Universität Basel

Research Project

Unraveling the common mechanisms between EMT and therapy resistance

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Project title Unraveling the common mechanisms between EMT and therapy resistance
Principal Investigator(s) Christofori, Gerhard M. ;
Project Members Gao, Ruize ; Morand, Agathe ; Matsuda, Nami ;
Organisation / Research unit
Departement Biomedizin / Tumor Biology (Christofori)
Department
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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. Apparently, the migratory and invasive capabilities of cancer cells are critical parameters in the metastatic cascade. 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 an epithelial-to-mesenchymal transition (EMT), a multistage process that involves distinct genetic and epigenetic alterations. A plethora of signaling pathways leading to the activation and expression of a variety of transcription factors, miRNAs, and lncRNAs are known to regulate the dramatic transcriptional reprogramming of cells undergoing an EMT. Some of the transcription factors act as master switches during embryonic organogenesis, tissue homeostasis or in a variety of pathological processes. Recent work has clearly demonstrated that an EMT induces a stem cell-like behavior of cancer cells, also furnishing them with an intriguing resistance to a variety of cancer therapies, including chemotherapy, targeted therapy and immunotherapy, and to reactive oxygen species (ROS). However, the actual contribution of an EMT to the metastatic process is still highly debated, yet currently referred to an increased cancer cell plasticity occurring during a transient EMT/MET. Hence, we need to better understand the molecular networks underlying the cell plasticity conferred by an EMT or MET and its functional contribution to malignant tumor progression and therapy resistance.As a main scientific aim of our project, we propose to dissect at a comprehensive level the molecular and cellular pathways which are induced by an EMT and underlie the development of cancer cell resistance to pharmacological therapies and to ROS. Importantly, it is currently not known whether an overall EMT process governs all these cellular capabilities or whether distinct subprograms administer an EMT, metastasis formation, stem cell-like behavior and therapy resistance. Moreover, our own preliminary data suggest that these pathways may differ between cancer cells cultured on plastic as compared to three-dimensional organoids or tumors growing in vivo. Here, we will employ novel mouse models of metastatic breast cancer in which cancer cells undergoing an EMT can be traced by genetic fate mapping. These mice and cell lines derived from their tumors, as well as tumor organoids generated from these cell lines, will be treated with various chemotherapies to induce an EMT and/or therapy resistance. The molecular pathways and gene activities during an EMT and during the development of therapy resistance will be identified by RNA sequencing and integrated bioinformatics analysis. The functional role of newly identified potential master regulators of EMT and therapy resistance will be validated in proof-of-concept experiments in cultured breast cancer cells in vitro and then in mouse models in vivo. Finally, from the resulting analytical bioinformatics data we will generate gene expression signatures of therapy resistance and test their diagnostic and prognostic val-

ue for clinical outcome in cancer patients. From these experiments, we not only anticipate novel insights into the molecular regulation of malignant tumor progression and cancer metastasis, but also envision to contribute to the design of new strategies towards innovative cancer diagnosis and prognosis and towards overcoming therapy resistance.

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