形態形成過程におけるMT1-MMPの機能発現制御機構の解析

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Research Abstract

マトリックスメタロプロテアーゼ(MMP)、特に膜型MMP(MT1-MMP)は組織形態形成および癌の浸潤・転移、炎症性疾患などの病態と密接に関係している。本研究では発現クローニング法によりMT1-MMP活性制御因子及び新規基質を同定し、その生理的意義の解明を行った。
1)我々はこれまでにMT-MMP阻害因子としてTestican-3のスプライシングバリアントであるN-Tesを同定した(Cancer Res.,61,8896-8902,2001)。今回、Testicanファミリー間の相互作用を発見し、特にグリオーマの浸潤に果たす意義を明らかにした(Cancer Res.,2003,63,3364-3369)。
2)発現クローニングによりMT-MMPの新規基質としてシンデカン-1を同定しその生理的意義を解明した。シンデカン-1はコラーゲン上での細胞運動を負に制御するが、MT1-MMPによるシンデカン-1の切断はがん細胞の運動性を亢進することを見い出した(J.Biol.Chem.278,40764-40770,2003)。
3)発現クローニングによりMT-MMPの新規基質としてがん転移抑制因子であるKiSS-1/metastinを同定し、MT-MMPによるMetastin分解はがん細胞の運動性を亢進することを明らかにした(Oncogene,22,4617-4626,2003)。
4)発現クローニングによりMT-MMPの新規基質として細胞外マトリックス成分であるルミカンを同定した。ルミカンは、細胞にがん抑制遺伝子産物のひとつであるp21/Waf-1の発現を誘導するが、MT-MMPによるルミカンの切断はがん細胞の腫瘍原性を亢進することを見い出した。
以上のことなどからMT1-MMPはその多機能性によりがん細胞の浸潤・転移のみならず腫瘍原性をも亢進することが明かとなった。

Report (5 results)

2003 Annual Research Report

2002 Annual Research Report

2001 Annual Research Report

2000 Annual Research Report

1999 Annual Research Report

Research Products (42 results)

All Other

All Publications

[Publications] Takino T: "Tetraspanin CD63 promotes targeting and lysosomal proteolysis of membrane-type 1 matrix metalloproteinase"Biochem Biophys Res Commun.. 304. 160-166 (2003)

[Publications] Takino T: "Cleavage of Metastasis Suppressor Gene Product KiSS-1 Protein/Metastin by Matrix Metalloproteinases"Oncogene. 22. 4617-4626 (2003)

[Publications] Nakada M: "Testican 2 abrogates inhibition of membrane-type matrix metalloproteinases by other testican family proteins"Cancer Res.. 63. 3364-3369 (2003)

[Publications] Takino T: "CrkI adapter protein modulates cell migration and invasion in glioblastoma."Cancer Res.. 63. 2335-2337 (2003)

[Publications] Endo K: "Cleavage of Syndecan-1 by Membrane-Type Matrix Metalloproteinase-1 Stimulates Cell Migration"J.Biol.Chem.. 278. 40764-40770 (2003)

[Publications] Takino T: "Membrane-Type 1 Matrix Metalloproteinase Regulates collagen-dependent Mitogen-Activated Protein/Extracellular Signal-Related Kinase Activation and Cell Migration."Cancer Res.. 印刷中. (2004)

[Publications] 佐藤 博: "癌転移"日本臨床. 4 (2003)

[Publications] Mori, H., et al.: "CD44 directs membrane-type 1 matrix metalloproteinase to lamellipodia by associating with its hemopexin-like domain"EMBO J.. 21. 3949-3959 (2002)

[Publications] Maekawa K, et al.: "Inhibition of cervical lymph node metastasis by marimastat (BB-2516) in an orthotopic oral squamous cell carcinoma implantation model"Clin.Exp. Metastasis. 19. 513-518 (2002)

[Publications] Yamamura, T., et al.: "Expression of membrane-type-1-matrix metalloproteinase and metalloproteinase-2 in nonsmall cell lung carcinomas"Lung Cancer. 35. 249-255 (2002)

[Publications] Takino.T., et al.: "A scaffold protein in the c-Jun N-terminal kinase signaling pathway is associated with focal adhesion kinase and tyrosine-phosphorylated"Oncogene. 21. 6488-6497 (2002)

[Publications] Takino T., et al.: "Tetraspanin CD63 Promotes Targeting and Lysosomal Proteolysis of MT1-MMP"Biochem.Biophys.Res.Comm.. (印刷中). (2003)

[Publications] Takino T., et al.: "Cleavage of Metastasis Suppressor Gene Product Kiss-1 Protein/Metastin by Matrix Metalloproteinases"Oncogene. (印刷中). (2003)

[Publications] 佐藤 博: "実験医学増刊号(プロテオミクス時代のタンパク質研究)"羊土社. 5 (2002)

[Publications] Horikawa, T., et al.: "Induction of c-Met proteo-oncogene by Epstein-Barr virus latent membrane protein-i and the correlation with cervical lymph node metastasis of nasoDharvngeal carcinoma"Am. J. Pathol.. 159. 27-33 (2001)

[Publications] Miyamori, H, et al.: "Claudin Promotes Activation of Pro-MMP-2 Mediated by Membrane-Type Matrix Metalloproteinases"J. Biol. Chem.. 276. 28204-28211 (2001)

