学 位 論 文 の 要 旨

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学 位 論 文 名	Fractalkine-CX3CR1 Axis Regulates Tumor Cell Cycle and Deteriorates Prognosis after Radical Resection for Hepatocellular Carcinoma
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INTRODUCTION

Chemokines are a large family of chemoattractant cytokines that regulate leukocyte trafficking and homing, and they are classified into four groups: CXC, CC, C, and CX3C chemokines. Several recent studies have suggested that some chemokines can recruit various leukocyte types, and mediate antitumor immune host responses. Furthermore, the interactions between chemokines and their receptors appear to play an important role in regulating tumor progression and metastasis. Fractalkine (CX3CL1) is the only CX3C chemokine, and it is expressed in various organs, including endothelial cells, the brain, and liver. Its receptor (CX3CR1) is expressed on NK cells, $CD8^+$ T cells, monocytes, and dendritic cells (DC). Furthermore, a recent study suggested that CX3CR1 is expressed on cytotoxic effector lymphocytes with perforin and granzyme B. These characteristics explain why fractalkine expressed on tumor cells can recruit CX3CR1-positive cytotoxic effector lymphocytes to the tumor site, generating an immune response against the tumor. In addition, fractalkine has been identified as a direct transcriptional target of p53. Therefore, fractalkine may be an important

molecule in terms of cancer progression by influencing the immune response, apoptosis, and cancer cell proliferation.

MATERIALS AND METHODS

Fifty-six patients (42 males and 14 females) were included in this study. All the patients underwent radical hepatic resection for HCC between July 1985 and March 1998.

Serial (5 μm) sections of formalin-fixed, paraffin-embedded tissues were obtained and stained using the avidin-biotin-peroxidase complex method for fractalkine and proliferating cell nuclear antigen (PCNA). Immunoreactivity for fractalkine was evaluated according to the "maximum intensity of staining," "most extensive intensity level," and "extent of distribution of positive cells." The sum of these three parameters was used as the final staining score for fractalkine. The fractalkine-expressing tumors were divided into high and low expression groups using the mean value. The level of tumor proliferation was expressed as the PCNA labeling index (PCNALI). The PCNALI was expressed as the ratio of positively stained tumor cells to the total number of tumor cells counted. The PCNA-expressing tumors were divided into high and low expression groups for the PCNALI using the mean value.

Digital images of the immunoreactive bands of fractalkine and CX3CR1 were captured using a scanner and they were quantified. The CX3CR1-expressing tumors were divided into high and low expression groups using the mean value.

RESULTS AND DISCUSSION

Tumors with high expression of both fractalkine and CX3CR1 had significantly fewer intra- and extrahepatic recurrences, a low PCNALI, and different histological grade. Patients with tumors that expressed both had a significantly better prognosis in terms of disease-free and overall survival, and this finding was identified as one of the independent prognostic factors in the multivariate analysis. Interestingly, the tumor expression of fractalkine was positively

correlated with that of CX3CR1 in Spearman's rank correlation test. Based on these results, we postulate that the fractalkine-CX3CR1 axis modulates cell progression in HCC via the autocrine and/or paracrine system. The most important tumor-suppressor gene, p53 regulate the control of cell cycle arrest, including apoptosis, induce cellular differentiation, and promote angiogenesis. The PCNALI is used as a cell cycle marker, and a high PCNALI indicates increased cell proliferation. Several reports have shown that the PCNALI is inversely correlated with p53 expression. Recently, fractalkine was revealed as one of the direct targets of p53. Considering this evidence, we postulate that the fractalkine-CX3CR1 axis plays a crucial role in the control of the cancer cell cycle through p53. As a result, malfunction in this axis might reduce survival in patients with HCC. In this study, activation of the fractalkine-CX3CR1 axis was inversely correlated with PCNALI as a cell cycle marker and the degree of tumor differentiation in HCC. A tumor carrying mutated p53 could easily escape from the host immune response because of a malfunction in the fractalkine-CX3CR1 axis. In a tumor producing less fractalkine, even cytotoxic lymphocytes presented CX3CR1 might not migrate effectively and attach to tumor cells. Consequently, the tumor cells might escape the host immune response.

CONCLUSION

This study generated valuable evidence that the high expression of both fractalkine and CX3CR1 in HCC leads to a better prognosis in terms of both DFS and OAS after radical resection. In addition, our results suggest that the fractalkine-CX3CR1 axis in HCC plays a crucial role in regulating tumor progression and differentiation in an autocrine and/or paracrine manner. Finally, we postulate that this axis might be a novel therapeutic target against HCC.