Universität Basel

Research Project

Molecular mechanisms underlying normal and neoplastic mammary stem cells, progression to metastasis and resistance to therapy

Third-party funded project

Project title Molecular mechanisms underlying normal and neoplastic mammary stem cells, progression to metastasis and resistance to therapy
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Breast cancer is the second leading cause of cancer death in women and 2.1 million new patients are diagnosed with breast cancer annually. While 98% of patients survive 5 years or more after diagnosis of a localized (confined to the primary site) breast cancer, this number drops to 15-25% if the cancer has metastasized to distant organs. Curing metastatic breast cancer clearly represents an unmet medical need. Yet, the cellular and biochemical mechanisms orchestrating the steps leading to drug resistant metastases remain largely unknown. Their identification, which is the overarching goal of this application, should enhance the development of targeted therapies for this presently incurable disease.A thorough understanding of cellular pathways involved in tumor initiation, metastasis, and resistance to therapy is the appropriate basis to tailor therapy to the patient. Indeed, several inhibitors of the most common oncogenic pathways have been tested in preclinical models and are already included in the care of patients. Despite the specificity of many of these approaches, the clinical translation of most single therapies has been sub-optimal; they were either ineffective or transiently effective with subsequent emergence of resistance. Therefore, the mechanisms of limited therapeutic responses must be carefully assessed in order to better tailor the therapy to each cancer patient and to rationally design combinations of therapies. The overarching goals of this proposal are to assess the molecular mechanisms underlying normal and neoplastic mammary stem cells, progression to metastasis and resistance to therapy.Our preliminary data using the PiggyBac (PB) transposon insertional mutagenesis approach has revealed that this system increases self-renewal of normal and neoplastic mammary stem cells and metastasis, and results in resistance to therapy. Transposon integration sites in these preclinical models were revealed by splinkerette PCR and by next-generation sequencing, and potential new candidate regulators of self-renewal and resistance to therapy have been identified. Our specific aims are to: 1-Validate the identified candidate regulators of normal and neoplastic mammary stem cells.2-Assess pathways important for breast tumorigenesis and metastasis by in vivo mutagenesis.3-Validate the identified potential mechanisms of resistance to therapy by in vivo mutagenesis.This multiprong project uses both hypothesis-driven and unbiased state-of-the-art genetic approaches to identify and validate novel molecular mechanisms of normal and neoplastic stem cells, metastasis, and resistance to therapy, which should ultimately improve the clinical management of patients with metastatic breast cancer.

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