Metastatic potential of metastasis from gastro=intestinal cancer and its treatment from the viewpont of melecular level

1997 Fiscal Year Final Research Report Summary

METASTATIC POTENTIAL OF METASTASIS FROM GASTRO=INTESTINAL CANCER AND ITS TREATMENT FROM THE VIEWPONT OF MELECULAR LEVEL

Research Project

Project/Area Number

07457270

Research Category

Grant-in-Aid for Scientific Research (B)

Allocation Type

Single-year Grants

Section

一般

Research Field

Digestive surgery

Research Institution

KANAZAWA UNIVERSITY

Principal Investigator

MAI Masayoshi KANAZAWA UNIVERSITY CANCER,RES,INST,Professor, がん研究所, 教授 (80092807)

Co-Investigator(Kenkyū-buntansha)

WATANABE Michio KANAZAWA UNIVERSITY CANCER,RES,INST,ASSISTANT PROFESSOR, がん研究所, 助手 (30293385)
OHTA Takahito KANAZAWA UNIVERSITY CANCER,RES,INST,LECTURER, がん研究所, 講師 (10233131)
TAKAHASHI Yutaka KANAZAWA UNIVERSITY CANCER,RES,INST,ASSOCIATE PROFESSOR, がん研究所, 助教授 (10179541)

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gastointestinal cancer / metastatic potential / angiogenesis / MT-MMP / orthotopic metastatic model of liver / MMPs / TIMP-1 gene / MMP-2

Research Abstract

In considering the main steps in the process of tumor invasion and metastasis, the mechanism for invasion of tumor cells through tissue barriers are not well understood, but they appear to involve both mechanical and enzymatic activity. Matrix metalloproteinases (MMPs) play a key role in degradation of the extracellular matrix (ECM) associated with cancer invasion and metastasis. We have proviously studied the production of MMP-1,2,3, and 9 in human gastric carcinomas compared with normal gastric mucosa. Among these MMPs, activation as well as production of the zymogen of MMP-2 (progelatinase A) was well correlated with local invasion and lymphatic permeation and vessel invasion of the gastric cancer. Since proMMP-2 activation is thought to be caused by MT-MMP in vivo, expression of MT-MMP-1 was studied in the same samples. Our data indicated that MT-MMP-1 is exclusively expressed in the carcinoma cells and its expression is well correlated with pro MMP-2 activation.
It also is well kno wn that the activation of MMPs is regulated by tissue inbitors of metalloproteinases (TIMPs). In considering negative regulators of TIMPs, we examined inhibition of metastasis in human gastric cancer cells transfected with TIMP-1 gene in vivo, As a metastatic model we used the cell line established from human gastric carcinoma, KKLS at our department. KKLS cell was transfected with exogenous TIMP-1 gene by the Chen-Okayama method and we obtained two clones KT-CL-1 and and KT-CL-14 expressed different levels of TIMP-1. The KKLS cells and these transfectants were orthotopically transplanted into nude mice (murine stomach) and metastasis in the murine liver was detected. Our experimental data showed that KT-CL-1 and KT-CL-14 transfected the cDNA for TIMP-1 gene resulted in dramatic inhibition of metastatic colonies of 46.7% and 26.7% compared with those of parental KKLS cells and K-Neo cell as control. Consequently, the MMPs are therapeutic targets that may evoke cytostatic, as are adhesion molecles, signal transduction pathway, growth factor and angiogenesis. The hope is that by use of selective inhibitors for these targets, we can achieve a halt in tumor invasion and metasitasis without significant toxicity and our encouraging results lead to conclude that they indicates a promising new direction in cnacer therapy.▲ Less

Research Products (12 results)

All | Other

All | Publications (12 results)

[Publications] Yasumoto K, et al: "Molecular analysis of the cytokine network involved in cachexia in colon 26 adenocarcinoma-bearing mice." Cancer Research. 55. 921-927 (1995)

[Publications] Nomura H, et al: "Expression of membrane-type matrix metalloproteinase in human gastric carcinomas." Cancer Research. 55. 3263-3266 (1995)

[Publications] Takahashi Y, et al: "Site-dependent expression of vascular endothelial growth factor,angiogenesis and proliferation in human gastric carcinoma." International Journal of Oncology. 8. 701-705 (1996)

[Publications] Ooi A, et al: "Numerical chromosome alterations in colorectal carcinomas detected by fluorescence in situ hybridization Relationship to 17p and 18q allelic losses." Virchows Arch. 428. 243-251 (1996)

[Publications] Nomura H, et al: "Enhanced production of matrix metalloproteinases and activation of matrix metalloproteinase 2 (gelatinase A) in human gastric carcinomas." International Journal of Cancer. 69. 9-16 (1996)

[Publications] Watanabe M, et al: "Inhibition of metastasis in human gastric cancer cells transfected with tissue inhibitor of metalloproteinase 1 gene in nude mice." Cancer. 77. 1676-1680 (1996)

[Publications] Yasumoto K,et al: "Molecular analysis of the cytokine network involved in cachexia in colon 26 adenocarcinoma-bearing mice." Cancer Research. 55. 921-927 (1995)

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