

Tumor Heterogeneity, Metastasis and Resistance



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Mechanisms of breast tumor heterogeneity, metastasis and resistance: From Bedside to Bench to Bedside and back again

Breast cancer is the leading cause of cancer death in women and 2.1 million new patients are diagnosed with this disease annually. Although the overall survival rates for breast cancer have improved over the last decades, more than 600,000 lives are lost to this disease annually because of drug resistant metastases. A thorough understanding of both cancer cell intrinsic (i.e., cell autonomous) and extrinsic (i.e., non-cell autonomous) mechanisms of breast cancer progression is urgently needed to end this stalemate.

The thread connecting the research topics in my lab is tumor heterogeneity. We assess fundamental mechanisms that influence normal and neoplastic breast stem cells, metastasis, and resistance to targeted therapies at the molecular, cellular, and whole organism levels. These interdisciplinary projects seek to leverage a mechanistic insight into personalized therapy, which is a focus of the translational research that we pursue in close collaboration with clinicians (Fig. 1) (www.bentireslab.org).

M. Bentires-Alj is the founder and president of the European Network for Breast Development and Cancer (www.enbdc.org) that fosters global interactions between labs in these areas, and co-founder of the Basel Breast Consortium (www.BaselBC.org), which is committed to promoting local basic, clinical, and translational interdisciplinary research projects within Switzerland.

Glucocorticoids promote breast cancer metastasis

Transcriptional profiling of tumours and matched metastases revealed cancer-site specific phenotypes and increased glucocorticoid receptor (GR) activity in distant metastases. GR mediates the effects of stress hormones and synthetic derivatives. We show that increase in stress hormones during breast cancer progression resulted in GR activation at distant metastatic sites, increased colonization, and ultimately reduced survival. The data also reveal that GR activation decreases the efficacy of the widely used chemotherapy paclitaxel. Corticosteroids such as dexamethasone are widely used in the treatment of breast cancer to combat side-effects of chemotherapy and to treat symptoms related to advanced cancer. Our results suggest that GR activation increases heterogeneity and metastasis and, thus, call for caution in the use of glucocorticoids in the treatment of BC patients with cancer related complications (Obradovic, Nature 2019).



