神経膠芽腫の浸潤関連遺伝子の解析

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2000 Fiscal Year Final Research Report Summary

The analysis of invasion associated gene in glioblastoma

Research Project

Project/Area Number

11470286

Research Category

Grant-in-Aid for Scientific Research (B).

Allocation Type

Single-year Grants

Section

一般

Research Field

Cerebral neurosurgery

Research Institution

Kanazawa University

Principal Investigator

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1999 – 2000

Keywords

glioblastoma / invasion / dissemination / MMP / ets-1 / integrin

Research Abstract

We revealed two points as follows. 1)Among proteinases, matrix metalloproteinases(MMPs)are thought to play a key role in the tumor progression through the degradation of extracellular matrix. We examined th role of MMP-2(gelatinase A)and membrane type 1-MMP(MT1-MMP, an activator of the zymogen of MMP-2=proMMP-2)together with their inhibitors, tissue inhibitors of metalloproteinases(TIMP-1 and TIMP-2), in the invasion of human astrocytic tumors. The investigations were performed using sandwich enzyme immunoassay systems, quantitative reverse transcription polymerase chain reaction(RT-PCR), gymography, Immunohistochemistry and cell transfection. The results suggest that MT1-MMP may contribute to the invasion and CSF dissemination of glioblastoma cells on the basis of an imbalance to TIMP-2. 2)Ets transcription factors are associated with tumor malignancy. We analyzed effects of Ets-DN-expression on cell adhesion, migration and phosphorylation of focal adhesion kinase(FAK). U251 cells expressing Ets-DN(U251-DN)showed reduced cell adhesion, spreading and extension of actin stress fibers on dishes coated with fibronectin but not on dishes coated with collagen. Phosphorylation levels of FAK in U251-DN cells were also attenuated on dishes coated with fibronectin. Reduced expression level of integrin α5 subunit in U251-DN cells was demonstrated by semi-quantitative RT-PCR analysis. Furthermore, down-regulation of transcription from the integrin α5 promoter by expression of Ets-DN was shown by luciferase reporter assay. Semi-quantitative RT-PCR of surgical samples of brain tumors revealed that the expression level of Ets-1 mRNA correlated with that of integrin α5 mRNA in glioma. These results suggest that Ets-1 contributes to glioma malignancy by upregulating expression of the integrin α5 subunit, which composes integrin α5β1, mediates intracellular signaling and the subsequent acceleration of the invasive process including cell adhesion and migration.

Research Products (8 results)

All Other

All Publications

[Publications] Kita D: "Ets-1 positively regulates expression of urokinase-type plasminogen activator(uPA)and invasiveness of astrocytic tumors."Cancer Res. in press.

[Publications] Nakada M: "Roles of membrane-type 1 matrix metalloproteinase and tissue inhibitor of metalloproteinases 2 in invasion and dissemination of human malignant gliomas."J Neurosurg. 94. 464-473 (2001)

[Publications] Nakada M: "Ets-1 positively regulates expression of urokinase-type plasminogen activator(uPA)and invasiveness of astrocytic tumors."J Neuropathol Exp Neurol. 58. 329-334 (1999)

[Publications] Nakada M: "Expression and tissue localization of membrane types 1,2 and 3 matrix metalloproteinases in human astrocytic tumors."Am J Pathol. 154. 428 (1999)

[Publications] I, Kita D, Et al: "Ets-1 positively regulates expression of urokinase-type plasminogen activator(uPA)and invasiveness of astrocytic tumors."Cancer Res. (in press).

[Publications] Nakada M, et al: "Roles of membrane-type 1 matrix metalloproteinase and tissue inhibitor of metalloproteinases 2 in invasion and dissemination of human malignant gliomas."J Neurosurg. 94. 464-473 (2001)

[Publications] Nakada M, et al: "Ets-1 positively regulates expression of urokinase-type plasminogen activator(uPA)and invasiveness of astrocytic tumors."J Neuropathol Exp Neurol. 58. 329-334 (1999)

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