Universität Basel

# Research Project

# Unraveling the regulatory network of EMT and malignant tumor progression

## Third-party funded project

**Project title** Unraveling the regulatory network of EMT and malignant tumor progression
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Most cancer deaths are due to the systemic dissemination of cancer cells and the formation of secondary tumors (metastasis) in distant organs. Despite the progress in metastasis research of the past years, we still lack sufficient insights into how cancer cells leave the primary tumor, disseminate throughout the organism and initiate metastatic outgrowth in a distant organ. 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-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. Disseminating cancer cells also acquire the ability to overcome the loss of substrate adhesion and immune surveillance in the blood stream. Moreover, experimental and clinical data indicate that metastatic cancer cells are highly refractory to chemotherapy.

The molecular events underlying the transition from a benign tumor to a malignant cancer and the subsequent formation of metastases are a major focus in our laboratory. During the past 20 years, we have delineated several molecular processes underlying an EMT and malignant tumor progression. However, the knowledge about the hierarchical organization of the regulatory networks of EMT at a comprehensive level, i.e. the functional interplay between transcription factor activities, miRNA targeting and signaling pathway activities, is still sparse. Recently, we have also reported that EMT promotes cancer cell drug resistance and tumorigenicity, both hallmarks of cancer stem cells, and we are now eager to find out how the regulatory networks of EMT functionally connect to cancer stemness, drug resistance and metastasis formation.

We have recently established a long list of protein encoding genes, miRNAs and lncRNAs that change in their expression during the consecutive morphological states of an EMT by RNA sequencing. In addition, we have performed a high-content microscopy screen with siRNAs libraries targeting all annotated transcription factors, kinases, and phosphatases in murine mammary epithelial cells undergoing a TGFb-induced EMT. These and subsequent validation experiments have identified most of the transcription factors and signaling molecules already known to play a role in EMT but also a substantial number of additional transcription factors, kinases and phosphatases and also miRNAs not previously implicated in an EMT. We have already reported on the detailed functions of some of the unexplored transcription factors and signaling pathways during an EMT and metastasis formation (Sox4, Klf4, Lhx2. Dlx2, Tead2, PI3K and PDGFR signaling).

Here, we propose to establish a comprehensive understanding of the regulatory networks underlying an EMT. Employing a combination of cell biology, biochemistry, high-content microscopy screening, mouse genetics, histopathological and computational approaches, we will address specific questions that range from an early characterization and correlation of potential pathways connecting EMT, cancer stemness, and drug resistance *in vitro* to the functional testing of some of these regulatory pathways during the metastatic process *in vivo*. We will focus on three subprojects that will 1. delineate the functional interconnection between a number of transcription factors, kinases and phosphatases and miRNAs and establish a comprehensive picture of the regulatory circuits of EMT and metastasis, 2. investigate the functional contribution of an EMT process to chemo-resistance of cancer cells and identify the underlying molecular mechanisms, and 3. assess how epigenetic modifications are affecting the reversibility and irreversibility of an EMT and of metastasis formation.

Together, the multipronged approaches proposed here will provide many independent insights into the functional connection of EMT, drug resistance and cancer stemness and their contribution to cancer metastasis. The combination of these results will enable us to pinpoint specific signaling pathways and transcriptional regulatory circuits that are critical for the development of drug resistance and/or for metastasis formation.

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