC. Therefore, CLAML3 can be a prognostic biomarker of HCC and possibly be a therapeutic target.

In summary, the new way of predicting the critical transition in metastasis by the DNB method has been demonstrated and this method has provided new insights into the molecular pathology of HCC pulmonary metastasis from the perspectives of dynamics and network. This methodology can be applied to other cancers; therefore, "dynamic" changes in searching the biomarkers for the specific situation can be realizable.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Llovet JM, Zucman-Rossi J, Pikarsky E, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2016;2:16018.
3. Yang JD, Roberts LR. Hepatocellular carcinoma: A global view. Nat Rev Gastroenterol Hepatol 2010;7:448-58.
4. Uka K, Aikata H, Takaki S, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol 2007;13:414-20.
5. Si MS, Amersi F, Golish SR, et al. Prevalence of metastases in hepatocellular carcinoma: risk factors and impact on survival. Am Surg 2003;69:879-85.
6. Han MS, Moon KS, Lee KH, et al. Brain metastasis from hepatocellular carcinoma: the role of surgery as a prognostic factor. BMC Cancer 2013;13:567.
7. Imamura I. Prognostic efficacy of treatment for extrahepatic metastasis after surgical treatment of

hepatocellular carcinoma. Kurume Med J 2003;50:41-8.
8. Natsuizaka M, Omura T, Akaike T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol 2005;20:1781-7.
9. Kamimura K, Kobayashi Y, Takahashi Y, et al. Tumor markers for early diagnosis for brain metastasis of hepatocellular carcinoma: A case series and literature review for effective loco-regional treatment. Cancer Biol Ther 2017;18:79-84.
10. Aino H, Sumie S, Niizeki T, et al. Clinical characteristics and prognostic factors for advanced hepatocellular carcinoma with extrahepatic metastasis. Mol Clin Oncol 2014;2:393-8.
11. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002;2:563-72.
12. European Association for the Study of the Liver; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182-236.
13. Llovet JM, Montal R, Sia D, et al. Molecular therapies and precision medicine for hepatocellular carcinoma. Nat Rev Clin Oncol 2018;15:599-616.
14. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
15. Abou-Alfa GK, Meyer T, Cheng AL, et al. Cabozantinib in patients with advanced and progressing hepatocellular carcinoma. N Engl J Med 2018;379:54-63.
16. Bruix J, Qin S, Merle P, et al. Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;389:56-66.
17. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391:1163-73.
18. Nguyen DX, Massague J. Genetic determinants of cancer metastasis. Nat Rev Genet 2007;8:341-52.
19. Whittaker S, Marais R, Zhu AX. The role of signaling pathways in the development and treatment of hepatocellular carcinoma. Oncogene 2010;29:4989-5005.
20. Chen L, Liu R, Liu ZP, et al. Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers. Sci Rep 2012;2:342.
21. Liu R, Wang X, Aihara K, et al. Early diagnosis of complex diseases by molecular biomarkers, network biomarkers, and dynamical network biomarkers. Med Res Rev 2014;34:455-78.
22. Li M, Zeng T, Liu R, et al. Detecting tissue-specific early-warning signals for complex diseases based on dynamical network biomarkers: study of type-2 diabetes by cross-tissue analysis. Brief Bioinform 2014;15:229-43.
23. Li M, Li C, Liu WX, et al. Dysfunction of PLA2G6 and CYP2C44-associated network signals imminent carcinogenesis from chronic inflammation to hepatocellular carcinoma. J Mol Cell Biol 2017;9:489-503.
24. Yang B, Li M, Tang W, et al. Dynamic network biomarker indicates pulmonary metastasis at the tipping point of hepatocellular carcinoma. Nat Commun. 2018;9:678.
25. Yaswen P, Smoll A, Peehl DM, et al. Down-regulation of a calmodulin-related gene during transformation of human mammary epithelial cells. Proc Natl Acad Sci USA 1990;87:7360-4.

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