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Molecular profiling to predict hepatocellular carcinoma outcome

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Hepatocellular carcinoma (HCC) is one of major health problems being the third leading cause of cancer death in the world [1]. Besides the high prevalence in developing countries, the incidence has continued to increase in developed countries mainly due to chronic infection with hepatitis C virus [2]. Early stage tumor can be treated with surgical resection, transplantation, or local ablation. However, tumor recurrence is common after local treatments, and there is still no curative therapy once the tumor gets into advanced stage.

A recent clinical trial has shown that molecular targeted approach is a promising strategy to improve prognosis of HCC patients [3]. To increase the chance to apply currently existing or experimental medical interventions for potential cure, identification of patients at risk of recurrence is critically important. To this end, precise understanding of its molecular mechanism is the key. This editorial briefly discusses the pattern of tumor recurrence specific to HCC, and the strategy to predict the risk of recurrence by means of gene-expression profiling.

Two types of HCC recurrence

It is well known that there are two distinct types of HCC recurrence [4–6]. In general, recurrent tumor arises from residual tumor cells disseminated in the remnant organ. In HCC, malignant phenotypes of the tumor, e.g., larger size, vascular invasion, satellite lesions, and high serum alpha-fetoprotein, are known to be predictive of this type of recurrence, which is usually observed within 2 years after surgery (“early recurrence”)

In addition to “early recurrence”, there is another type of HCC recurrence. A vast majority of HCC appears as a consequence of chronic viral hepatitis accompanied with advanced liver fibrosis. The diseased liver serves as a field for carcinogenesis (“field effect”) [7]. The “field effect”, which cannot be surgically treated, produces *de novo* metachronous tumors independently from the completely removed primary tumors. This type of recurrence is clinically enriched more than 2 years after surgery (“late recurrence”).

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These two types of recurrence appear in distinct biological contexts, and their clinical courses are different: “early recurrence” is associated with more aggressive clinical behavior and poor prognosis, whereas the risk of “late recurrence” is not associated with the status of primary tumor. For efficient clinical management of HCC patients who receive surgical or ablative treatment, it is important to precisely monitor the risk of each type of recurrence. Several genomic technologies have been utilized to discriminate these recurrences [8–10]. In addition, “late recurrence” may be a good target of new chemopreventive treatment [6].

Increasing early HCC and decreasing early recurrence

HCC surveillance focusing on patients with liver fibrosis has successfully detected HCC tumors at an early stage, which can be subjected to potentially curative surgical or ablative treatment [11] and improved clinical outcome of the patients [12,13]. With this shift toward early stage HCC, clinical tumor characteristics, i.e., the risk factors of “early recurrence”, have become less informative to predict outcome because the pattern of recurrence has also shifted from “early recurrence” to “late recurrence” [8]. Hence, when attempting to discover molecular information predictive of the outcome, this shift highlights the necessity to know which type of the recurrence is the major determinant of outcome in patients enrolled in each particular study.

Molecular prediction of HCC outcome using non-tumor liver tissue

Gene-expression profiling has become a tool to monitor molecular status of clinical tissue, and it currently serves as a flexible source for discovery of diagnostic and/or prognostic biomarkers. In HCC, previous studies reported that gene-expression signatures derived from the tumor are able to predict “early recurrence” [14,15], and patient survival [16] after surgery. However, most of these studies included patients with relatively advanced HCC, where “early recurrence” is the primary driver of the outcome. In fact, in series of earlier stage HCC patients diagnosed through the tumor surveillance commonly performed in developed countries, the outcome is mainly determined by “late recurrence”, and the tumor-derived survival-predictive signature showed no association with survival [8]. This result indicates that the molecular feature of tumor itself needs to be complemented by the information coming from outside the tumor for the purpose of outcome prediction in early HCC increasingly diagnosed in modern clinical practice.

In fact, in non-tumor adjacent liver tissues, there exists a gene-expression signature predictive of HCC outcome driven by “late recurrence” [8]. The poor-prognosis-related part of the signature includes genes associated with inflammatory response (interferon and NF-kB pathways), oxidative stress response (NOS, GPX), and growth signaling (IL-6 pathway). The good-prognosis-related part contains normal liver function-associated genes encoding plasma proteins and various drug-metabolizing enzymes, which reflect extent of liver damage due to chronic hepatitis and/or cirrhosis more sensitively than conventional histological evaluation or clinical assessment of liver function like Child-Pugh system [17]. This observation is consistent with the notion of “field effect”, which is a manifestation of inflamed carcinogenic milieu diffusely or focally affecting the entire organ [7,18]. This may explain why the gene-expression signature in tumor-adjacent liver tissue, which is removed together with tumor at the time of surgery, predicts clinical outcome of HCC patients.

Interestingly, Budhu et al. suggested that Th2-dominant cytokine gene expression profile in non-tumor liver tissue is associated with higher risk of intra-hepatic metastasis (driver of “early recurrence”) in hepatitis B-related HCC [19]. This study also supports the idea that non-tumor liver tissue is an extremely useful source of molecular information for therapeutic target identification as well as clinical decision-making.

Future directions

As Sherman discussed, if the "field effect" is presented diffusely in the liver, the signature may be detected in randomly sampled needle biopsy specimen [7]. In addition, if the signature really captures the risk of *de novo* carcinogenesis, it may predict the initial HCC development in patients with cirrhosis. This may have huge implication in chemopreventive strategies and tailored surveillance programs. Furthermore, the strategy to utilize non-tumor tissues to monitor the "field effect" may be relevant to other cancers associated with chronic inflammation, e.g., cervical, gastric, esophageal, prostate cancers, and melanoma [18].

The non-tumor liver signatures assumedly represent mixture of multiple molecular signals from various cell types involved in the biology of HCC development. These signals may be induced by viral infection, abnormal metabolic condition, hereditary genetic factors, etc., and some of them may be utilized as molecular targets for HCC chemoprevention. Establishment of experimental models representing any of these molecular aberrations, combined with high-throughput drug screening system [20], will greatly facilitate the development of personalized preventive medicine [21].

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