Functional analyses and regulation of the metabolism of tissue microenvironmental factors by metalloproteinases

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【Outline of survey】

Tissues and organs of our body are comprised of cells and intercellular substances. The latter is composed of extracellular matrix and physiologically active substances (growth factors, cytokines and chemokines etc), and constitutes the tissue microenvironments, which control various cellular functions in vivo. Although previous biological and medical studies have neglected the tissue microenvironments by focusing on only the cells, the tissue microenvironments have recently been paid attention in various fields such as tumorigenesis and cancer progression, tissue destruction and fibrosis in inflammatory diseases and regenerative medicine. Our previous pioneering work has demonstrated that members of the MMP (matrix metalloproteinase) and ADAM (a disintegrin and metalloproteinase) gene families are involved in the metabolism of tissue microenvironmental factors (extracellular matrix and physiologically active substances). In the present projects, we aim to elucidate the molecular mechanisms of the metabolism of tissue microenvironmental factors by MMPs and ADAMs in malignant tumors and non-neoplastic diseases, with a view to designing novel targeting therapies for the diseases.

【Expected results】

By carrying out the proposed projects, we expect to determine the regulation mechanism of the activities of the cancer cell-derived MMPs and ADAMs, which could play a key role in cancer cell proliferation, invasion and metastases, and also the biological meanings of the MMPs and ADAMs derived from cancer-associated stromal cells. In addition, studies on the substrate specificity and regulators of ADAMs in non-neoplastic diseases and a project on the development of ADAM species-specific inhibitors are considered to give us a big progress in the ADAM research. Based on the new information about MMPs and ADAMs, we will better understand the molecular mechanisms for the metabolism of tissue microenvironmental factors and provide basic information about the novel targeting therapies to treat the diseases that involve the metabolism of the tissue microenvironmental factors.

【References by the principal investigator】

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・Matsumura S., Iwanaga S., Mochizuki S., Okamoto H., Ogawa S. and Okada Y.: Targeted deletion or pharmacological inhibition of MMP-2 prevents cardiac rupture after myocardial infarction in mice. J. Clin. Invest. 115:599-609, 2005.

【Term of project】 FY2007－2011	【Budget allocation】 31,500,000 yen (2007 direct cost)

【Homepage address】 http://web.sc.itc.keio.ac.jp/patho/index-jp.html