Role of p120 catenin in migrational plasticity of breast cancer cells

Research Theme: Women's cancers

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Introduction. Cancer mortality results primarily from metastatic disease. Early steps in metastasis comprise local invasion of tumor cells into the adjacent tissue. The past decade, controversy has existed whether downregulation of the cell-cell adhesion molecule E-cadherin is required for migration and invasion of cancer cells. Downregulation of E-cadherin is associated with a switch from collective to single cell migration which may both be used by cancer cells to overcome different local tissue barriers and negotiate their way through heterogeneous local tissue[1]. Thus, dynamic modulation of E-cadherin expression may occur in cancer cell migration and migrational plasticity may be a key concept facilitating cancer cell translocation. A major regulator of E-cadherin dynamics is p120 catenin (hereafter p120, Fig. 1). In addition, p120 activates signaling pathways which control cell motility.

Specific aims and techniques. We hypothesize that p120 controls cancer cell migrational plasticity. The aim of the project is thus to determine the role of p120 in migrational plasticity induced by the extracellular environment. To this end, breast cancer and normal mammary cells are cultured and allowed to migrate in 3D collagen I matrices, which simulate breast interstitial tissue. The 3D-cultured cells will be exposed to different microenvironmental factors that modulate migration and represent heterogeneity of tissue encountered by migrating cancer cells, such as matrix density, hypoxia and growth factors. The function of p120 will be analyzed using stably modified cells overexpressing or lacking p120. Read-outs will be migration phenotype (bright-field microscopy, time-lapse movies), molecular expression patterns (SDSPAGE/WB), subcellular localization (confocal microscopy, fractionation) and biochemical interactions (co-immunoprecipitation).

Supervision and research environment. The project will be performed in the Cell Dynamics group of Prof. Friedl, which is dedicated to unraveling mechanisms of metastasis, using *in vitro* and *in vivo* models for tumor cell migration. Its expertise includes confocal microscopy and multiphoton intravital microscopy. Several lines of research within the group focus on different aspects of breast cancer migration. The MMD student will participate in weekly progress reports meetings (Friedl group) and literature discussions (dept. of Cell Biology) and biweekly informal subgroup meetings, ensuring a firm embedding of the student project within the group.

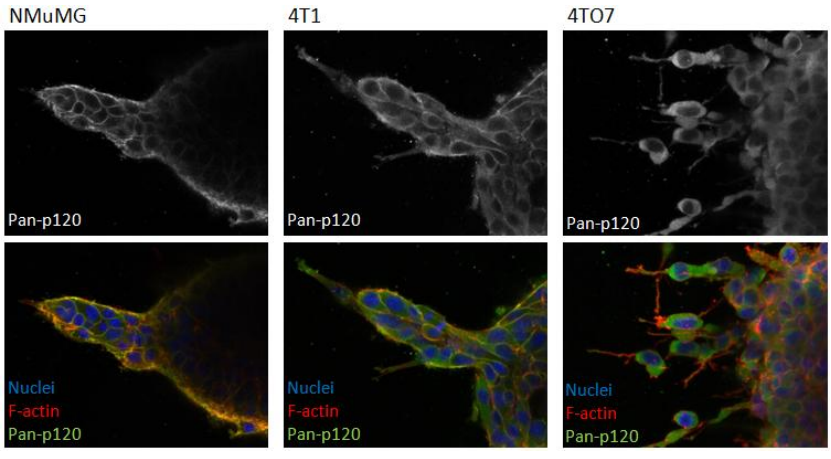

Figure 1: Subcellular localization of p120 in normal mammary epithelial cells (NMuMG) and collectively and individually migrating cancer cells (4T1, 4TO7 resp). p120 is clearly observed at the membranes of cells that migrate collectively (i.e., NMuMG and 4T1) implying its role in the stabilization of cell-cell contacts, whereas p120 is exclusively cytosolic in individually migrating cells (4TO7). *(Jan-Hendrik Venhuizen, unpublished data)*

References:

1. Friedl and Wolf (2009), *Plasticity of cell migration: a multiscale tuning model*, J. Cell Biol. Vol. 188, 11–19