学位論文の要旨

氏 名　百留 美樹

学位論文名	Increased Expression of Fractalkine Is Correlated With a Better Prognosis and an Increased Number of Both $CD8^+$ T Cells and Natural Killer Cells in Gastric Adenocarcinoma.
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著者名	Miki Hyakudomi, Takeshi Matsubara, Ryoji Hyakudomi, Tetsu Yamamoto, Shoici Kinugasa, Akira Yamanoi, Riruke Maruyama, Tsuneo Tanaka

論文内容の要旨

INTRODUCTION

Chemokines are a large family of small molecules capable of recruiting various leukocyte subsets to certain physiological and pathological sites, as well as in tumor tissues. Over the past few years, the correlation between chemokines and tumor progression has attracted significant attention. Several recent studies have suggested that some chemokines intensify innate and adaptive antitumor immune responses by recruiting specific subsets of leucocytes. The chemokines can be grouped into the C, CC, CXC, CX3C subfamilies based on the spacing of the N-terminal cysteine residues. Fractalkine is the only member of the CX3C subfamily. Its receptor CX3CR1 is typically expressed on peripheral blood cytotoxic effector lymphocytes commonly armed with intracellular perforin and granzyme B, including NK cells, $\gamma\delta$ T cells, terminally differentiated $CD8^+$ T cells, and a minor

fraction of $CD4^+$ T cells in humans, but only on monocytes, NK cells and dendritic cells in mice. Therefore, it is likely that Fractalkine might induce an antitumor immune response by recruiting these effector cells into tumor tissues and thereby inducing adhesion between tumor cells and these effectors.

We investigated the expression of Fractalkine in 158 surgical specimens of gastric adenocarcinoma and analyzed any association with the clinicopathological factors, including tumor-infiltrating lymphocytes (TILs), while also evaluating the impact on the prognosis.

MATERIALS AND METHODS

Tissue sections from 158 patients with curatively resected T2 or T3 gastric adenocarcinoma were immunohistochemically stained for Fractalkine. Furthermore, to evaluate $CD8^+$ T cells and NK cells infiltration, antibodies to CD8 and CD57 protein were respectively used for immunohistochemistry.

RESULTS AND DISCUSSION

In gastric adenocarcinoma, 67 patients (42.4%) showed strong Fractalkine expression, whereas 91 (57.6%) demonstrated weak expression. The Fractalkine expression was evaluated regarding sex, age, the size of the tumor, histological grade, Lauren's classification, the depth of invasion, lymph vessel invasion, blood vessel invasion, Lymph node metastasis, and over all stage. There was no statistically significant association between the Fractalkine expression and any of the clinicopathological characteristics. The high Fractalkine expression group showed a significantly better prognosis than the low Fractalkine expression group regarding the disease-free survival (P = 0.0016). In a

multivariate analysis, the Fractalkine expression was identified as one of the independent prognosticators for disease-free survival (risk ratio, 2.5; P = 0.0147). Furthermore, The Spearman-rank test showed a statistically significant positive correlation between the Fractalkine expression and $CD8^+$ T cells (ρ = 0.212, P = 0.0080) or NK cells (ρ = 0.236, P = 0.0031), respectively. TILs are thought to be a manifestation of the host immune response to cancer cells and related to the prognosis with various tumors. Most TILs are cytotoxic T lymphocytes, which are related to tumor specific immunology. NK cells, which act nonspecifically against cancer cells, make up a small fraction of the TILs. Therefore, a major goal of immunotherapy is further accumulation of such immune effector cells in the tumor microenvironment. Based on these considerations, increasing attention has been paid to chemokines, because of their ability to recruit lymphocytes to cancer sites. Although Fractalkine has been demonstrated to play an important role in the antitumor responses in vitro and in a previous study on mice, the clinical significance of Fractalkine remains controversial. In the present study, the patients' survival was clearly better in those patients expressing high levels of Fractalkine. Moreover, the tumor expression of Fractalkine also significantly correlated with the density of $CD8^+$ T cell and NK cells, respectively, at the tumor sites.

CONCLUSION

Our results suggest that the expression of Fractalkine by tumor cells enhances the recruitment of $CD8^+$ T cells and NK cells and induces both innate and adaptive immunity, thereby yielding a better prognosis in gastric adenocarcinoma. Fractalkine could therefore be a new independent predictor of prognosis and thus is considered to be a novel candidate for the development of a more effective therapeutic strategy for gastric carcinoma.