General Summary of Division of Molecular Virology and Oncology

Recent studies have demonstrated that members of the matrix metalloproteinase (MMP) gene family play a central role in the degradation of extra cellular matrix (ECM) macromolecules under various physiological and pathological conditions. Degradation of ECM is one of the first steps for tumor invasion and metastasis, and MMP have been strongly implicated in this step. Membrane type-1 MMP (MT1-MMP, MMP-14) was identified as the first physiological activator of latent MMP-2 (proMMP-2). The role of MT1-MMP in pericellular proteolysis is not restricted to proMMP-2 activation as MT1-MMP is a functional enzyme that can also degrade a number of ECM components and hence can play a direct role in ECM turnover. Accumulating evidences have demonstrated that MT1-MMP expression level is closely associated with invasiveness and malignancy of tumors, suggesting that MT1-MMP is one of the most critical factors for tumor invasion and metastasis. Thus, we believe that MT1-MMP could be a molecular target for diagnosis and therapy of malignant tumors.

A) Pro-MMP-2 Activation by MT1-MMP:

The suggested model for pro-matrix metalloproteinase-2 (proMMP-2) activation by MT1-MMP implicates the complex between MT1-MMP and tissue inhibitor of MMP (TIMP)-2 as a receptor for proMMP-2. Due to the complicated mechanism for pro-MMP-2 activation, physiological significance of pro-MMP-2 activation remained unclear. We created an artificial receptor for pro-MMP-2, which enabled us to examine the mechanism and physiological significance of pro-MMP-2 activation by MT1-MMP.

B) Substrate Specificity of MT1-MMP:

While degradation of ECM is an important aspect of MMP biology, growing evidence has demonstrated specific processing/activation or degradation of cell surface receptors and ligands by MT1-MMP. We have been developing expression cloning strategy to identify MT1-MMP substrates, which were not only ECM components but also cell-surface receptors and ligands.

C) Regulation of Cell Migration by MT1-MMP:

Although MMPs were known to be involved in cell migration, the molecular mechanism had remained elucidated. We demonstrated that degradation of ECM by cell-surface MT1-MMP induces a rapid turn-over of focal adhesion, which stimulates a sustained signal through the MEK/ERK pathways. This sustained ERK activation in turn stimulates cell migration on ECM.