Fig. 1: Research areas within the Bentires-Alj lab: <https://bentireslab.org/>

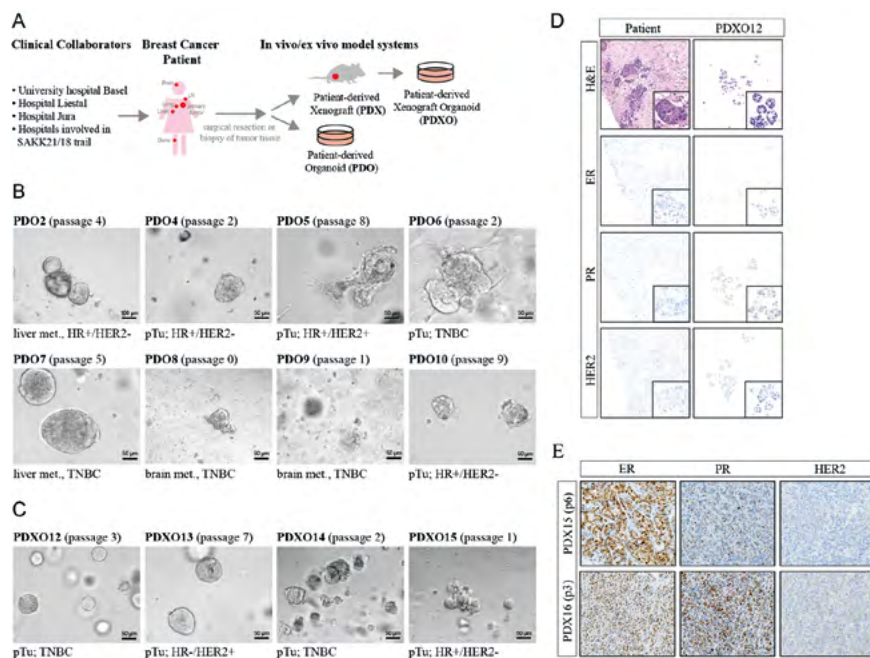


Fig. 2: Basel personalized breast cancer program: *Ex vivo* and *in vivo* model systems from breast cancer patients. A. Scheme displays our clinical collaborators and derived patient-derived organoids (PDO), patient-derived xenografts (PDX) and PDX-derived organoids (PDXO) models from different human primary breast tumors (pTu) and metastases (met). B,C. Representative bright field images of established PDO (B) and PDXO (C) cultures. D. Images of sections of a primary tumor and corresponding PDXO models. E. Images of sections of PDXs from ER+ breast tumors. Expression of ER, PR and HER2 was analyzed by IHC.

Connection to Clinical Practice

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Hippo kinases LATS1/2 control human breast cell fate via crosstalk with ERα

Using a high-content confocal image-based shRNA screen for tumor suppressors regulating human breast cell fate, we have discovered that ablation of the Hippo kinases large tumor suppressors (LATS) 1 and 2 promotes luminal fate and increases the number of bipotent and luminal progenitors, the proposed cell-of-origin of most human breast cancers. Mechanistically, we revealed a crosstalk between Hippo and ERα signaling. In the presence of LATS, ERα was targeted for ubiquitination and DCAF1-dependent proteasomal degradation. Our findings reveal a non-canonical effect of LATS in the regulation of human breast cell fate (Britschgi, Nature 2017).

Swiss Personalized Oncology

The Swiss Personalized Oncology (SPO) driver project, part of the Swiss Personalized Health Network, is chaired by Profs. Bentires-Alj and Michielin (CHUV). SPO is a Switzerland-wide effort that aims at integrating clinical and molecular information from cancer patients, which should ultimately enable more precise diagnoses and thus treatments tailored to individual patients. SPO'S main goal is to achieve interoperability of the clinical and laboratory data from cancer patients in Switzerland.

Personalized breast cancer treatment

While the SPO is a nationwide effort, we have assembled, a local group of clinicians to make up a breast cancer personalized medicine team that should ultimately improve treatment of patients. Our goal is to collect patient samples and to use multiomics, combined with drug response profiling and computational analysis, in the assessment and modeling of cancer and tumor microenvironment heterogeneity in a longitudinal way (Fig. 2).

Selected Publications

- Obradović MMS, Hamelin B, Manevski N, Couto JP, Sethi A, Coissieux A, Müntz S, Okamoto R, Kohler H, Schmidt A, Bentires-Alj M (2019). Glucocorticoids promote breast cancer metastasis. Nature 567, 540–54.
- Britschgi A, Duss S, Kim S, Couto JP, Brinkhaus H, De Silva D, Mertz KD, Kaup D, Varga Z, Voshol H, Vissieres A, Leroy C, Roloff T, Stadler M, Koren S, Scheel C, Miraglia L, Orth PA, Bonamy GMC, Reddy V, Bentires-Alj M (2017). The Hippo kinases LATS1/2 control human breast cell fate via crosstalk with ERα. Nature 541, 541–545.
- Leroy C, Ramos P, Cornille K, Bonenfant D, Fritsch C, Voshol H, Bentires-Alj M (2016). Activation of IGF1R/p110β/Akt/mTOR confers resistance to α-specific PI3K inhibition. Breast Cancer Research, 18(1):41.
- Koren S, Reavie L, Silva J, De Silva D, Stadler M, Roloff T, Britschgi A, Eichlisberger T, Kohler H, Aina O, Cardiff RD, Bentires-Alj M (2015). PIK3CAH1047R induces multipotency and multi-lineage mammary tumors. Nature, 525(7567):114–8.
- Couto J and Bentires-Alj M. (2017) Mouse models of breast cancer: deceptions that reveal the truth. Breast Cancer – Innovations in Research and Management, Textbook, Springer. Edited by U Veronesi and PG Pelicci.