Universität Basel

Research Project

Is an EMT really responsible for therapy resistance and metastasis?

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Project title Is an EMT really responsible for therapy resistance and metastasis?
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Epithelial cancers make up the vast majority of cancers and, during the transition from benign adenoma to malignant carcinoma and metastatic dissemination, differentiated epithelial tumor cells acquire a de-differentiated, invasive phenotype accompanied by dramatic changes in cellular morphology, the loss and remodeling of cell-cell and cell-matrix adhesion and the gain of migratory and invasive capabilities. These changes are hallmarks of an **E**pithelial-**M**esenchymal-**T**ransition (**EMT**), a multistage process involving distinct genetic and epigenetic alterations and a high degree of cellular plasticity. Notably, during an EMT cells also acquire profound survival capabilities and are able to overcome cell death by apoptosis-inducing signals or by the loss of substrate adhesion (anoikis), to escape from immunosurveillance in the blood stream and even to resist to chemotherapy. Moreover, cancer cells undergoing an EMT exhibit hallmarks of cancer stem cells, such as increased growth as spheroids, colony formation in clonal growth assays and high tumorigenicity upon transplantation into mice. Thus, an EMT may be a principal mechanism for metastatic cancer cells to escape therapy and to continue to seed metastasis. These findings indicate that EMT is regulated on the level of both morphogenesis and cell survival, and propose a concept that cancer metastasis and drug resistance could be therapeutically targeted on the same level. While the contribution of an EMT to the development of therapy resistance has been previously demonstrated, the functional requirement of an EMT to metastasis formation is still highly debated. The vast majority of experimental data supports this notion, yet conclusive experiments demonstrating a causal relationship or using fate mapping of cancer cells that undergo an EMT during metastasis formation *in vivo* are still lacking.

Here, we employ genetic fate mapping of cancer cells undergoing an EMT in a transgenic mouse model of metastatic breast cancer. Cancer cells that undergo an EMT will be visualized by a fluorescence color switch from red to green. They thus can be imaged in histological tumor sections and by live cell imaging in tumor slice cultures, and they can be isolated by flow cytometry for further genetic, transcriptomic and biochemical analysis. Furthermore, we will treat these mice with conventional chemotherapy and assess whether the number and localization of cancer cells undergoing an EMT will change. Subsequent isolation and molecular analysis will be performed to identify and validate the signaling pathways underlying EMT, therapy resistance and cancer stemness, three critical features of malignant tumor progression and metastasis.

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In particular, we will address the following questions:

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(1) Fate mapping of breast cancer cells undergoing an EMT: is an EMT involved in primary tumor invasion, in cancer cell intravasation and in lung metastasis?

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(2) Are cancer cells undergoing an EMT more therapy-resistant in vivo?

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From these experiments, we envisage not only to obtain critical new insights into the molecular regulation of malignant tumor progression and metastasis, but we also hope to open new avenues for the development of innovative therapeutic approaches to overcome cancer drug resistance and metastasis formation.

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