【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)

Title of Project：Study of MT1-MMP in cancer

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Research Area：Oncology

Keyword：Characteristics of cancer cells, Invasion, Metastasis, Cell adhesion and movement

【Purpose and Background of the Research】

Cancer arises from epithelial cells that cover surface of tissues and organs. During tumor progression epithelial phenotype of cancer cells is frequently lost and mesenchymal phenotype becomes apparent. This phenotypic conversion is called as epithelial-mesenchymal transition (EMT) and it accompanies acquisition of invasive and metastatic ability of cancer cells.

My group has been studying on membrane-type 1 matrix metalloproteinase (MT1-MMP) since we discovered it in 1994. MT1-MMP is frequently expressed in malignant cancer cells and promotes invasion and metastasis by degrading pericellular proteins. Regulation of MT1-MMP expression in cancer cells is tightly linked to the EMT program. Once MT1-MMP was expressed in cancer cells it regulates not only invasion but also diverse functions of malignant cancer cells such as growth, motility, and VEGF expression etc. The diverse biological outcomes of MT1-MMP action depends on substrates of which functions are modified by MT1-MMP-dependent processing.

The aim of this study is to identify new substrates that are important to regulate cancer cell functions and regulators of cell functions that are tightly linked to the use of MT1-MMP by cells.

【Research Methods】

We took mass spectrometry analysis to identify MT1-MMP-associating proteins. We isolated MT1-MMP-containing complexes from malignant carcinoma and sarcoma cells and subjected them to the analysis. Identified proteins contained membrane protein substrates as about half of the proteins were indeed cleaved by MT1-MMP at least in vitro or by cell-based assay. Through the analysis of MT1-MMP-associaitng membrane proteins, we already identified HB-EGF is a new substrate of MT1-MMP. Processing of HB-EGF by MT1-MMP converted HB-EGF to a potent growth factor that does not require heparin as a co-factor.

Many cytoplasmic proteins were also identified and most of them were confirmed to be co-immunoprecipitaed with MT1-MMP. We already characterized that one of them has an ability to bind $p27^{kip1}$ that is a well-known cell cycle regulator. Recently $p27^{kip1}$ is known to localize in cytoplasm as well to inhibit activation of RhoA by binding to GDP-RhoA and preventing RhoA to bind GEFs for activation. We named this protein as p27RF-Rho and demonstrated that it localizes at inner surface of cell-ECM interaction sites. Upon stimulation of cells RhoA activation was observed at the sites where p27RF-Rho localizes and invadopodia were formed accompanying MT1-MMP on the outer surface. We are extending this line of study to identify new substrates and regulators that promotes cancer progression by using MT1-MMP.

【Expected Research Achievements and Scientific Significance】

This study will contribute to further understanding cellular strategy to use MT1-MMP during cancer progression and the results are expected to provide clues to develop new strategies for treatment of cancer patients and finding biomarkers to monitor the patients.

【Publications Relevant to the Project】

Itoh, Y. and Seiki, M. MT1-MMP: a potent modifier of pericellular microenvironment. J Cell Physiol 2006;*206*: 1-8.

Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E., and Seiki, M. A matrix metalloproteinase expressed on the surface of invasive tumour cells. Nature 1994;*370*: 61-5.

【Term of Project】 FY2010-2013

【Budget Allocation】 164,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/cancercell/index.html