Membrane-type Matrix Metalloproteinases in Pericellular Proteolysis and Melanoma Cell Invasion

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Olga Tatti defended her PhD thesis at the University of Helsinki, Finland, on May 31, 2013. The thesis was supervised by Associate Professor Kaisa Lehti, Genome Scale Biology Research Program, University of Helsinki, and Professor Jorma Keski-Oja, Departments of Pathology and Virology, Haartman Institute, Helsinki University Hospital and Translational Cancer Biology Research Program, University of Helsinki, Helsinki, Finland. The opponent was Professor Cornelia Mauch, Department of Dermatology and Venereology, University of Cologne, Cologne, Germany. The thesis is available at: http://urn.fi/URN:ISBN:978-952-10-8775-2.

Tumour microenvironment comprised of extracellular matrix (ECM) and non-malignant cells has profound effects on cancer progression. Membrane-type matrix metalloproteinases (MT-MMPs) expressed by both tumour and stroma cells are involved in the modulation of tumour microenvironment and thereby regulate tumour cell proliferation, invasion and dissemination. MT1-MMP is a prototype of MT-MMP family, which is overexpressed in many types of cancer, where it promotes tumour cell invasion through collagen-rich tissues. The biological functions of another member of the MT-MMP family, MT3-MMP, have remained largely unknown. Unlike MT1-MMP, MT3-MMP cannot cleave native collagen type I. MT3-MMP is expressed in the adult brain, as well as various cancer types such as brain tumours and nodular melanoma. The purpose of this thesis was to elucidate the functions of MT1-MMP and MT3-MMP in melanoma cell invasion. To understand the pericellular growth regulation, we searched for endogenous enzymes which could release latent TGF-β from endothelial cell extracellular matrix.

Neovessel formation (angiogenesis) is a prerequisite for tumour growth. Pericellular modulation of the ECM by MT1-MMP releases matrix-associated growth factors and bioactive peptides, which further affect angiogenesis and tumour cell biology. We found that MT1-MMP mRNA expression and activity were induced after morphological activation of endothelial cells, which mimics the initial phases of angiogenesis. MT1-MMP modulated subendothelial extracellular matrix, and cleaved latent TGF–β binding protein-1 (LTPB-1), with subsequent release of latent TGF–β complexes from the ECM. TGF–β can both promote and inhibit endothelial cell proliferation, and the opposing effects of TGF-β depend on its concentration. Thus, MT1-MMP-mediated LTBP-1 cleavage provides a mechanism for the tightly controlled release of matrix-associated TGF–β at the sites of neovessel formation.

To elucidate the functions of MT-MMPs in melanoma cell invasion, we analysed the expression of MT1-MMP and MT3-MMP from biopsies of normal human skin, benign naevi, and melanoma metastases. MT3-MMP was upregulated in lymph node metastases of human melanoma, while MT1-MMP expression was comparable in all biopsies. By culturing melanoma cells in 3D collagen and fibrin matrices, we found that MT3-MMP was associated with expansive melanoma growth in 3D collagen, but promoted their sprouting growth in 3D fibrin. In *in vivo* xenograft experiments, MT3-MMP expressing melanoma xenografts grew slowly, while MT3-MMP silencing enhanced tumour growth rate by over two fold. Interestingly, high MT3-MMP expression in murine xenografts and a human melanoma tumour was associated with prominent lymphatic vessel invasion but negligible blood vessel invasion of melanoma cells. Silencing of MT3-MMP reduced lymphatic invasion but facilitated blood vessel invasion of melanoma cells >10-fold. MT3-MMP reduced cell surface MT1-MMP *in vitro* and *in vivo*, resulting in limited collagen invasion *in vitro* and collagen accumulation *in vivo*. This suggested that low collagenolytic ability of MT3-MMP-expressing melanoma cells resulted in decreased blood vascular invasion. These cells invaded instead into more permissive lymphatic vessels. Since lymphatic vessel invasion is associated with metastatic spread in melanoma, MT3-MMP expression may serve as a new prognostic factor in this disease.

Olga Tatti defended her PhD thesis on membrane-type matrix metalloproteinases in Helsinki, Finland on 31st May, 2013. *Left to right:* Professor Jorma Keski-Oja, PhD Olga Tatti, Opponent, Professor Cornelia Mauch, Associate Professor Kaisa Lehti.