Universität Basel

Research Project

The Role of Plakoglobin in Signal Transduction and Cell Fate of Metastatic Cancer Cells

Third-party funded project

Project title The Role of Plakoglobin in Signal Transduction and Cell Fate of Metastatic Cancer Cells
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Project start 01.11.2015
Probable end 31.03.2016
Status Completed

Breast cancer is the most common cancer in women, resulting in as many as 500,000 deaths per year worldwide. Patients with breast cancer die unequivocally because of the development of incurable distant metastases and not because of symptoms related to the primary site. Understanding the complex,

yet fundamental signaling pathways influencing metastasis is critical to develop therapies tailored to this disease.

The current understanding of how metastasis occurs is derived primarily from mouse models and largely dominated by the notion that single migratory cancer cells within the primary tumor can actively disseminate to distant sites and develop as metastatic deposits. Unexpectedly, our very recent study on patient blood samples has shown instead that cancer cell groupings, a.k.a. circulating tumor cell (CTC)-clusters, held together through plakoglobin-dependent intercellular junctions, can break off the primary tumor and form a metastatic lesion up to 50 times more efficiently than single migratory cancer cells (Aceto et al., Cell, 2014). These findings lead to new open questions, yet highlight a previously unappreciated and targetable mechanism of cancer dissemination. While targeting plakoglobin is a challenge given its lack of extracellular or catalytic domains, the understanding of the signaling networks regulated by plakoglobin (and more broadly, by cell-cell junctions) in metastatic cells has the potential to reveal key vulnerabilities. Currently, the role of plakoglobin in cellular signaling and cell fate is unknown, and no therapies are available to target CTC-clusters.

Our preliminary results suggest that neoplastic cells are more sensitive than normal cells to plakoglobin knockdown, highlighting an exciting therapeutic window. Further, we developed first-of-akind human CTC-derived models of breast cancer metastasis that position us exclusively to study relevant signaling networks of rare metastatic cells. Altogether, we aim to a) define the effects of plakoglobin-dependent cancer cell clustering on signaling and cell fate, and b) identify targetable

signaling nodes downstream of plakoglobin. Our research has the long-term ambition to lead to a novel class of therapeutic agents tailored to target CTC-clusters and prevent the metastatic spread of cancer.

Keywords plakoglobin, circulating tumor cells, metastasis
Financed by
Swiss National Science Foundation (SNSF)

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