[Publications] Nakada, M., et al.: "Suppression of MT1-MMP-mediated MMP-2 activation and tumor invasion by testican 3 and its splicing variant gene product N-Tes"Cancer Res.. 61. 8896-8902 (2001)

[Publications] Itoh, Y., et al.: "Dimer formation of MT1-MMIP is essential for proMMP-2 activation and promoting tumor cell invasion"EMBO J.. 20. 4782-4793 (2001)

[Publications] Kita, D., et al.: "Expression of dominant negative form of Ets-1 suppresses fibronectin-stimulated cell adhesion and migration through down-regulation of integrin a5 expression in U251 glioma cell line"Cancer Res.. 61. 7985-7991 (2001)

[Publications] Mon N, et al.: "Human T-cell leukemia virus type I Tax transactivates the matrix metalloproteinase-9 gene : potential role in mediating adult T-cell leukemia invasiveness"Blood. 99. 1341-1349 (2001)

[Publications] 佐藤 博: "Advances in Cancer Treatment(がん治療のあゆみ)"最新医学社. 9 (2001)

[Publications] H.Miyamori: "Human membrane type-2 matrix metalloproteinase is defective in cell-associated activation of progelatinase A. "Biochem.Biophys.Res.Comm.. 267. 796-800 (2000)

[Publications] K-R.Kim: "Transformation of Madin-Darby canine kidney (MDCK) epithelial cells by Epstein-Barr virus latent membrane protein 1 (LMP1) induces expression of Ets1 and invasive growth."Oncogene. 30. 1764-1771 (2000)

[Publications] H.Yamanaka: "Expression and tissue localization of membrane-type 1,2, and 3 matrix metalloproteinases in rheumatoid synovium."Lab Invest.. 80. 677-687 (2000)

[Publications] S.Murono: "Aspirin inhibits tumor cell invasiveness induced by Epstein-Barr virus latent membrane protein 1 through suppression of matrix metalloproteinase-9 expression."Cancer Res.. 60. 2555-2561 (2000)

[Publications] H.Miyamori: "Expression of metastasis-associated mts1 gene is co-induced with membrane type-1 matrix metalloproteinase (MT1-MMP) during oncogenic transformation and tubular formation of Madin Darby canine kidney (MDCK) epithelial cells."Clinical and Experimental Metastasis. 18. 51-56 (2000)

[Publications] T.Yoshizaki: "Elevation of antibody against Epstein-Barr virus genes BRLF1 and BZLF1 in nasopharyngeal carcinoma."J.Cancer Res.Clin.Oncol.. 126. 69-73 (2000)

[Publications] K.Nakanishi: "Human membrane type-2 matrix metalloproteinase is defective in cell-associated activation of progelatinase A."Human Pathology. 31. 193-200 (2000)

[Publications] Y.Misumi: "An essential cytoplasmic domain for the Golgi localization of Coiled-coil proteins with a COOH-terminal membrane anchor."J.Biol.Chem.. (印刷中).

[Publications] 佐藤博: "肝転移"医学書院. 10 (2000)

[Publications] 佐藤博: "MMPと疾患・基礎と臨床"現代医療社. 6 (2000)

[Publications] 佐藤博: "タンパク質分解・分子機構と細胞機能"シュプリンガー・フェアラーク東京. 9 (2000)

[Publications] 佐藤博: "耳鼻咽喉科免疫アレルギー「発癌と悪性化の分子機構」"日本耳鼻咽喉科免疫アレルギー学会. 5 (2000)

[Publications] H. Nakamura, et al.: "Enhanced production and activation of progelatinase A mediated by membrane-type 1 matrix metalloproteinase in human papillary thyroid carcinomas"Cancer Research. 59. 467-473 (1999)

[Publications] H. Noritake, et al.: "Overexpression of tissue inhibitor of matrix metalloproteinase-1(TIMP-1) in metastatic MDCK cells transformed by v-src"Clinical an Experimental Metastasis. 17. 105-110 (1999)

[Publications] H. Takeshita, et al.: "Matrix metalloproteinase 9 is induced by Epstein-Barr virus latent membrane protein 1 C-terminal activation regions 1 and 2"Journal of Virology. 73. 5548-5555 (1999)

[Publications] Y. Kitagawa, et al.: "Expression of messenger RNAs for membrane-type 1, 2, and 3 matrix metalloproeinases in human renal cell carcinomas"Journal of Urology. 162. 905-909 (1999)

[Publications] H. Miyamori, et al.: "Human membrane type-2 matrix metalloproteinase is defective in cell-associated activation of progelatinase A"Biochem. Biophys. Res. Comm.. (印刷中).

[Publications] K-R. Kim, et al.: "Transformation of Madin-Darby canine kidney (MDCK) epithelial cells by Epstein-Barr virus latent membrane protein 1(LMP1) induces expression of Ets1 and invasive growth"Oncogene. (印刷中).

[Publications] 佐藤博: "タンパク質分解-分子機構と細胞機能"シュプリンガー・フェアラーク東京(印刷中).

[Publications] 佐藤博: "MMPと疾患-基礎と臨床"現代医療社(印刷中).

[Publications] 佐藤博: "肝転移"医学書院. 3-13 (2000)

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