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MT1-MMP as a potent modulator of Tumor Microenvironment

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Membrane-type 1 matrix metalloproteinase (MT1-MMP/MMP-14) is a potent modulator of cell physiology by degrading multiple proteins in the pericellular milieu. Expressed in tumor cells, MT1-MMP is shown to be involved in tumor growth, invasion, and metastasis. The roles of MT1-MMP are mediated by its proteolytic activity on the cell surface. Possible substrates include extracellular matrix (ECM) proteins, cell adhesion molecules, cytokines, and latent forms of proMMPs. However, our knowledge of the physiological substrates of MT1-MMP is still limited and identification of these substrates should enable a better understanding of the biological functions of MT1-MMP.

During the migration and invasion of cells, MT1-MMP localizes to the leading edges and invadopodia of cells. Although the exact mechanisms that determine the localization of MT1-MMP are not well understood, the binding of MT1-MMP to cellular proteins linked to the actin cytoskeleton, such as CD44 or integrin, is thought to be a factor determining its localization. Thus, identification of the proteins that interact with MT1-MMP on the cell surface provides us important clues to understand the mechanisms and functions of MT1-MMP.

We aimed to identify a catalog of proteins that associate either directly or indirectly with MT1-MMP. To do this, we purified MT1-MMP from cell lysate together with its associating proteins. A specific set of membrane proteins was co-purified with MT1-MMP. The purified proteins were analyzed by a nano-flow liquid chromatography-tandem mass spectrometry (nano-LC-MS/MS). We identified more than hundred proteins in the MT1-MMP complex obtained from human tumor cell lines. These are membrane proteins, cytoplasmic proteins, receptors, etc. including functionally unknown proteins. About half of the membrane proteins tested can be cleaved by MT1-MMP in cells. Analysis of the identified membrane proteins and cytoplasmic proteins will be reported.

S8-3
Macrophages, Microenvironment and Metastasis.

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Macrophages are abundant cells in the tumor microenvironment and in clinical studies their density is usually positively correlated with poor prognosis. This suggests that macrophages are tumor promoting. Consistent with this hypothesis studies in mouse models show that genetic or chemical ablation of macrophages results in a reduction in tumor progression and metastasis (1).

In our mechanistic studies using genetic models of macrophage ablation as well as gain-of-function experiments we showed that tumor-associated macrophages regulate the angiogenic switch required for the malignant transition through the production of VEGF and that they also promote tumor cell invasion, migration and intravasation as a consequence of reciprocal EGF and CSF-1 signaling (2, 3). These macrophage-tumor cell interactions can also be visualized in mouse models that exploit fluorescent labeling through expression of fluorescent proteins from tissue specific promoters (4). In addition to these effects at the primary tumor site we have recently identified a sub-population of macrophages that are required for metastatic seeding and persistent growth at distant sites. These data together with that of others suggest that targeting macrophages and their unique signaling pathways could offer new therapeutic strategies against metastatic disease (5).