Roles of Membrane-Type Matrix Metalloproteinase-1 in Tumor Invasion and Metastasis

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Throughout the process of tumor metastasis, microenvironment surrounding tumors regulates tumor cell migration, proliferation and survival. Modification of extracellular matrix (ECM), whose major components are collagen, fibronectin and so on, is one of initial steps for tumor invasion and metastasis. Matrix metalloproteinases (MMPs) may play important roles in it. In 1994 we identified first membrane-type MMP (MT1-MMP) as an activator of MMP-2. Among 23 human MMPs so far reported, MT1-MMP is one of the most important proteases. Although MT1-MMP was first identified as an activator of MMP-2, later its multi functions at cell-ECM interface were demonstrated to contribute to malignant phenotype of tumor cells. A variety of molecules have been identified as substrates for MT1-MMP, which are relevant to tumor malignancy. They are ECM components, cell surface receptors e.g. CD44 and syndecan-1, and small ligand molecules e.g. KiSS-1/metastin.

ECM acts as physical barrier for tumor-cell invasion, but at the same time it provides cells with various signals for growth, survival, differentiation, migration and so on. Degradation of ECM at focal adhesions accelerates the turnover, in which MT1-MMP plays a central role and regulates signal transduction. Thus, inhibition of MT1-MMP reduces not only tumor cell invasion/migration but also proliferation/survival of tumor cells in ECM. Although MT1-MMP is essential for tumor invasive growth in ECM, MT1-MMP alone is not enough, but needs coordinate action of other proteases for effective invasion. Recently, we identified a membrane-type serine protease inhibitor Hepatocyte Growth Factor Activator Inhibitor-1 (HAI-1) as a new substrate for MT1-MMP, and showed that cleavage of HAI-1 by MT1-MMP rescues membrane-type serine protease matriptase. The role of MT1-MMP as a trigger of protease activation cascade, which may accelerate tumor growth, invasion and metastasis will be discussed in the symposium.

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EDUCATIONS/TRAINING

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POSITIONS AND HONORS

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1996-1998	Visiting Professor at Lineberger Cancer Center, University of North Carolina at Chapel Hill
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2005-2009	Director of Cancer Research Institute, Kanazawa University
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