Editorial

OPN sesame

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Abstract: Osteopontin (OPN) is a growth regulatory protein for hepatocellular carcinoma (HCC) and a potent chemoattractant for macrophages. Zhu and colleagues recently reported significant clinical associations between poor postoperative prognosis and the concurrent detection of tumoral OPN expression and peritumoral macrophage (PTM) infiltration. An in-depth understanding on the complex interaction between tumoral OPN and macrophage-infiltrated microenvironment opens new doors to novel anticancer treatments.

Keywords: Metastasis; cancer recurrence; inflammation; early detection

Submitted Feb 10, 2014. Accepted for publication Feb 13, 2014.
doi: 10.3978/j.issn.2304-3881.2014.02.09
View this article at: http://dx.doi.org/10.3978/j.issn.2304-3881.2014.02.09

Hepatocellular carcinoma (HCC) is an aggressive cancer which ranks as the fifth most common solid tumors and the third leading cause of cancer-related death worldwide. Early-stage HCC is treated by curative methods, including surgical resection, radiofrequency ablation and liver transplantation based on international guidelines (1). However, effects of "curative" resection are often compromised by a high recurrence rate after surgery. Intra- and extra-hepatic metastasis was reported to occur in 50% of surgically treated patients within three years (2). Thus, prevention of postoperative recurrence in HCC remains an unmet medical need.

To address this issue, continuous attempts have been made to search for effective prognostic predictors from the resected liver specimens, either from the tumoral or peritumoral regions. Molecular characteristics of malignant cells in individual patients can be identified from the tumoral regions. However, all tumoral regions are totally removed during the surgery and the molecular signatures in the tumors can serve as prognostic predictors only when one believes that the same oncogenic pathways are followed during the subsequent cancer recurrence. On the other hand, the characteristics of peritumoral regions are largely preserved after surgery. They are considered tumor-nurturing microenvironment which should carry important clues.

In a recent issue of *Annals of Surgical Oncology*, Zhu and colleagues reported the interaction of two prognosis factors, tumoral osteopontin (OPN) and peritumoral macrophage (PTM) infiltration (3). In this study, OPN and PTM jointly stratified the patients into three groups with distinct time to postoperative recurrence and overall survival. OPN or PTM alone, however, was not associated with time to recurrence. A multivariate analysis showed that the associations remained significant after adjusted for prognosis-related clinicopathological factors.

In the study, three groups of patients were compared: (I) both OPN and PTM were negative; (II) either OPN or PTM was positive; (III) both OPN and PTM were positive. Subsequent analysis revealed that group (III) had a significant poorer prognosis than the other two groups. Two cohorts of patients were analyzed. The first cohort comprised 96 patients where 80 patients were Barcelona Clinic Liver Cancer (BCLC) stage 0-A and 16 patients stage B. The second cohort comprised 278 patients who were all stage 0-A by the BCLC criteria (1). Zhu and colleagues were careful enough to demonstrate that when the analysis of the first cohort was restricted to BCLC stage 0-A patients, the prognosis predicting effect sustained. The authors further restricted the analysis to patients with baseline serum alpha-fetoprotein (AFP) levels <400 ng/mL. They discovered that the co-detection of OPN and PTM still correlated significantly with the prognosis in both cohorts ($P \leq 0.008$).

The OPN and PTM duet

Zhu's data suggested that tumoral OPN and PTM infiltration together exerted a two-hit synergistic effect on HCC recurrence. Recent studies indicated that although accumulation of inflammatory cells, such as PTM infiltration, could launch immunological attack against cancer cells, it could also generate an inflammatory microenvironment which provides cellular factors to promote the growth of a wide spectrum of cancer types (4). Although the two effects seemed contradictory, the oncogenic effect could dominate eventually under certain conditions (5). Tumor-associated macrophages are either derived from activated residential macrophages in the peritumoral tissues or attracted from the circulation to the tumor site. They produce chemicals such as inflammatory reactive oxygen species and nitrogen intermediates, causing somatic DNA damages and thus transforming normal/precancerous cells into malignant cells. This is consistent with the clinically-observed causal relationship between chronic hepatitis and HCC. Furthermore, macrophages secrete many oncogenic cytokines and extracellular matrix proteases including IL6, IL11, TNF, IL1B, MMP2 and MMP9, facilitating cancer cell proliferation, angiogenesis, anti-apoptosis and metastasis (5). The inflammatory response can also result in local immunosuppression (5). These proposed oncogenic mechanisms are supported by other clinical correlations between intratumorial/PTM infiltration and poor postoperative prognosis in HCC patients (6,7).

OPN is an integrin-binding glycoprotein also known as secreted phosphoprotein 1 (SPP1). OPN is so named because it was first discovered in osteoblasts and osteoclasts. The latter is developed from the macrophage lineage. OPN protein has a secreted form and an intracellular form (8). The secreted OPN has two integrin-binding domains which can adhere to integrins on the surfaces of macrophages, making it a potent chemoattractant as well as an activator of macrophages (8,9). In innate immunological cells such as dendritic cells, OPN can be activated upon infection. The OPN-integrin binding can trigger downstream macrophage activities including TNF secretion, producing an inflammatory microenvironment. Poor prognosis of HCC was correlated with elevated OPN RNA (10), tissue OPN protein levels (11,12) and pre-operative serum OPN protein levels (13,14). An anti-OPN antibody has been shown to defer the growth and metastasis of breast cancer in a mice model (15). As macrophages can also secret OPN, PTM and OPN form a vicious autocrine/paracrine cycle for the progression of cancer. Thus, in the future, novel strategies to break this cycle could bring to new anti-HCC treatments.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Liang KH, Yeh CT. OPN sesame. Hepatobiliary Surg Nutr 2014;3(3):112-114. doi: 10.3978/j.issn.2304-3881.2014.02.09

