Public Abstract
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Title:MEMBRANE TYPE 1 MATRIX METALLOPROTEINASE PROTEOLYTIC ACTIVITY IN INITIAL ADHESIVE AND INVASIVE EVENTS OF OVARIAN CANCER METASTASIS

Epithelial ovarian cancer (EOC) is one of the most common gynecologic malignancies, generally developing in women over the age of forty. When EOC are diagnosed prior to metastatic dissemination, the overall 5-year survival rate is 92%; however, nearly 85% of women with EOC are diagnosed with metastasis already present, dropping the survival rate to less than 30%. EOC, arises, arguably, from the single layer of cells that cover the ovary or fallopian tube. Metastatic ovarian tumors develop once an epithelial cell transforms, inducing detachment from the primary tumor site. These shed cells travel throughout the peritoneal cavity, escaping anoikis to survive as single cells and multicellular aggregates (MCA), and metastasize intraperitoneally through adhesion to and invasion of the mesothelial cell layer covering the peritoneum, the primary microenvironment for ovarian cancer metastasis. These mesothelial cells lie atop a collagen type I-rich extracellular matrix; subsequent to the initial attachment of ovarian cancer cells, proteolytic activity catalyzes migration through the mesothelial monolayer and promotes invasion of the sub-mesothelial matrix. Elucidating the early molecular mechanisms involved in this metastatic process, specifically the adhesion of EOC cells to mesothelial cells and penetration of the associated sub-mesothelial extracellular matrix, is essential to the development of future therapeutic agents.

Enzymatic activity of matrix type 1 metalloproteinase (MT1-MMP), a transmembrane proteinase that degrades interstitial collagen, has been shown to be critical to this process. MT1-MMP activity has been directly implicated in both the invasion of the sub-mesothelial collagen I matrix, and in the shedding of metastatic MCA, but the molecular mechanisms behind these events are not completely understood. Considering the well-established role of MT1-MMP in the EOC metastatic process, identification of the molecules contributing to these pro-metastatic phenotypes is critical to future understanding of EOC metastatic spread.

This research investigated the initial adhesive and invasive events of ovarian cancer metastasis, as associated with MT1-MMP proteolytic activity. Specifically, the effect of MT1-MMP activity on ovarian tumor cell ectodomain shedding and the *in vitro*, relationship between MT1-MMP and a potential phosphorylator, integrin linked kinase (ILK), on adhesion and invasion was assessed. Investigations utilized *in vitro* models of homotypic and heterotypic cell-cell adhesion, meso-mimetic invasion assays, and *ex vivo* tissue explants.

Results suggest that ILK activity may catalyze phosphorylation of MT1-MMP to promote pro-metastatic events, including strengthening of adhesive contacts, invasion of the collagen-rich sub-mesothelial matrix, and MCA formation. Additionally, MT1-MMP expression may induce MUC16/CA-125 ectodomain shedding, which may then expose integrins at the ovarian tumor cell surface for high affinity cell-cell and cell-ECM binding.