Universität Basel

Research Project

Breast cancer metastasiX: Mathematical modelling of tumor heterogeneity during progression to metastases and clinical validation

Third-party funded project

Project title Breast cancer metastasiX: Mathematical modelling of tumor heterogeneity during progression to metastases and clinical validation
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Project start 01.01.2015
Probable end 31.12.2017
Status Completed

Each year 1.4 million new cases of breast cancer will occur among women worldwide and 450,000 women will die from this disease. In most cases, metastasis is the cause of death. Although progress has been made in broadly understanding the biology of breast tumors and metastases, most of the relevant molecules and pathways remain undefined. Moreover, the integration of multiple signaling pathways into networks and their dynamic changes during progression to metastases is still missing.

The design and development of new therapies require a more thorough systems level **understanding of the quantitative behavior of breast cancer growth and progression to metastases** that arises from the dynamic interplay of cancer cell subpopulations and of signaling networks. **The predominant goal of this project is to use a systems biology approach to unravel, integrate and mathematically model the cellular and molecular determinants of breast cancer progression to metastases**. We will use pathophysiologically relevant models of metastatic breast cancer and validate our findings by investigating patient histopathology and blood specimens and corresponding clinical outcome data.

We propose **three interweaved and complementary approaches**. The first will use transcriptomic, phosphoproteomic, and single-cell mass cytometry to identify signaling networks driving the different stages of breast tumor progression to metastases and to assess the cellular heterogeneity in the various stages of the metastatic process. The second approach will use these datasets, to mathematically infer and model molecular and cellular dynamics during tumor progression and generate experimentally testable hypotheses and eventually identify the metastasis-initiating cells and their signaling network. Finally, proof of concept experiments using cellular systems *in vitro* and animal models *in vivo* will validate the predictions of the mathematical models and test the merit of candidate pathways and molecules as targets for therapy interfering with metastatic spread.

The combined use of pathophysiologically relevant models of metastatic breast cancer, clinical specimens and outcome data, state-of-the-art technologies for analyzing global signaling networks at the single cell level, and high end computational and mathematical tools put our complementary team in a unique position for: a) modeling changes in cellular heterogeneity and signaling networks specific for each breast tumor cell subpopulation during tumor growth and progression to metastases and b) assessing the clinically relevant molecular determinant of metastasis. We not only use state-of-the-art technologies, but also cross the boundaries between the dry and wet labs and the ward. **The mathematical model will allow computer simulation, generate experimentally testable predictions, and**

will ultimately pinpoint novel network-based targets for therapy that will improve the clinical management of patients with metastatic breast cancer.

Keywords breast cancer, cancer stem cells, metastasis, tumor heterogeneity
Financed by
Swiss Government (Research Cooperations)

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