Universität Basel

Research Project

High content identification and modulation of signaling pathways underlying epithelial-mesenchymal-transition (EMT) and cancer metastasis

Third-party funded project

Project title High content identification and modulation of signaling pathways underlying epithelial-mesenchymal-transition (EMT) and cancer metastasis

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Project Website https://biomedizin.unibas.ch/nc/research/research-group-details/home/resear chgroup/tumor-biology/

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Status Completed

Most cancer deaths are due to the systemic dissemination of cancer cells and the formation of secondary tumors (metastasis) in distant organs. Obviously, the migratory and invasive capabilities of cancer cells are critical parameters in the metastatic cascade. 90% of all cancers originate from epithelial tissues, and to leave the primary tumor and to invade into the surrounding tissue tumor cells dissolve their cell-cell contacts and adjust their cell-matrix adhesion sites to a more transient, migratory and invasive mode. Such temporary and reversible phenomenon is known as epithelial-to-mesenchymal transition (EMT), a multistage process that involves distinct genetic and epigenetic alterations and leads to metastasizing, tumor-seeding cells with stem cell-like capabilities, potentially cancer stem cells.

Employing various cellular models of EMT *in vitro* and mouse models of cancer *in vivo*, we have recently observed that EMT is accompanied by a dramatic change in gene expression and the expression and activities of many transcription factors, also indicating a switch in signal transduction pathway activities. Here, we propose to take a focussed approach to identify the signaling pathways and their specific kinase and phosphatase components that functionally contribute to EMT and malignant tumor progression and to modulate the function of these signaling pathways in order to prevent EMT or to differentiate cancer cells into non-malignant, differentiated tumor cells. In particular, we will

(1) ă identify the signaling pathways and ă their specific components that contribute to EMT by performing a high content microscopy screen to interfere with EMT in cultured cells using siRNA libraries against the full mammalian kinome and phosphatome.

(2) use a combination of pharmacological and genetic approaches to interfere with specific components of signaling pathways to prevent cancer metastasis in mouse models *in vivo.*

Employing mainly loss of function approaches in a variety of cellular experimental systems *in vitro* we will characterize the role of signaling pathways during EMT in normal murine mammary epithelial cells and in murine breast cancer cells. In particular, employing state-of-the-art high content microscopy screening with siRNA libraries against all mammalian kinases and phosphatases we will identify the signaling components and signaling pathways that are critical for an EMT to occur. Subsequently, we will employ a combination of pharmacological and RNAi-mediated approaches to interfere with EMT in breast cancer cells *in vitro* and with tumor metastasis in syngeneic transplantation models of breast cancer *in vivo.*

From these experiments we envision not only critical new insights into the molecular regulation of malignant tumor progression but we also hope to open new avenues towards the development of innovative cancer prognosis and therapy.

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